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Quality of Healthcare in the Aftermath of the COVID-19 Pandemic



Anastasius S Moumtzoglou



Quality of Healthcare in the Aftermath of the COVID–19 Pandemic

Anastasius Moutzoglou
P&A Kyriakou Children's Hospital, Greece

A volume in the Advances in Healthcare
Information Systems and Administration (AHISA)
Book Series



Published in the United States of America by

IGI Global

Medical Information Science Reference (an imprint of IGI Global)

701 E. Chocolate Avenue

Hershey PA, USA 17033

Tel: 717-533-8845

Fax: 717-533-8661

E-mail: cust@igi-global.com

Web site: <http://www.igi-global.com>

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Library of Congress Cataloging-in-Publication Data

Names: Mourtzoglou, Anastasios, 1959- editor.

Title: Quality of healthcare in the aftermath of the Covid-19 pandemic /

Anastasios Mourtzoglou, editor.

Description: Hershey, PA : Medical Information Science Reference, [2022] |

Includes bibliographical references and index. | Summary: "The book examines the massive stress on healthcare professionals' formal training, their creed to no harm, and the patient safety movement during the recent Covid-19 pandemic and offers suggestions on how healthcare professionals might provide their services differently "-- Provided by publisher.

Identifiers: LCCN 2021029421 (print) | LCCN 2021029422 (ebook) | ISBN

9781799891987 (hardcover) | ISBN 9781799891994 (ebook)

Subjects: MESH: Quality of Health Care--standards | Quality Assurance, Health Care--standards | COVID-19 (Disease) | Health Information Systems | Digital Technology

Classification: LCC RA644.C67 (print) | LCC RA644.C67 (ebook) | NLM W 84.41 | DDC 362.1962/414--dc23

LC record available at <https://lcn.loc.gov/2021029421>

LC ebook record available at <https://lcn.loc.gov/2021029422>

This book is published in the IGI Global book series Advances in Healthcare Information Systems and Administration (AHISA) (ISSN: 2328-1243; eISSN: 2328-126X)

British Cataloguing in Publication Data

A Cataloguing in Publication record for this book is available from the British Library.

All work contributed to this book is new, previously-unpublished material. The views expressed in this book are those of the authors, but not necessarily of the publisher.

For electronic access to this publication, please contact: eresources@igi-global.com.



Advances in Healthcare Information Systems and Administration (AHISA) Book Series

Anastasios Moumtzoglou

Hellenic Society for Quality & Safety in Healthcare and P.
& A. Kyriakou Children's Hospital, Greece

MISSION

ISSN:2328-1243

EISSN:2328-126X

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Medical Information Science Reference • © 2020 • 287pp • H/C (ISBN: 9781799829492) • US \$275.00



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*This book is dedicated to my daughter Maria-Georgia MOUNTZOGLOU
A.M.*

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Chapter 1

Pandemic, Panresponsibility, and Pandemonium	1

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This chapter addresses the epidemiological and social imperatives associated with controlling a public health emergency and preventing outbreaks. Using population behaviors as a determinant of the extent to which events progress to alter populations, geographic regions, or the globe, this chapter borrows from epidemiology and social behavior the author builds on his worldwide to propose the crucial need of having a shared global responsibility. While the impetus of this chapter is the COVID-19 pandemic, the generic predisposing factors and past public health outbreaks are used to place the ravages of the present pandemic into a framework of interpretation as well as for prediction of future events and associated social and public health preparedness. Without the use of analytic methods of inquiry, this chapter addresses the core aspects of fear and hope all populations and societies have to balance to understand, accept, and co-exist with events that befall upon them and encroach on their existing lifestyle and quality of life expectations.

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Anastasius S. Moumtzoglou, P&A Kyriakou Children's Hospital, Greece

Abraham Pouliakis, National and Kapodistrian University of Athens, Greece

Population health management (PHM) is a discipline that studies and facilitates care delivery across the general population. On the other hand, currently, there is a significant outgrowth of precision medicine within the science of individuality that recognizes the uniqueness and digitization of the individual. The chapter focuses on five technologies that significantly impact precision medicine, arguing that cloud computing, big data, and m-health technologies offer the resources to succeed in dealing with the shortcomings of population health management. Finally, it contends that quantum computing and artificial intelligence are the necessary keystones, as they provide the required enormous processing power and algorithmic tools.

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We have learned from COVID-19 to humanize our society and seriously challenge the rising inequalities, racism, and discrimination that exist in our contemporary human world. One of the apparent discriminations in our society is based on the government's approach and treatments towards people with disabilities. This chapter is about the Australian people with disabilities from culturally and linguistically diverse backgrounds and how the Australian National Disability Insurance Scheme has responded to the needs of these people within the Australian society during COVID-19.

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Spreading Stochastic Models Under Ising/Potts Random Fields: Spreading Diseases 65

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Stochastic models have become a powerful necessary statistical tool to estimate parameters where data are represented by regions of interests under uncertain areas. Due to the high dimensionality of the spatial patterns, investigation of the stochastic modeling simulations must be applied based on spatial variability. Models for spreading diseases are given based on whether or not the disease succeeds or fails to appear in the region. Based on this assumption, an Ising/Potts random fields model has to be introduced to analyze the spatial pattern of spreading. In this work, the spatial pattern models for spreading diseases have been analyzed considering Markov random fields auto-models. The Gibbs sampler would be used to simulate example images for various parameter combinations. In this work, a spatial analysis methodology based on Bayesian analysis was introduced, and procedures to solve the problem with spatial variability are described based on spatial model estimation techniques.

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The COVID-19 Pandemic and Relevant Concerns for Pediatric Neurologists..... 79

Shampa Sarkar Biswas, Presidency University, India

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Novel coronavirus SARS-CoV-2 is being speculated to have a profound effect on the neurological health of children. This chapter addresses the risk of neurological symptoms in children susceptible to COVID-19, which might help pediatric neurologists. As existing research has been mainly focused on adults, this chapter is a compilation of past and present data to understand better the diseases associated with pediatric neurology and COVID-19 and its repercussions. Consequently, this chapter aims to enlighten the level of alertness in pediatric specialists to assess potential neurological involvement of this virus and its probable long-term neuropsychiatric and medical consequences.

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Yiannis Koumpouros, University of West Attica, Greece

The internet and the latest technological developments promise new and innovative work and learning environments and capabilities. The COVID-19 pandemic has radically changed the way people work, communicate, and learn. Many traditional infrastructures, such as the internet, have been tested to the fullest extent. Education has faced the most significant challenge as it had to serve people with different needs and backgrounds. Cheap technology solutions combined with increased computing and storage capabilities enable the education system to cope on time. Nevertheless, the need to adequately serve special population groups remains a challenge. The chapter presents an example of a methodological approach to designing an effective solution employing game-based learning techniques for children with autism or other learning difficulties. The latest pedagogical approaches are combined with appropriate gamification techniques to produce the desired outcome. It concludes by presenting critical issues in designing game-based learning applications for children with special educational needs.

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Dimitrios G. Katehakis, Foundation for Research and Technology, Hellas, Greece

Angelina Kouroubali, Foundation for Research and Technology, Hellas, Greece

This work presents, analyzes, and discusses the digital transformation challenges that need to be addressed for the development of quality electronic medical record (EMR) systems in Greece in the aftermath of the 2019 coronavirus disease pandemic. The authors highlight quality EMR characteristics and provide an overview of factors affecting their adoption within the wider context of the European digital single market towards supporting continuity of care. Key challenges addressed include the linking of EMRs with the medical practice workflow in a standardized manner, building trust and acceptance by making the best use of champions to build capacity, and by financing the digital transformation transition and sustainability in a coordinated manner. Foreseen benefits include better support of medical decisions across all stages of the patient journey, patient empowerment through virtual dossiers with clinically significant information, enhancement of vendor potential to implement innovative tools to support continuity of care, and acceleration of evidence-based research.

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Amit Roy Chowdhury, Indian Institute of Engineering Science and Technology, Shibpur, India

3D printing technology has influenced the healthcare and medical sector during the COVID-19 pandemic. 3D printer machines fabricated numerous medical kits and accessories. These include face shields, specimen collectors, personalized face masks, ventilators, protective eyewear, personal protection equipment (PPE), and isolation wards/chambers. All these were fabricated in a short period as requirements were increasing expressively. The chapter describes several of these applications of 3D printing, which assisted in looking after numerous lives throughout the COVID-19 pandemic. The cooperation of the 3D-printing knowledge with the worldwide healthcare community will develop innovative and essential prospects in the upcoming days. Also, numerous important proposals are described that were applied to fight against the COVID-19 outbreak, monitored by a discussion about the upcoming trend of how additive manufacturing can help people worldwide to control any upcoming pandemic situation.

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RFID Applications for Patient Safety in the Healthcare Sector..... 155

Moutaz Haddara, Høgskolen Kristiania, Norway

Anne Staaby, Kristiania University College, Norway

Internet of things (IoT) is revolutionizing industries through enabling object identification, traceability, real-time communication, and monitoring. In healthcare (HC), IoT can reduce the unneeded physical contact through the possibilities of remote monitoring and tracking of patients, which can be used in pandemic control scenarios. One area of paramount importance in HC is patient safety. Published statistics suggest a mounting number of patient mistreatments due to the erroneous identification of the patient or the drug administered. Radio frequency identification (RFID) is envisioned as a disruptive innovation in HC and represents several opportunities for increased safety. The authors explore the potentials and challenges of RFID adoption in HC with a focus on patient safety. The findings suggest that there has been a surge in IoT applications in HC research in the last two years concerning pandemic control. However, the high costs of adoption and implementation, security and privacy concerns, and human safety risks are among the main barriers to adopting IoT in HC.

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Blockchain Technology and Healthcare Applications: A Comprehensive Study..... 180

Anita Venaik, Amity University, Noida, India

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Blockchain technology (BCT) is an evolving digital technology that changes digital operations' dimensions by conducting distributed ledger transactions without the involvement of third parties. The chapter aims to examine the use of BCT in healthcare and develop a hierarchical theoretical framework. The framework is based on the stakeholder principle and exposes BC's effect on smart healthcare. Its decentralised existence is an ideal catalyst for the much-needed transition toward well-organised healthcare as it solves the most pressing issues.

Chapter 11

New Aspects and an Artificial Intelligence Approach for the Detection of Cervical Abnormalities:
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The COVID-19 pandemic has challenged health systems worldwide by decreasing their reserves and effectiveness. In this changing landscape, the urge for reallocation of financial and human resources represents a top priority. In screening, effectiveness and efficiency are most relevant. In the quest against cervical cancer, numerous molecular ancillary techniques detecting HPV DNA or mRNA or other related biomarkers complement morphological assessment by the Papanicolaou test. However, no technique is perfect as sensitivity increases at the cost of specificity. Various approaches try to resolve this issue by incorporating several examination results, such as artificial intelligence are proposed. In this study, 1,258 cases with a complete result dataset for cytology, HPV DNA, HPV mRNA, and p16 were used to evaluate the performance of a self-organizing map (SOM), an unsupervised artificial neural network. The results of the SOM application were encouraging since it is capable of producing maps discriminating the necessary tests and has improved performance.

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The Implementation of Clinical Laboratory Quality Indicators in the Era of the COVID-19
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The use of quality indicators (QIs) and risk assessment are valuable tools for maintaining the quality of laboratory tests. Both are requirements of ISO 15189: 2012 and are usually based on standard statistical and empirical data. In this chapter, the authors focus on evaluating clinical laboratory quality indicators in the era of the COVID-19 pandemic. The goal is to pose and discuss, based on the authors' experience, the quality evaluation and risk assessment through the collection, study, and analysis of quality indicators covering the pre-analytical, analytical, and post-analytical phases of the laboratory testing process. QIs were evaluated using the Six Sigma method. Moreover, FMEA risk analysis was performed, and the degree of risk priority was assessed using the Pareto method. The results show that in the analytical phase, the laboratory's performance is satisfactory, while the pre-and post-analytical phases need further preventive/corrective actions.

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Christina Seitopoulou, General Hospital of Nikaia Piraeus "Agios Panteleimon", Greece

Clinical laboratories produce test results that support the diagnosis, prognosis, and patient treatment. Test results must be relevant, accurate, and reliable for patient care. International bibliographic data estimate that approximately 62.0% of the errors made in clinical laboratories are due to errors during the pre-analytical stage. This chapter presents a failure modes and effects analysis (FMEA) to analyze potential failure risks within the pre-analytical phase and classify them according to severity and likelihood. FMEA allows molecular laboratories to lower costs and drive better outcomes through high-quality nucleic acid extraction, sensitive detection, and accurate quantification. RT-PCR technology continues to be the gold standard for the clinical detection of SARS-CoV-2 RNA in individuals suspected of COVID-19. It is essential to use highly sensitive assays to detect active infections and reduce the likelihood of false-negative results.

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Implementation of Static Telecytology Applications for Accreditation Purposes According to ISO 15189..... 244

Stavros K. Archondakis, 401 General Military Hospital of Athens, Greece

Ourania S. Oustampasidou, Alpha Prolipsis Medical Laboratories, Greece

Telecytology can be defined as the process of diagnostic cytology performed on digital images. The process of diagnostic cytology performed on digital images can be used for teaching, professional examinations, obtaining expert opinions on severe cases, and routine diagnosis of the entire laboratory workload. However, little information exists about its possible use for proficiency testing purposes. The existing studies have found a high (90%–95%) concordance between telecytological and glass slide diagnoses, but they refer to a small number of cases. Thus, the purpose of the chapter is to examine the feasibility of developing a proficiency testing scheme for cytology labs wishing to be accredited according to ISO 15189:2012 by using low-cost telemedical applications.

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Implementation of Videos Captured by Static Telecytological Applications for Obtaining Expert Opinions 259

Stavros K. Archondakis, 401 General Military Hospital of Athens, Greece

Ourania S. Oustampasidou, Alpha Prolipsis Medical Laboratories, Greece

Published studies compare static and dynamic telecytology systems. Still, no study has focused on implementing short videos captured by static telecytology stations for telemedical applications. The chapter aims to evaluate the diagnostic reproducibility of telecytology in thyroid fine-needle aspiration specimens prepared using liquid-based cytology among four cytopathologists using representative short duration videos captured by a static telecytology station. It also examines the agreement between the contributor's and the reviewer's diagnoses.

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A Light Into the Current COVID-19 Pandemic in the Context of the Ancient Indian Science..... 271

Fatima Siddiqua, Gauhati University, India

Rashmi Husniwara Rahman, Gauhati University, India

Ancient science relating to plants has always been a source of drug discovery, and in ancient times, people used medicinal plants to fight against pandemics. Researchers suggest ancient medical practices like Ayurveda, Unani, and traditional herbal medicine as a potential source to cure or prevent diseases like COVID-19. The internet of things (IoT) aims to help solve real-world problems by connecting all modern-day devices. An internet of healthcare things (IoHT), a branch of IoT, is creating a revolution in medicine. We can incorporate ancient knowledge into the IoT system and help people worldwide fight this pandemic by spreading the knowledge of Ancient Indian medicinal practice.

Chapter 17

Electrical, Magnetic Radiation and Power Density Analysis of Electronic Gadgets During Yajna... 285

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All of us are aware that the modern mechanical and electrical systems in collaboration with AI, CPS, and IoT have affected our lives drastically. At one end, they have provided ease and comfort. On the other end, the electrical and magnetic radiations emitted by them have threatened the mental and physical fitness. Surprisingly, the Asian Agnihotra process effectively reduces the electrical, magnetic radiations emitting from electronic devices. The chapter deals with the computational analysis of electrical, magnetic radiation, and power density measurement of environmental effects and gadgets after the Homa therapy. In the gap of a specific time, readings were recorded, and it was observed that drastic reduction occurred at the place where Yajna was performed. This gap was curtailed gradually as time increased. The phenomenon can undoubtedly be used to address human health threats due to electronic gadgets in the 21st century. Also, it supports the concepts of smart cities where one can quickly identify the numerous effects of the Yajna process.

Chapter 18

Facets of the Evolving Healthcare Management Model	303

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The pandemic represents an opportunity to reimagine future healthcare and rethink healthcare management unbound by preconceived notions based on the following three main drivers that emerged during the pandemic. These include transformed business models, new care delivery models disrupted by ubiquitous data and technology, intelligent spaces, and digitally-enabled hospitality. In this context, it is imperative to reexamine all facets of healthcare management, considering that applying linear models to healthcare management has improved our understanding of their system structure and function. However, such models often fall short of explaining experimental results or predicting future abnormalities in complex nonlinear systems. Nonlinear models may better explain how the individual components collectively act and interact to produce a dynamic system in constant flux. They also assist in filling in some of the results which linear models do not adequately explain. Finally, chaos theory might provide new insights into standard as well as abnormal behavior within systems.

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Preface

The COVID-19 pandemic exerts tremendous stress on management, the formal training of healthcare professionals, their creed to no harm (Siddiqui, 2020), as well as the patient safety movement. So far, we have explicitly been teaching healthcare professionals that the best way of treating a patient is through its vicinity with multiple providers. Moreover, we argue that healthcare education requires a pack of healthcare workers from varied educational backgrounds and training levels for the nuances of a disease.

However, the novel coronavirus (COVID-19), a respiratory disease that has spread to many countries around the world, affects not only all aspects of daily life but also the organizational culture and values of healthcare. In this context, healthcare institutions experience absenteeism, change in patterns of commerce, and interrupted supply/delivery. In this context, we have given healthcare professionals intellectual, moral, and social instructions to (OSHA, 2020):

- Use ‘hierarchy of controls’ in selecting ways to control workplace hazards.
- Control a hazard by removing it from the workplace systematically.

On the other hand, during the pandemic, healthcare professionals are also in danger. They rank at a very high exposure risk according to the four exposure risk levels of the Occupational Risk Pyramid, which represents the probability distribution of risk.

There is also collateral damage of COVID-19 that reaches much farther than those who get the virus (Love, 2020). Specifically, there are ripple effects related to the delay or avoidance of healthcare from fear of the virus leading to complications in surgeries or creating disease burdens that we have to deal with after the pandemic is over.

Overall, a broad overview of the implications first includes concerns about national security (McIntosh, 2020). The pandemic took countries by surprise, despite its drumbeat being heard across the globe. As a result, we must invest in health as we do in security. That means rethinking national budgets to dedicate strategic resources to research, development, and training in the medical sector and purchasing and producing materials. The key to success in resisting pandemic attacks is logistics. Second is the crucial importance of collaboration between citizens and official institutions and understanding that the idea of a public good is interrelated with personal autonomy ideas. In Western democracies, there is a constitutional limit to the obligations imposed on citizens, hence the importance of personal responsibility. The third element is mobilizing technology, while the fourth challenge is retaining and building upon the changes in delivery, particularly remodeling service delivery. New roles have emerged that have the potential to enhance independence and increase health autonomy for practitioners. These maxims have come to the fore with the medical and health professions fulfilling the goals of the value-based agenda

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through integrated provision (Bromley and McIntosh, 2016). The fifth element is combining big data and creating operational models of a national learning health system. There is a data-driven transformation of health policy and planning, service delivery and evaluation, and provision. A multidisciplinary effort is also essential to design, characterize, and evaluate interventions shaping behavior, especially self-management (Cottom, 2020). Self-management can be defined as a set of steps that aim to enable individuals to feel that they can live well with a long-term condition on their terms. Such methods include a spectrum of support to help patients learn about their condition, acknowledge its impact on their lives, make changes, and identify areas where they require additional support. One of the mechanisms responsible for these improvements in health status is self-efficacy (Moumtzoglou, 2019). Adherence to medical treatment is closely linked to the patient's ability to self-manage their chronic pain and is shown to be an essential factor in increasing self-efficacy (Nicholas, 2007).

Furthermore, looking towards the post-pandemic future, it is clear that chronic disabilities could be an outcome for those who have survived COVID-19 infection. Ultimately, this will cause additional pressure on pain management clinics, many of which are already months or years behind, as they begin to look at the resources such as waiting lists. Following this, there is certainly a growing need to provide a more diverse service for chronic pain patients. It is also imperative to ensure that future service delivery includes continuing monthly supported self-management sessions containing face-to-face and online service provision elements. It must also be highlighted that not everyone experiencing chronic pain needs a referral to a secondary care chronic pain clinic.

It is also of decisive importance to take proactive steps in building emotional resilience and minimizing workplace stress. That means being good role models by looking after ourselves, supporting individual emotional needs and acting to ensure our organizations adapt working practices where needed. That is best done when models of supervision are holistic and feed upwards to information systems. To facilitate a resilient organization and workforce and avoid mass burnout, line managers must have the expertise and time to undertake high-quality supervision and enable debrief.

Moreover, we must not forget the potential for burnout and prioritize meaningful, well-articulated supervision to continue supporting and building the staff. Finally, as hospitals and health systems respond to and recover from the impact of COVID-19, their strategic and financial plans will inevitably change. Similarly, the organization's available capital capacity and the prioritization of projects in its allocated capital portfolio will need adjustment. Nonetheless, the underlying process of capital allocation and management should stay the same, relying on the fundamentals of structure, discipline, rigor, and skill to accommodate necessary changes.

Taking heed of the previous processes, we argue that:

- Leadership style becomes a critical aspect of management after the pandemic.
- There is a need for wise motivation, as professionals should appreciate their work.
- The proper and balanced workload for employees should be redefined.
- Peer support should be encouraged.
- Wellness and mental health should be ensured.
- Exemplary teamwork should be built.
- Employee control over their work should be increased.
- Achievements should be reviewed regularly.
- Unnecessary gatherings at work should be cancelled.

Overall, shared leadership will play a fundamental role in improving healthcare performance through social capital.

THE CHALLENGES

The COVID-19 pandemic has created unique challenges for the healthcare systems due to the staggering mismatch between capacity and patient demand. The healthcare industry adopts digital innovation slowly due to the conventional belief that humans need to be at the center of healthcare delivery tasks. However, in the setting of the COVID-19 pandemic, artificial intelligence (AI) is used to carry out specific tasks such as pre-hospital triage and enable clinicians to deliver care at scale.

A summary of worldwide technological efforts during the pandemic in 2020 included (Meskó, B., Dhunnoo, P., 2020; Moumtzoglou, 2020):

- Microsoft launched an interactive Bing map, which details the number of active, recovered and fatal cases globally and countrywide.
- BlueDot, which first sounded the alarm back in December 2019, uses artificial intelligence (AI)-based algorithm that identifies the trend, which epidemiologists then analyze.
- Alibaba developed a new AI algorithm that detects COVID-19 infections from CT scans of patients' chests with 96% accuracy.
- The UAE collaborates with telecom companies to set up the first virtual hospital in the Middle East, while the CDC and WHO advocate telemedicine to monitor patients and reduce risks.
- In Italy, Paginemediche launched an online chatbot developed to support remote triage of potential COVID-19 cases.
- South Korea's authorities used data from CCTV footage, bank transaction and phone use to locate people exposed to COVID-19 in managing the outbreak.
- Singapore launched the TraceTogether app. as a community-driven means for contact tracing.
- Headspace was offering its Premium option of the mental wellbeing app. for free, through 2020, to healthcare professionals working in the US public health.
- Owners of wearables from companies like Apple, Fitbit, and Garmin helped spot viral outbreaks and aid healthcare authorities to take prompt actions by opting for the DETECT study.
- The WHO, to raise awareness about the coronavirus among younger audiences, used TikTok.
- Open-sourced masks and mechanical ventilators for milder symptoms were 3D-printed in Spain. Moreover, in Italy, a 3D-printing startup supplied hospitals with valves required to connect respirators to oxygen masks as the company making those had trouble keeping up with the demand. In a similar vein to open-sourcing designs for 3D-printing medical equipment, other communities are leveraging the power of the community to fight COVID-19 with free resources.
- Foldit is an online computer game where players can solve puzzles by folding protein structures without prior biochemistry knowledge. The University of Washington Institute for Protein Design in Seattle tested and manufactured the best ones.
- In China, e-commerce giant JD.com deployed self-driving robots to deliver medical goods to Wuhan. Moreover, the startup Shanghai TMIRob sent robots to disinfect wards, intensive care units and operating rooms in hospitals. Back in January, doctors in a US hospital used a robot to assist them in taking vitals of a patient infected with the COVID-19 virus. Robots are repurposed

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in Thailand to measure patient fever and allow physicians to communicate with patients via video call. The Belgian robotics company ZoraBots provided their robots to care centers to assist elderly contact remotely.

- Researchers working with the gene-editing tool CRISPR are taking an interest in the COVID-19 fight. Scientists from the New York Genome Center and New York University published their findings on a new CRISPR technique to suppress gene expression.

Furthermore, during the COVID-19 pandemic, several countries developed makeshift hospitals by converting public venues to medical facilities, aiming to substantially upgrade the health system's capacity in very little time. This change management capability is among the fundamental elements of infrastructure future-proofing.

Finally, Medical 4.0, which is now emerging as the fourth medical revolution (Haleem & Javaid, 2020), represents:

- The applications of electronically supported information technology.
- Microsystem.
- High level of automation.
- Personalized therapy.
- Artificial Intelligence (AI).

Moreover, robotics is evolving in healthcare and allied areas with unique concerns relating to managing and controlling the spread of the COVID-19. The prime utilization of robots is to reduce person-to-person contact and ensure cleaning, sterilization and support in hospitals and similar facilities such as quarantine.

SEARCHING FOR A SOLUTION

The Covid-19 pandemic prompts us to consider that we live in a highly unpredictable and complicated world. It has presented many challenges, including managing the supply chain for personal protective equipment (PPE) and adjusting workforce capacity to cope with financial loss. Amid these challenges lies healthcare leaders' opportunity to better position and transform their organizations for a future of unpredictable surprise.

The Covid-19 pandemic is a clear demonstration of the ability of a minor, surprise event in one part of the world to influence the daily operations of medical practices and hospitals around the globe. Three dimensions can characterize a surprise event (Begun & Jiang, 2020):

- The complexity of its source.
- The speed of its spread, and
- The unpredictability of its scale and impact.

Faced with these acute challenges, health care organizations can find guidance in complexity science which is the multidisciplinary study of complex systems composed of interacting agents and units within a boundary. These systems are complex because the agents and teams within the system are highly interdependent, heterogeneous, and dynamic.

Complexity science studies how complex systems change over time or adapt to external environmental changes. From a complexity science perspective, the external environment is interrelated to and coevolves with the organization instead of being independent of it. The environment is highly unpredictable because of the complex and nonlinear relationships among many of the environmental elements. A complex system's adaptation to a sudden change in the environment is hastened when agents and units are qualified and empowered to react to external events and supply real-time feedback to decision-makers. Complex adaptive systems manifest feedback loops between agents and the environment through which information travels and leads to minor changes, nurturing learning capacity and continuous adaptation.

Overall, complex adaptive systems are similar to an organism, with self-awareness, the desire to survive, and the ability to adapt to environmental changes.

The prospect of organizations as complex adaptive systems is fundamentally different from the traditional view of organizational systems, as machines produce outputs through tightly controlled and standardized processes. Instead, complex adaptive systems are built for adaptation, flexibility, and learning (Begun & Jiang, 2020).

'Simple rules' such as underlying cultural norms and values help ensure that agents and units react to change in a timely and coordinated manner. Relatively broad guidelines or constraints are imposed on the system from the top-down management. As a result, agents and teams have substantial autonomy to respond to change. That means responses will vary from system to system, which is 'customized' to local needs.

Sensemaking, the process by which people understand their collective experience, is critical in complex adaptive systems. It is essential in times of distress and uncertainty. Guidelines such as 'use simple rules', 'set simple rules', and 'provide minimum specifications' demonstrate the futility of micromanaging unpredictable and emergent events.

The concept of simple rules was popularized in health care with the 'Ten Simple Rules for the 21st Century Health Care System' promulgated by the Institute of Medicine's 'Crossing the Quality Chasm' report in 2001. Rephrased examples of the IoM's ten simple rules include 'establish the patient is the source of control', 'use evidence-based decision making', and 'consider safety as a system property'.

Organizations that are internally highly connected encompassing elements of their environment are the most adaptable to 'connect' and 'build connections', which accelerate the flow of information and share resources in times of surprise.

As a result, complexity science emphasizes communication, collaboration, and innovation, carried out expeditiously by frontline information and evidence (Begun & Jiang, 2020). Extensive communication, collaboration, and innovation need to happen quickly in response to significant surprises. Underlying conditions necessary for a quick response include pre-existing structures and cultures that encourage widespread and diverse participation on the frontlines of care.

Moreover, reports of effective responses to the Covid-19 pandemic often include formal leadership's general attitude of 'humility'. Humble leadership requires complex adaptive systems because the future is unknown, and sensemaking is a communal activity.

Overall, COVID-19 introduced an exponential threat to the theory and practice of quality.

Applying linear models to human systems, healthcare management, and quality has improved our understanding of their system structure and function. However, such models often fall short of explaining experimental results or predicting future abnormalities in complex nonlinear systems, which help dissect and analyze individual system components.

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Nonlinear models may better explain how the individual components collectively act and interact to produce a dynamic system in constant flux (Moumtzoglou, 2020). They also assist in filling in some of the results which linear models do not adequately explain. Chaos theory also provides new insights into standard as well as abnormal behavior within systems. Applications of chaos, especially fractals, may detect disease in its early stages and proves valuable in managing illness. At the same time, the pursue of complexity theory provides new insights regarding the genetic encryption of the environment in the context of biological evolution, cellular automata, and modulation of protein production using biological pulse signals (Lewin, 1999).

However, as not all medicine is nonlinear, linear modeling should not be abandoned, as the use of both models is complementary and leads to a complete understanding of system behavior. We could easily consider the integration of linear and nonlinear theories in healthcare quality and management in this context. We can draw the initial conditions of chaotic behavior from the standardization of the linear theory. Moreover, we can distinguish between desirable and undesirable variation relegating statistical process control only to issues of high certainty regarding the outcome.

Finally, given the critical role complex systems play in daily life, their understanding, mathematical description, prediction, and eventually, control is one of the significant intellectual and scientific challenges of the 21st century. The advent of Network Science is a clear demonstration that science can live up to this challenge (Barabási, 2016).

Network Science is rooted in the discovery that despite the apparent diversity of complex systems, the networks' structure and evolution is driven by a standard set of fundamental laws and principles. Therefore, notwithstanding the striking differences in form, size, nature, age, and scope of real networks, most networks are driven by common organizing principles.

Management also tends to rely on the informal network, capturing who communicates with whom. Furthermore, accurate mapping of organizational networks can help identify individuals who play an essential role in bringing different departments and products together and exposing the lack of interactions between critical units. There is also increasing evidence that employee's productivity is determined by their position in the informal organizational network (Wu et al., 2008). Therefore, numerous companies offer tools and methodologies to map out the actual structure of an organization. These companies provide a host of services, from identifying opinion leaders to reducing employee churn, optimizing knowledge and product diffusion and designing teams with the diversity, size and expertise to be the most effective for specific tasks.

In the same direction, modern healthcare has explicitly accepted and internalized the idea of a network by adopting:

- The transparency of quality.
- The infrastructure of cross-continuum connectedness.
- The renaissance of accessibility.
- The integration of ecosystem partners.

The book provides a compendium of terms, definitions and explanations of concepts, processes and acronyms. Additionally, it presents chapters authored by leading experts offering an in-depth description of key terms and concepts.

ORGANIZATION OF THE BOOK

In Chapter 1, Vahe Kazandjian addresses the epidemiological and social imperatives associated with controlling a public health emergency and preventing outbreaks. Using population behaviors as a determinant of the extent to which events progress to alter populations, geographic regions, or the globe, this chapter borrows from epidemiology and social behavior. The author builds on his worldwide experience to propose the crucial need for having a shared global responsibility. While the impetus of this chapter is the COVID-19 pandemic, the generic predisposing factors and past public health outbreaks are used to place the ravages of the present pandemic into a framework of interpretation as well as for prediction of future events and associated social and public health preparedness. Without analytic methods of inquiry, this chapter addresses the core aspects of fear and hope all populations and societies have to balance to understand, accept, and co-exist with events that occur upon them and infringe on their current lifestyle and quality of life expectations.

In Chapter 2, Anastasios Moutzoglou and Abraham Pouliakis argue that population health management (PHM) is a discipline that studies and facilitates care delivery across the general population. On the other hand, currently, there is a significant outgrowth of precision medicine within the science of individuality that recognizes the uniqueness and digitization of the individual. The chapter focuses on five technologies that significantly impact precision medicine, arguing that Cloud computing, Big Data, and M-Health technologies offer the resources to succeed in dealing with the shortcomings of population health management. Finally, it contends that Quantum Computing and Artificial Intelligence are the necessary keystones, as they provide the required enormous processing power and algorithmic tools.

In Chapter 3, Hossein Adibi contends that we have learned from COVID-19 to humanize our society and challenge the rising inequalities, racism, and discrimination in our contemporary world. One of the apparent discriminations in our society is based on the governments' approach and treatments towards people with disabilities. This chapter is about the Australian people with disabilities from culturally and linguistically diverse backgrounds and how the Australian National Disability Insurance Scheme has responded to the needs of these people within the Australian society during COVID-19.

In Chapter 4, Stelios Zimeras asserts that stochastic models have become a powerful statistical tool to estimate parameters, where regions of interest represent data under uncertain areas. Due to the high dimensionality of the spatial patterns, investigation of the stochastic modeling simulations must be applied based on spatial variability. Models for spreading diseases are given based on whether or not the disease succeeds or fails to appear in the region. Based on this assumption, an Ising/Potts random fields model is introduced to analyze the spatial pattern of spreading. The spatial pattern models for spreading diseases have been analyzed considering Markov random fields auto-models in this work. The Gibbs sampler is used to simulate example images for various parameter combinations. This work introduces a spatial analysis methodology based on Bayesian analysis, and procedures to solve spatial variability are described based on spatial model estimation techniques.

In Chapter 5, Shampa Sarkar Biswas and Piyali Mazumdar claim that the novel coronavirus SARS-CoV-2 is being speculated to affect children's neurological health profoundly. This chapter addresses the risk of neurological symptoms in children susceptible to COVID-19, which might help pediatric neurologists. As existing research has been mainly focused on adults, this chapter is a compilation of past and present data to understand better the diseases associated with pediatric neurology and COVID-19 and its repercussions. Consequently, this chapter aims to enlighten the level of alertness in pediatric specialists.

to assess potential neurological involvement of this virus and its probable long-term neuropsychiatric and medical consequences.

In Chapter 6, Yiannis Koumpouros maintains that the Internet and the latest technological developments promise new and innovative work and learning environments and capabilities. The COVID-19 pandemic has radically changed the way people work, communicate and learn. Many traditional infrastructures, such as the Internet, have been tested to the fullest extent. Education has faced the most significant challenge as it has to serve people with different needs and backgrounds. Cheap technology solutions combined with increased computing and storage capabilities enable the education system to cope on time. Nevertheless, the need to adequately serve special population groups remains a challenge. The chapter presents an example of a methodological approach to designing an effective solution employing game-based learning techniques for children with autism or other learning difficulties. The latest pedagogical approaches are combined with appropriate gamification techniques to produce the desired outcome. It concludes by presenting critical issues in designing game-based learning applications for children with special educational needs.

In Chapter 7, Dimitrios Katehakis and Angelina Kouroubali present, analyze and discuss the digital transformation challenges that need to be addressed to develop quality electronic medical record (EMR) systems in Greece in the aftermath of the pandemic. The authors highlight quality EMR characteristics and provide an overview of factors affecting their adoption into the broader context of the European digital single market towards supporting continuity of care. Critical challenges addressed include linking EMRs with the medical practice workflow in a standardized manner, building trust and acceptance by making the best use of champions to build capacity, and financing the digital transformation transition and sustainability in a coordinated way. Foreseen benefits include better support of medical decisions across all stages of the patient journey, patient empowerment through virtual dossiers with clinically important information, enhancement of vendor potential to implement innovative tools to support continuity of care, and acceleration of evidence-based research.

In Chapter 8, Ranjit Barua, Pallab Datta, and Amit Chowdhury assert that 3D printing technology has influenced the healthcare and medical sector during the COVID-19 pandemic. 3D printer machines fabricated numerous medical kits and accessories. These include face shields, specimen collectors, personalized face masks, ventilators, protective eyewear, personal protection equipment (PPE), and isolation wards/ chambers. All these were fabricated in a short period as requirements were increasing expressively. The chapter describes several of these applications of 3D printing, which assisted in looking after numerous lives throughout the COVID-19 pandemic. The cooperation of the 3D-printing knowledge with the worldwide healthcare community will develop innovative and essential prospects in the upcoming days. Also, numerous important proposals are described that were applied to fight against the COVID-19 outbreak, monitored by a discussion about the upcoming trend of how additive manufacturing can help people worldwide to control any upcoming pandemic situation.

In Chapter 9, Moutaz Haddara and Anne Staaby argue that the Internet of things (IoT) is revolutionizing industries through enabling object identification, traceability, real-time communication and monitoring. IoT can reduce the unneeded physical contact through the possibilities of remote monitoring & tracking of patients, which can be used in pandemic control scenarios. One area of paramount importance in healthcare is patient safety. Published statistics suggest a mounting number of patient mistreatments due to the erroneous identification of the patient or the drug administered. Radio Frequency Identification (RFID) is envisioned as a disruptive innovation in healthcare & represents several opportunities for increased safety. The authors explore the potential & challenges of RFID adoption in healthcare

with a focus on patient safety. Their findings suggest that there has been a surge in IoT applications in healthcare research in the last two years concerning pandemic control. However, the high costs of adoption and implementation, security & privacy concerns, and human safety risks are the main barriers to adopting IoT in healthcare.

In Chapter 10, Anita Venaik, Sanjeev Bansal, and Rinki Kumari contend that Blockchain Technology (BCT) is an evolving digital technology that changes digital operations' dimensions by conducting distributed ledger transactions without the involvement of third parties. The chapter aims to examine the use of BCT in healthcare and develop a hierarchical theoretical framework. The framework is based on the stakeholder principle and exposes BC's effect on smart healthcare. Its decentralized existence is an ideal catalyst for the much-needed transition toward well-organized healthcare as it solves the most pressing issues.

In Chapter 11, Dr. Abraham Pouliakis, Dr. George Valasoulis, Mr. Georgios Michail, Dr. Evangelos Salamalekis, Dr. Niki Margari, Prof. Christine Kottaridi, Dr. Aris Spathis, Dr. Effrosyni Karakitsou, Mrs. Alina-Roxani Gouloumi, Mrs. Danai Leventakou, Dr. George Chrelias, Dr. Maria Nasioutziki, Prof. Maria Kyrgiou, Prof. Alexandros Daponte, and Prof. Ioannis G Panayiotides argue that the Covid-19 pandemic has challenged health systems worldwide by decreasing their reserves and effectiveness. In this changing landscape, the urge for reallocation of financial and human resources represents a top priority. In screening, effectiveness and efficiency are most relevant. In the quest against cervical cancer, numerous molecular ancillary techniques detecting HPV DNA or mRNA or other related biomarkers complement morphological assessment by the Papanicolaou test. However, no technique is perfect as sensitivity increases at the cost of specificity. Various approaches try to resolve this issue by incorporating several examination results, such as artificial intelligence. In this chapter, 1258 cases with a complete result dataset for cytology, HPV DNA, HPV mRNA and p16 were used to evaluate the performance of a Self Organizing Map (SOM), an unsupervised artificial neural network. The results of the SOM application were encouraging since it was capable of producing maps discriminating the necessary tests.

In Chapter 12, Antonia Mourtzikou, Marilena Stamouli, Georgia Kalliora, Ioanna Petraki, Christina Seitopoulou, and Panagiotis Koumpouros examine the use of quality indicators (QIs) and risk assessment as tools for maintaining the quality of laboratory tests. Both are requirements of ISO 15189: 2012 and are usually based on standard statistical and empirical data. This chapter focuses on evaluating clinical laboratory quality indicators in the era of the COVID-19 pandemic. Their goal is to discuss, based on their experience, the quality evaluation and risk assessment through the collection, study, and analysis of quality indicators covering the pre-analytical, analytical, and post-analytical phases of the laboratory testing process. QIs were evaluated using the Six Sigma method. Moreover, FMEA risk analysis was performed, and the degree of risk priority was assessed using the Pareto method. The results show that the laboratory's performance is satisfactory in the analytical phase, while the pre-and post-analytical phases need further preventive/corrective actions.

In Chapter 13, Antonia Mourtzikou, Marilena Stamouli, Georgia Kalliora, Panagiotis Koumpouros, Ioanna Petraki, and Christina Seitopoulou state that clinical laboratories produce test results that support the diagnosis, prognosis and patient treatment. Test results must be relevant, accurate and reliable for patient care. International bibliographic data estimate that approximately 62.0% of the errors made in clinical laboratories are due to errors during the pre-analytical stage. This chapter presents a failure modes and effects analysis (FMEA) to analyze potential failure risks within the pre-analytical phase and classify them according to severity and likelihood, based on our experience. FMEA allows molecular laboratories to lower costs and drive better outcomes through high-quality nucleic acid extraction,

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sensitive detection, and accurate quantification. RT-PCR technology continues to be the gold standard for the clinical detection of SARS-CoV-2 RNA in individuals suspected of COVID-19. They conclude that it is essential to use highly sensitive assays to detect active infections and reduce the likelihood of false-negative results.

In Chapter 14, Stavros Archondakis and Ourania Oustampasidou claim that telecytology can be defined as the process of diagnostic cytology performed on digital images. The process of diagnostic cytology performed on digital images can be used for teaching, professional examinations, obtaining expert opinions on severe cases, and routine diagnosis of the entire laboratory workload. However, little information exists about its possible use for proficiency testing purposes. The existing studies have found a high (90%–95%) concordance between telecytological and glass slide diagnoses, but they refer to a small number of cases. Thus, the purpose of the chapter is to examine the feasibility of developing a proficiency testing scheme for cytology labs wishing to be accredited according to ISO 15189:2012 by using low-cost telemedical applications.

In Chapter 15, Stavros Archondakis and Ourania Oustampasidou claim that published studies compare static and dynamic telecytology systems. Still, no study has focused on implementing short videos captured by static telecytology stations for telemedical applications. The chapter aims to evaluate the diagnostic reproducibility of telecytology in thyroid fine-needle aspiration specimens prepared using liquid-based cytology among four cytopathologists using representative short duration videos captured by a static telecytology station. It also examines the agreement between the contributor's and the reviewer's diagnoses.

In Chapter 16, Fatima Siddiqua and Rashmi Rahman declare that ancient science relating to plants has always been a source of drug discovery. In ancient times, people had used medicinal plants to fight against pandemics. Researchers suggest ancient medical practices like Ayurveda, Unani, and traditional herbal medicine as a potential source to cure or prevent diseases like COVID-19. The Internet of Things (IoT) aims to help solve real-world problems by connecting all modern-day devices. An Internet of Healthcare Things (IoHT), a branch of IoT, is creating a revolution in medicine. As a result, the authors argue that we can incorporate ancient knowledge into the IoT system and help people worldwide fight this pandemic by spreading the knowledge of Ancient Indian medicinal practice.

In Chapter 17, Rohit Rastogi, Mamta Saxena, T. Rajeshwari, Neeti Tandon, Sheelu Sagar, Mukund Rastogi, and Mayank Sharma proclaim that all of us are aware that the modern mechanical and electrical systems in collaboration with AI, CPS, and IoT have affected our lives drastically. At one end, they have provided ease and comfort. On the other end, the electrical and magnetic radiations have threatened mental and physical fitness. Surprisingly, the Asian Agnihotra process effectively reduces the electrical, magnetic radiations emitting from electronic devices. The chapter deals with the computational analysis of electrical, magnetic radiation and power density measurement of environmental effects and gadgets after the Homa therapy. In the gap of a specific time, readings were recorded, and it was observed that drastic reduction occurred at the place where Yajna was performed. This gap was curtailed gradually as time increased. The authors suggest that this phenomenon can undoubtedly address human health threats due to electronic gadgets in the 21st century. They also support the concepts of smart cities, where one can quickly identify the numerous effects of the Yajna process.

In Chapter 18, Anastasios Mourtoglou envisages the pandemic as an opportunity to reimagine future healthcare and rethink healthcare management unbound by preconceived notions based on the following three main drivers that emerged during the pandemic. These include transformed business models, new care delivery models disrupted by ubiquitous data and technology, intelligent spaces and digitally-

enabled hospitality. In this context, it is imperative to reexamine all facets of healthcare management, considering that applying linear models to healthcare management has improved our understanding of their system structure and function. However, such models often fall short of explaining experimental results or predicting future abnormalities in complex nonlinear systems. Nonlinear models may better explain how the individual components collectively act and interact to produce a dynamic system in constant flux. They also assist in filling in some of the results which linear models do not adequately explain. Finally, chaos theory might provide new insights into standard as well as abnormal behavior within systems. Consequently, the book supports students to understand the effect of various domains of knowledge relating to healthcare; helps healthcare professionals better understand the needs of their patients; acts as an assistant for patients to derive more benefits from their healthcare; encourages e-health systems' designers and managers to ground everyday practice on the science of individuality. The prospective audience includes undergraduate and extended degree programs students, graduate students of health care quality and health services management, executive education and continuing education, health care managers and professionals.

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Acknowledgment

I want to thank the reviewers for the care with which they reviewed the manuscripts and all the authors for their diverse and outstanding contributions to this book.

Chapter 1

Pandemic, Panresponsibility, and Pandemonium

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ABSTRACT

This chapter addresses the epidemiological and social imperatives associated with controlling a public health emergency and preventing outbreaks. Using population behaviors as a determinant of the extent to which events progress to alter populations, geographic regions, or the globe, this chapter borrows from epidemiology and social behavior the author builds on his worldwide to propose the crucial need of having a shared global responsibility. While the impetus of this chapter is the COVID-19 pandemic, the generic predisposing factors and past public health outbreaks are used to place the ravages of the present pandemic into a framework of interpretation as well as for prediction of future events and associated social and public health preparedness. Without the use of analytic methods of inquiry, this chapter addresses the core aspects of fear and hope all populations and societies have to balance to understand, accept, and co-exist with events that befall upon them and encroach on their existing lifestyle and quality of life expectations.

INTRODUCTION

I remember when I first discovered the microcosm of social structure and behaviors. It was during a camping trip when I was twelve years old. I came across a colony of ants, a very large colony. These were thousands of ants, all looking alike. I sat down, and despite my teenage impulse to move around, I observed the ants.

They looked alike, although I knew they were different. I did not know how to distinguish; perhaps that was because I was looking from a distance, looking at the larger picture, where the individual was not important for the character of the panorama. I looked at their work, carry grains, carry droppings, carry twigs. I was very young and then unaware of the stories millions before me had recanted about their observations of and inspirations from ants at work.

DOI: 10.4018/978-1-7998-9198-7.ch001

Looking back, I think it was my first subconscious encounter with the concept; later, I will accept it as a predisposition. And it was almost in a scientific way that I observed, did not interfere and tried to find a pattern in movement and behavior. Almost factually. Evidence-based. My first realization was that it was the group that counts. In the larger picture, what happens to the individual over time has no intrinsic value in describing what befalls upon the group, unless a critical mass of events happens to individuals to constitute a group or population event.

I did not know then that epidemiology was the westernized definition of Epi-Demos-Logos or the science of what befalls upon populations.

So, individuals did not matter until their experience builds a critical mass, a threshold. Either of joy or misery. Of health or disease. But a threshold. And that is when the group, the colony, the population, perhaps the world notices the unexpected critical mass and develops a reaction to it.

That is how epidemics and pandemics affect the world and history.

And I recall seeing a dead ant on the side of the file and rank that moved incessantly carrying grain, droppings, and twigs. I could not see a difference in the behaviour of the thousands of ants that passed next to the dead ant. There were those going into the holes that would surely lead to the underground labyrinth of the ant hill's colony. Others were coming out of another hole, visually creating a bicycle chain in movement. Every ant knew the traffic flow and respected it. Of course, I could not tell if some ants from one line would verbally abuse other ants, call them "roach!" There was no traffic rage, physical assaults that I could see.

Everyone kept their prescribed social distance.

So, why did the one ant die? For no real reason, other than all of them will die at some time. That one's timing was unique. Perhaps every ant's departure time is unique. Perhaps, time does not matter. What did that one ant do to the colony, the larger population of time-bound ants? Seemingly nothing. Maybe it was a lonely ant. Perhaps it was the unfriendly type. Or perhaps, friends and family did not hear the news to run and see him. Possibly ants do not have friends. I did not know. The important thing was that a twelve-year-old boy, in the mystical mountains of Lebanon, in a village called Beit-Mery, on that day reached the understanding that populations change predisposition. Perhaps destiny. He also believed that the destiny of individuals could not be changed – just that of groups, by having the people with similar destiny come together at the appropriate time. Perhaps by sheer chance.

... Since that day, five decades have passed. I experienced a civil war. Came out of it with an understanding of ant nests, colonies and collective goals that a young man cannot learn from books. I have since changed countries and continents. I waited in line for filling out forms, for interviews, for acceptance, and rejections. In each waiting time and space, I looked at the people around me and thought of the ants. What I came to understand is that people, then groups have a *threshold for dissociation*.

That threshold for dissociation varies across people. I also think it changes in amplitude with time. In a way, it is the reverse of habitual dependencies, such as on stimulants, self-administered or external. I also think the threshold for dissociation increases in amplitude with its usage. In a counter-intuitive way, we need it less frequently. We learn to live with reality. With people. With ourselves. We do so because we increasingly become comfortable with the group's predisposition to go where it is supposed to go. Eventually. Perhaps, it will take a few detours. Will be delayed. But it will get there.

Destiny and predisposition have different social manifestations and determinant. Sometimes it is a rain-dance, other time a nuptial embrace. Destiny is often rejected, only to be discovered later – when the joints ache at sunrise. When the joints ache in the prediction of the coming rain. Destiny is for the lived, for the living. It is to age what age is to time. It is to the nest what the nest is to the tree—a harbour

from the elements around. Destiny and predisposition, as its more quantifiable, alter ego, lead to a time for reflection. Ultimately, for the wise and the wisening, predisposition becomes truth in its capricious splendour. In its timing.

And I became an epidemiologist. I understood what befalls upon people but mostly understood how people act upon the new event and rediscover their reality. Infectious agents decimated populations like spring rain would flood ant nests. People wore garlic necklaces to combat the Black Plague. They wore masks to resist influenza. Drank milk and got closer to seas and oceans to treat tuberculosis. And they danced and prayed for those who could change destiny.

Epidemics re-emphasize the desire for immortality. Not representing the absence of death, but the presence of death among the living. In a vivid way, or ways subtle and unmarked. Through sex. Sexuality is the transformer of destiny and the assurer of immortality. Did that ant have sex? Did it share its genetics with another ant? Other ants? Or did he keep his social distance, not knowing what the other ants may be carrying? Did it live in shape, mind and perhaps soul in another ant or an interminable number of ants? Forever?

Eventually, the sequelae of widespread threats to well-being become the identity of a colony. Domestic violence, substance abuse, child abuse, obesity, depression, compulsive work habits are all among the plethora of what befalls upon people. Immunity requires exposure, not only to a virus but to philosophy, attitude or expectation. So, we become more resistant, more accepting. But when these threats befall more than expected, we define the situation as an epidemic. Healthwise or as social challenges.

But when the epidemic is due to infectious agents, it brings back the historical fear of the unknown that affects our destiny. It comes out of nowhere, steals lives upon its passage, and leaves us to wonder if garlic necklaces can work against it when science seems taken by surprise.

In short, our threshold for dissociation gets challenged. It is not the news about deaths on the highways because of substance abuse by the drivers; it is not the number of women coming to the Emergency Room with broken clavicles and who had swallowed their teeth. No, it is a virus that left the small hairy body of a rodent or a flying mammal and befell upon humans. It is indiscriminate; it robs youth and old age alike.

The COVID-19 pandemic is my third “rodeo”, as they say in the American Southwest. I was in Asia during the SARS epidemic. And in Saudi Arabia during MERS. I have seen the fear of governments about complete and timely data and the fear of populations from incomplete accountability. I worked for ages to prevent domestic violence against women. And I applied epidemiologic methods to quantify poor quality and medical errors in hospitals.

As an epidemiologist, I learned that in today’s cultures, what befalls upon ant colonies, human societies, and biological existence may still be interpreted as Greek philosophers proposed during the Hellenistic period. Namely, we can face our existence, including epidemics and pandemics, as either Stoics or Epicureans. Human decisions follow a preset or predetermined path for the former, and the consequences of these decisions happen accordingly. Epicureans, however, proposed that if we “train our desires”, we can prevent inevitable consequences from befalling upon us.

Stoics or Epicureans, when we develop global herd immunity mainly through vaccination, the Coronavirus pandemic will metamorphose into a flat and predictable curve or line. And for years to come, we, the herd, will behave like a colony of ants, celebrating the comfort of appropriate social distancing in a new and perhaps asocial way.

And in that distance, we may find our *panresponsibility*.

However, the concept of panresponsibility is not absolute – there will always be pockets of resistance to vaccination or other preventive measures keeping the door open for the opportunistic virus to remain

dormant but endemic, mutate and then manifest its threat through localized outbreaks and perhaps epidemics.

Let us explore the continuum of epidemics and pandemics, the realization of their control via pan-responsibility, and the pandemonium that plagues the process along the way.

EPIDEMICS AND PANDEMICS

By now, most of the world realizes that an epidemic is localized in a population or region, while a pandemic is global. Consequently, no one is safe during a pandemic, especially when due to a virus in a world where all humans (and some animals that can carry the virus) are in constant move and travel.

While epidemics have been part of human and animal groups for millennia, pandemics are not rare or new, and the Covid-19 pandemic will not be the last one.

For example, the Greek historian Thucydides wrote about the 430 BC epidemic that took around 100,000 Athenian lives during the war between Athens and Sparta. The overcrowding during the five-year war may have facilitated possibly a typhoid fever based on the description of Thucydides *“in good health were all of a sudden attacked by violent heats in the head, and redness and inflammation in the eyes, the inward parts, such as the throat or tongue, becoming bloody and emitting an unnatural and fetid breath”* (Burke A. Cunha, 2004).

Epidemics not only lead to death and social destabilization but can lead to the decline of empires. Indeed, the bubonic plague is one of the events that precipitated the decline of the Byzantine Empire when the plague led to the loss of territory that Emperor Justinian had included in his empire from the Middle East to Western Europe from 527 to 565 A.D.

Perhaps the most documented extension from an epidemic to a pandemic is the bacterium *Yersinia pestis* which is the cause of the Black Death. Indeed, the bacterium found its way from Asia to Europe by fleas on rodents, probably via sea vessels. Then it spread like wildfire from Russia to Western Europe, and with more than a million deaths, the impact of the Black Death on Europe's economy changed the course of history.

We are most familiar with the polio epidemics in the US and Europe and the Zika virus epidemic in South and Central Americas in the modern era. But the past century has also seen four pandemics with sequelae still part of our lives – the infamous Spanish Flu of 1918, AIDS, the H1N1 Swine Flu of 2009, and Ebola in West Africa 2014-2016.

PANRESPONSIBILITY

I believe that this rarely used word most succinctly describes the response to a global health issue. Indeed, the response should be global, but it has to be anchored in the belief that it is a responsibility to assure the well-being of our planet and its inhabitants. For example, the Justinian bubonic plague epidemic accelerated the rate of the Byzantine Empire, and the AIDS epidemic challenged social norms around the globe. The bacteria and viruses responsible for epidemics and pandemics also cause a disturbance in the social, cultural and economic homeostasis necessary for the health of populations and their contribution to the planet-wide equilibrium and advances.

Past epidemics and pandemics have been controlled either by understanding the mode of causative agent transmission and taking precautions to minimize their rapid spread or outright eradicate their existence.

Long before my career in public health, a high school Middle Eastern literature teacher once said, “sometimes the cure for an illness is the cause of that very illness,” and he quoted a line from a controversial Arabic poet from the 750s, Abu Nawas, who proposed that wine could be the cure of his alcoholism! He wrote, “*Heal me with what was the cause of my illness*”. Years later, when I learned about variolation, the use of smallpox material for inoculation against smallpox by the Chinese centuries before the first true vaccine by Edward Jenner, I recalled that line from Abu Nawas. Smallpox is now eradicated, but social epidemics (perhaps pandemics) struggle with the poet’s suggestion.

So, a vaccine is an example of panresponsibility, and the worldwide race for a vaccine against the coronavirus responsible for the Covid-19 pandemic was a perfect example of that joint effort. A year after the onset of the pandemic, countries donating unused vaccines to countries unable to purchase the vaccine(s) is undoubtedly an act of global responsibility.

But not all causative agents of epidemics or pandemics have been controlled through vaccines alone.

In the 1990s and early 2020, I was involved in public health and hospital care projects in Europe and Asia, and I was a lecturer in a few universities. For example, my visits to the University of Ferrara helped me understand how a number of cities in Northern and Central Italy addressed the bubonic after the Great Plague of Milan (1629 to 1631) wiped out more than half the population in Parma and Verona and killed more than 45,000 people in Venice. The public measures were a mix of policy, public health prevention and personal hygiene. Specifically, Ferrara and a few Northern Italian cities imposed border control to restrict travel from regions affected by the plague and minimize the intrusion of *Yersinia pestis* via fleas on rodents; sanitary laws were applied to keep “local” rodents away from the population; quarantining suspected carriers was meticulously followed; isolation of the infected and sick was the norm, and campaigns were developed to teach populations about the importance of personal hygiene.

Panresponsibility at its best.

PANDEMONIUM

The origin of the word is, of course, Greek, where “παν”, means “all” and “δαίμόνιον” refers to “little angel”. But, interestingly, the word became best known from John Milton’s poem “*Paradise Lost*”, where he named the capital of hell Pandæmonium. Hence, the original meaning of “little angels” became the “place of all demons”.

And that meaning changed further over time. Today the Cambridge English Dictionary defines pandemonium as “*a situation in which there is a lot of noise and confusion because people are excited, angry, or frightened.*”

That is the meaning I am using in this section – noise and confusion because people are excited, angry, or frightened. So, let’s take each of these descriptors in turn.

When the aetiology of an epidemic or a pandemic is unclear, there is much noise and speculation. And this is not new – the Black Death was believed to be a punishment from God for mortal sins. In recent memory, AIDS followed the same speculation.

Noise and confusion lead to anger. Often anger against fellow humans based on historic social beliefs that some groups or cultures cause a disruption in the equilibrium of a region or perhaps the world. None

of these accusations is based on science or rational understanding, but this has been a pattern throughout human history.

Finally, when the “curse” continues to befall upon population and region, fear takes over. Frightened people get distanced from science, opt for alchemy and mysticism.

But then, a breakthrough happens. The causative agents of infections are identified, and inoculations, quarantine, self-hygiene and protection demonstrate the path to controlling an epidemic/pandemic, or in some cases such as smallpox and bubonic fever, to practically eradicating them.

Still, the distrust in science, medicine and public health remain in segments of populations who opt for explanations derived from alchemy and mysticism. Covid-19 abundantly demonstrated this – distrust and rejection of vaccines and vaccination, opposition to wearing masks, the belief that some people are immune to the virus remain challenges for policy and public health measures implementation around the world.

And these rejections are not because society is otherwise opposed to science or medicine. I have seen examples around the world as a public health professional. From rejecting clean water pumps in Egypt and Sudan to avoid Schistosomiasis, an endemic debilitating disease caused by waterborne flatworms, to communities in the Bible Belt of Netherlands refusing to take polio and measles vaccines (College of Physicians of Philadelphia, 2018). During a research project in the Netherlands, I met a few people in Zwolle who had survived the iron lungs but were debilitated by polio. Even today, about 80 miles north of Amsterdam, a village of 15,000 inhabitants, Staphorst, has a quarter of its population unvaccinated against polio. And, in 1971, there was an outbreak of polio, mostly in children, taking five lives. But the attitude towards vaccination has not changed – in September 1992; polio was back in the northern region with 67 cases.

WHAT HAVE WE LEARNED FROM THE COVID-19 PANDEMIC?

My mother used to teach me via metaphors and sayings, and that old-world approach has influenced my reaction to events perhaps more than all the books I have read. For example, she often assessed a new situation by saying, *“every time history repeats itself, the price goes up.”* Indeed, raven beak-shaped masks were used by doctors during the Black Death when they did not know about viruses and bacteria but assumed something was being transmitted through the air. They were wrong as it is fleas carried by rodents that transmitted *Yersinia pestis*. So, the masks were useless against the plague but still made a statement about personal protection. Centuries later, during the Great Manchurian plague of 1910-1911 when Dr Wu Lien-the, a young Chinese doctor, hypothesized that respiratory droplets spread the plague, not by fleas. And he wore a mask. His French colleague rejected the hypothesis, did not wear a mask, and he died (Crawley, 1914).

When history repeats itself, the price goes up, especially when we do not learn from history.

Another of my mother’s sayings goes like this: *“every time you point your finger at someone, remember that three other fingers are pointing back at you.”* I used to love demonstrating this to my students by choosing one of them at random and pointing my index finger at him or her. So, who have we accused as the “cause” for the Covid-19 pandemic – animals, labs, people, or destiny? And consequently, what have we done to prevent the outbreak and it’s becoming a pandemic? What is the role of leadership, policy, timely action taken to get the preventive message out and facilitate people’s adherence to a recommendation based on science-based new knowledge?

Pandemic, Panresponsibility, and Pandemonium

Like in many past epidemics and pandemics, we often just pointed the index finger and forgot about the other four.

Finally, in broken Italian, she said, “Le cinque dita sono tutte diverse ma lavorano insieme in armonia” (the five fingers are not the same but work together harmoniously).

Maybe that is what we learned from the Covid-19 pandemic – that working in harmony, no matter how diverse our interests are, is the best demonstration of panresponsibility. And the best recipe for returning a new equilibrium to our planet.

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Chapter 2

Population Health Management and the Science of Individuality in the Era of Quantum Computing

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ABSTRACT

Population health management (PHM) is a discipline that studies and facilitates care delivery across the general population. On the other hand, currently, there is a significant outgrowth of precision medicine within the science of individuality that recognizes the uniqueness and digitization of the individual. The chapter focuses on five technologies that significantly impact precision medicine, arguing that cloud computing, big data, and m-health technologies offer the resources to succeed in dealing with the shortcomings of population health management. Finally, it contends that quantum computing and artificial intelligence are the necessary keystones, as they provide the required enormous processing power and algorithmic tools.

INTRODUCTION

Public health connotes a relatively narrow field with activities carried out by agencies granted with official functions. 'Population health', a term with broader content, is related to a field relevant to studying several essential factors for health. As a result, it involves many terms, such as outcomes, disparities, determinants, and risk factors (Kindig, 2007).

DOI: 10.4018/978-1-7998-9198-7.ch002

Notwithstanding the term ‘population health’ combines both health and population concepts, every term has an essential meaning of its own. The population is related to a group of persons being organized into numerous different units of analysis. Similarly, the term health was defined negatively, i.e., the absence of disease. Nowadays, the modern understanding stresses the positive aspects as well, and health is considered to be related to all life issues. To summarize, today, it is debated whether population health and public health are different or identical. Nevertheless, population health is defined as health outcomes and their distribution in a population (Kindig, 2007).

Population health management (PHM) has been defined as ‘the technical field of endeavor which utilizes a variety of individual, organizational and cultural interventions to help improve the morbidity patterns (i.e., the illness and injury burden) and the health care use behavior of defined populations (Hillman, 2002). It is differentiated from disease management because it includes (Howe & Spence, 2004):

- More chronic conditions and diseases.
- Uses a single point of contact and coordination and predictive modeling across multiple clinical conditions.

Moreover, PHM is considered a broader term than disease management, as it includes (Coughlin, Pope, & Leedle(Jr), 2006):

- Intensive care management for individuals at the highest level of risk.
- Personal health management for those at lower levels of predicted health risk.

At the provider level, there are three highlighted components (Care Continuum Alliance, 2012):

- The leadership and the central care delivery role of the primary care physician.
- The critical importance of patient activation.
- The capacity expansion of care coordination.

In this context, to successfully achieve all of these requirements, an organization should provide proactive, preventive and chronic care services to all managed patients. Additionally, this should take place both during encounters of patients with the healthcare system and in between. Therefore, providers should maintain regular contact with their patients and support them in managing their health. Additionally, providers must manage patients at high risk to prevent the deterioration of their health and avoid complications. Finally, evidence-based protocols for diagnosing and treating patients consistently and cost-effectively are also required if a provider-based PHM approach is followed.

The Federal Agency for Healthcare Research and Quality (AHRQ) developed the concept of ‘practice-based population health’ (PBPH) and defined it as “an approach to care that uses information on a group of patients within a primary care practice or group of practices to improve the care and clinical outcomes of patients within that practice.’ (Cusack, Knudson, Kronstadt, Singer, & Brown, 2010).

The implementation of health IT is among the essential components and requirements for planning and implementing PHM. The adoption of Electronic Health Records is just the first step toward the creation of the requisite infrastructure. However, a wide range of other IT applications to automate PHM, track results and engage the patients in their health care is required. Additionally, IT systems should

repeatedly be evaluated because of rapid technological changes, new government regulations and new approaches to patient management (Moumtzoglou & Pouliakis, 2015).

AHRQ recommends health IT tools for the stratification and monitoring of populations, as follows:

- Target patients being in greatest need of health services by stratifying the patients and narrowing subpopulations.
- Make patient-related data actionable by generating alerts to the patients.
- Make data actionable by generating alerts for health providers about patient care needs.

Conclusively, population health management is designed around the collective. However, nowadays, to truly drive high-quality care at lower cost, these endeavors must work for the individual, align with their personal goals and intermix with their reality. In this context, the objective of the chapter is two-fold. First, it will deal with the greatest misconception about population health; population health is not about the population. Ultimately, it is about the individual. Secondly, it will show how to connect the dots from the science of individuality to improving health on a massive scale - a bottom-up approach that uses Cloud and Quantum Computing technologies, Big Data, M-Health.

AUTOMATION AND ARTIFICIAL INTELLIGENCE AS THE TERRAIN OF HEALTHCARE PROFESSIONALS

Although compassionate care, empathy, creativity, problem-solving and profound human connection will never cease to be the terrain of healthcare professionals, it will soon be enhanced by automation which is the use of technology to fulfill tasks with minimal human input. Automation incorporates (Hardie, Horton, Willis, & Warburton, 2021):

- The full and the partial automation of tasks.
- Technologies that operate autonomously or semi-autonomously.
- The use of technologies to support humans.
- Applications of technologies such as robotics and artificial intelligence.

(Brynjolfsson & McAfee, 2016) contend that automation can be divided into two periods:

- The first incorporates the period in which machines were introduced to conduct physical tasks.
- The development of computing enabled the second period.

Moreover, Autor (2003) categorized tasks based on two properties:

- Routine versus non-routine.
- Manual versus cognitive.

Routine manual tasks require a 'methodical repetition of an unwavering procedure' while non-routine manual tasks have a more limited scope for automation.

A second approach to considering tasks amenable to automation is to analyze the skills and knowledge they require. A third approach refers to look at different task ‘functions’ and think what level of automation might be appropriate.

Automation has a long-standing history in health care. Although we might not think of them as automation, many examples are well established. These include:

- The first electrocardiogram.
- The kidney dialysis machine.
- Computers integrated into clinical pathways.

Moreover, robots have been used in medicine and health and social care for over 30 years.

The different ways in which automation relates to human task performance in health care include:

- **Replacing**

That happens when an automated system performs tasks to a similar level to human workers. On other occasions, it might significantly exceed human capabilities. Thus, replacing human input provides an opportunity to improve task performance.

- **Assisting**

Healthcare automation can be used to support than replace healthcare professionals. That can happen by automating either one component of a task or by providing additional capacity or functionality. On other occasions, technologies may extend human capabilities, even though they are not intended to operate autonomously.

The definition of Artificial Intelligence (AI) presents many intricacies. However, the definition of AI focuses on technology as a sub-field of computer science, mathematics and physics and how machines might imitate human intelligence. As a result, it can be tentatively defined as a branch of computer science dealing with the simulation of intelligent behavior in computers. That feature of AI was demonstrated by a test developed by Alan Turing, a British mathematician who profoundly influenced the science of computing. The Turing Test is a method of testing a computer’s ability to exhibit intelligent behavior equivalent to or indistinguishable from a human. Moreover, Alan Turing is also considered a founding father of AI due to his theorizing that the human brain is a digital computing machine.

AI attempts to simulate the neurologic functions that are responsible for (Catania, 2020):

- Speech recognition and natural language processing.
- Visual perception and pattern recognition.
- Analysis and planning.
- Problem-solving and decision-making.
- Learning, reasoning, and remembering.

The introduction of AI into healthcare experienced resistance in the 1970s and 1980s due to practitioner conservatism and uncertainties of evolving technology. However, the possibilities for AI are endless. There are examples of automation and AI that have shown their potential along the patient pathway. For

instance, machine learning potentially enables a high degree of accuracy in pattern recognition and the classification of images. Significant progress has also been made in radiology, with AI being used to screen for breast cancer conditions.

AI can also assist clinical decisions by using data to assess risks and make predictions while increasing interest in its potential to help clinicians, and laboratory doctors make triage decisions (Karakitsos, Cochand-Priollet, Guillausseau, & Pouliakis, 1996; Karakitsos et al., 1997; Pantazopoulos et al., 1998; Perroti et al., 2018; Pouliakis et al., 2018; Pouliakis et al., 2019b; Salamalekis et al., 2019).

Furthermore, several companies have also developed patient-facing symptom checkers, that is, ‘chatbots’ that use AI to compare patient’s data. Data tools and AI can also be used to support better treatment decisions and planning. At the same time, AI can be coupled with genomics, research and best practice data and help tailor treatments to individual patients and support people to manage their health.

Moreover, to present a coherent portrait of population health, AI methods extract health and non-health data at different levels of degree, coordination, and integration about populations (Collins & Varmus, 2015). Health intelligence is the critical metric of initiatives such as precision medicine. AI is also used to process personalized data, elicit patient preferences, and help patients and their families participate in the care process. It is ideally suited to analyze that data to help providers identify patients’ needs. It can also power analytic health tools to help doctors make more informed treatment decisions.

Finally, AI applications allow health analytics to use data mining, text mining and big data analytics, assisting healthcare professionals in disease prediction, diagnosis, and treatment. The ‘Internet of Things (IoT)’ serves as a platform to obtain health-related data in numerous applications. It is a digital technology that connects physical objects that are accessible through the Internet. These physical objects are connected using RFID technologies. Combining health care analytics within IoT enables all the relevant data to be turned into actionable insight. The data mining techniques fall under the following four categories of analytics:

- Descriptive.
- Diagnostic.
- Predictive.
- Prescriptive.

However, fragmented silos of data and communication must be dismantled.

THE SCIENCE OF INDIVIDUALITY, PERSONALIZED AND PRECISION MEDICINE

The population health management concept requires extensive data, which currently flows from the beneficiaries towards data centers. Such data include a multitude of health and well-being information collected manually or automatically. Moreover, algorithms are required to process such information and alert when health-related actions should be taken. On the other hand, nowadays, some technologies provide both data storage and processing capacity. At the same time, the mobile device (especially the mobile phone) and inter-connectable devices (health gadgets) may serve as data acquisitions points on the individual level.

However, there is a significant deficiency of contemporary medicine reflected by experts’ use to make recommendations or guidelines for a large proportion of decisions for which no or minimal data

exists. These guidelines are published in major specialty journals, which have a pronounced impact, as they are believed to represent the standard of care. Overall, there is too much literature evidenced by the statistic that only 0.5 percent of the 38 million published papers are cited more than two hundred times, and half were never cited. Moreover, when pooled analyses of prior studies are published, many relevant papers are excluded (Topol, 2012).

That should be considered ‘eminence-based medicine.’ (Topol, 2012).

Better studies might be part of the solution. However, as we can accrue more meaningful data and information for individuals, the hope is that we can override our dependence on such recommendations. We need evidence that is built not on populations but individuals.

Fortunately, our capacity to get just that information is rapidly arising. An era characterized by the right drug and dose at the correct cost and timing has begun (Topol, 2012). Medicine for the common good is not sufficient. A rebooted life science, instead of a mass-population-directed strategy, would leverage the science of individuality, getting the relevant digital readout from an individual to shape a therapy. For the first time, we now have the devices to promote a level of prescription precision we have never seen before (Topol, 2012).

The era of individualized medicine ultimately promises to do away with terms like ‘cryptogenic’ and ‘essential,’ fully recognizing the uniqueness of the individual who needs to be seen and treated with utter respect for his individuality. It will not be long until digitizing a person unlocks the cause for what is wrong, creating valuable knowledge that can save a life or markedly improve the quality of life. That is a significant outgrowth of the science of individuality.

In this context, as medicine is getting to grips with individuality and treatments are increasingly tailored to the patient’s environment, genes, and activities, the entire classification system of medical conditions and diagnoses is about to be rewritten. Instead of our current reductionist model for which individuals are unwisely assigned to such patient categories of a particular organ, the science of individuality will promote a new molecular taxonomy that invokes the primary biologic basis regarding genes or pathways.

That is easily understood if we delve into the terms of personalized and precision medicine. Personalized medicine refers to an approach that considers the patients’ genetic makeup and attention to his preferences, beliefs, attitudes, knowledge and social context. On the other hand, precision medicine describes a healthcare delivery model that relies heavily on data, analytics, and information. It goes beyond genomics and has vast implications in health care. However, it must embrace patient-centeredness and engagement, digital health, genomics and other molecular technologies, data sharing and data science.

Precision Medicine (PM) was just a promise a few years ago. However, it is now a reality for some diseases like cancer. PM is defined as “the tailoring of medical treatment to the individual characteristics of each patient to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side-effects for those who will not” (“President’s Council of Advisors on Science and Technology (PCAST),” 2008).

As a result, the individual characteristics for patient classification will include (Bilkey et al., 2019):

- Traditional clinical phenotypes.
- Family history.
- Lifestyle and environmental data.
- Invariable patient-specific characteristics.
- Variable’ omics’ characteristics.

The first two types of information are routinely recorded for each patient in a clinical setting, while lifestyle and environmental data are collected by wearable devices (Jeong et al., 2019). Finally, the invariable patient-specific characteristics and variable ‘omics’ characteristics can be detected by high-throughput methods, such as next-generation sequencing (NGS) techniques (Goodwin, McPherson, & McCombie, 2016).

THE TECHNOLOGIES OF INDIVIDUALITY

The data for how many patients search health websites is staggering (Topol, 2012). Although this trend represents an outlier in many respects and an extreme of patient activism, these cases also demonstrate that the current level of being informed is not adequate. Furthermore, they capture a sense of inspiration and independence, the hunt for innovation, and the primacy of the individual. In essence, they are the precursors for the next phase of medicine, in which powerful digital tools will provide data that was previously unavailable.

Whether it is sequencing the genome of cancer tissue to determine a specific mutation or anticipating the likelihood of a fatal disease before it has ever manifested, our capabilities greatly expand based on the following technologies.

I. Cloud Technologies

Cloud computing has emerged rapidly as an exciting new paradigm that offers a challenging model of computing and services. Leveraging cloud computing technology, bioinformatics tools can be made available as services to anyone, anywhere, and through any device. The use of large bio-datasets, the highly demanding algorithms, and the hardware for sudden computational resources make large-scale bio-data analysis an attractive test case for cloud computing” (Hsu, Lin, Ouyang, & Guo, 2013). Cloud computing is a concept related to numerous computers that use Internet infrastructure to communicate, producing shared resources such as software, hardware, and storage. Nowadays, cloud computing is not widely used for the various tasks related to medicine; however, there are numerous fields that it could be employed; thus, cloud computing is an emerging field having the potential to change the everyday practice of medicine.

Cloud systems are categorized into three different groups according to the offered service type:

- Infrastructure as a Service (**IaaS**) means offering hardware, storage, and physical devices over the Internet.
- Software as a Service (**SaaS**), which means offering software and hosted applications over the Internet.
- Platform as a Service (**PaaS**) means offering the capability to deploy applications created using programming languages, libraries, services, and tools owned and supported by the provider.

The user/consumer does not manage or control the underlying cloud infrastructure for cloud computing but has control over the deployed applications and the offered services (i.e. storage, networking and processing power). Clouds, according to their hosting, may be public, private, hybrid, and community, especially adapted to the medical field:

- **Public Clouds** are for general use. The cloud owners are responsible for information hosting; public clouds are rarely utilized in medicine, and data is encrypted.
- **Private Clouds** are only for in-hospital use and are dealing with confidential patient data. The owners or the hospital premises are responsible for information hosting.
- **Hybrid Clouds** are hosting non-confidential information on public Clouds and confidential information in a private domain.
- **Community Clouds** are hosting information among members of the same community. Laboratories and hospitals can create a community Cloud while sharing the same infrastructure and software.

There are three fundamental aspects of Cloud-based services (Soman, 2011):

1) Browser-Based Applications

Browser-based applications are different from native applications, which run on personal computers. Native Applications are those that run entirely on the computer on which they are invoked. A native application uses only the computing resources and storage of the computer used to launch the application. Conversely, browser-based applications run from within Internet Browsers; however, the consumed resources are located on one or more servers. They are conceptually similar to Client-Server applications, which require a powerful central computer, but there are two distinct characteristics:

- Browser-based applications can only be invoked from inside a standard browser.
- The Client and the Server are not (necessarily) a part of a Local Area Network or a remote (however accessible) network.

2) Optimal Utilization of Server Resources

Cloud Service Providers see variable levels of utilization of their services. This variability has two components. Firstly, the number of concurrent users accessing the service is different at different times. Secondly, the processing and storage of resources required by any particular user are never constant.

Technologies for scaling and resource partitioning are at the heart of Cloud Services because without these technologies, the Cloud business model would not be feasible. Load Balancing denotes a mechanism for balanced or even distribution of load across multiple physical resources, such as servers, storage devices or communication links.

A server load balancer is responsible for balancing incoming requests among an array of physical servers. Virtualization allows a single physical resource to be used like many resources or multiple physical resources to be used as a single resource. There are several types of virtualization, depending on the nature of the physical resource that is 'virtualized.' In this context, server virtualization implies that a single physical server is converted into several logical servers, storage virtualization a single storage device that is converted into multiple logical storage devices, or vice-versa. Network virtualization allows the user to split a single communication link into separate channels assigned to different processes.

Finally, multi-tenancy is the principal of architecting applications. A single instance of the application running on the server is visible as separate cases of the same application for each client connected to it.

3) Data Centers

The data center is where the user's data is processed and stored. Some of the design considerations for data centers are as below (Moumtzoglou, 2014; Soman, 2011):

- Data centers are typically located in places where the risk of natural disasters and human-made disasters.
- Buildings used to house data centers typically do not accommodate other offices and businesses. The area around the data center is well-lit and easy to monitor. It is easy to control access to the premises where the data center is housed.
- Data centers have areas with raised flooring.
- Data centers have to air-condition.
- Data centers have different levels of physical security.
- Data centers have assured stable electric supply.
- Data centers have state of the art fire prevention and fire protection systems.

From a networking perspective (Moumtzoglou, 2014; Soman, 2011):

- Data centers have high-bandwidth data pipes with various levels of redundancy.
- Data centers have all the elements installed that are required to run Intranet services continually.
- Data centers achieve the most advanced network security tools, including intrusion detection, firewalls, antivirus systems, and systems that guard against spamming, denial of service attacks, and all known malware.

Lastly (Moumtzoglou, 2014; Soman, 2011):

- Data centers employ qualified system administrators.
- Data centers support systems and processes in place to keep smooth functioning 24x7 and throughout the year.
- Data centers have a disaster recovery plan.

CLOUD-BASED SYSTEMS FOR HEALTHCARE IT

The healthcare industry is different from most other industries. It is very delicate, and there are several entities that have to deal with healthcare data. That includes regulatory bodies, care providers, hospital administration staff, payers, labs, and patients themselves. The key differences between the healthcare industry and other industries in which Cloud-based systems have been used include (Soman, 2011):

- **High-risk industry**

The healthcare industry impacts individuals to a greater extent than any other industry.

- **Highly regulated**

Numerous regulations govern the provision of healthcare.

- **Multiple stakeholders**

There is a large number of interested parties in the healthcare industry. That includes the patients, the physicians, the nurse practitioners, the hospitals/clinics, their administrative staff members, the payers/insurance companies, employers, pharmaceutical companies, technology vendors, device manufacturers, government bodies, and so on.

- **Slow Pace of Adoption**

The healthcare industry has traditionally been slow to adopt IT, especially the smaller clinics and individual physician practices.

- **Small and Large Providers**

The small providers typically do not have the resources to evaluate or experiment with advanced IT systems. On the other hand, there are several large multi-specialty hospitals whose IT requirements are distinctly different from those of office practitioners.

- **Long-Term Relationships**

Changing IT systems often is not easy, and there is, therefore, an assumption that any product adopted would be advantageous to use for several years. This hypothesis does not follow the need for both the IT systems and individuals to adapt.

Given all of these differences, it is not clear that Cloud-based systems would work in the healthcare industry as they have in other industry verticals unless Cloud-based healthcare solutions address these specific attributes of the industry.

From a clinical perspective, an EMR (electronic medical record) improves the quality of care provided to patients. Cloud-based EMRs are, therefore, a vital component of any Cloud-based healthcare offering. An EMR is computer-based documentation of a patient's medical history, including illnesses, examinations, reports, diagnosis and the care administered. Electronic Medical Records are created and maintained by care providers when a patient receives service from the vendor.

The following key pieces of medical information are a part of virtually all EMR systems (Soman, 2011):

- Patient Identification information.
- Information about Patient Allergies and Habits.
- Immunization Record.
- Medical History.
- Benefits of EMR.

There are significant advantages to using EMR when compared to the traditional paper-based files and charts (Soman, 2011):

- Storage.
- Usage in Emergency.
- Duplication and Transportation costs.
- Uniformity.
- Risks.
- Audit/Reporting.
- Integration.
- Efficiency.

Cloud-based EMR systems have all the features and capabilities of in-house EMR systems. Many Cloud-based systems have rich and incredibly easy-to-use interfaces and customize the fields in the records. Cloud-based EMR systems make it even easier to access or transfer medical information to any point, for example, to the point of care in an emergency (Witzke & Specht, 2017). Cloud-based EMR systems also make it simpler to provide access to the patient's records via patient portals.

A Cloud-based medical practice management application enables a healthcare provider to manage and streamline business management tasks and workflows. A 'workflow' is a series of steps followed to achieve a specific purpose. Provision of healthcare involves implementing various workflows within the practice, mirroring the patient's movement within the system. Medical Practice Management relates to the operation of multiple workflows within the practice. At the same time, Medical Practice Management Systems are the key to ensuring that all transactions within the practice run smoothly and efficiently. Cloud-based Practice Management software supports features such as (Soman, 2011):

- Appointment scheduling of patients.
- Eligibility and authorization.
- Physician scheduling, scheduling surgery or other procedures for patients.
- Tracking patient referrals.
- Patient account management.
- Managing patients as they move from admission to discharge, including information on hospital rounds.
- Managing patient recall.
- Claims submission and processing, automated follow-ups, collections and remittance advice.
- Managing the schedules of employees of the clinic.
- Managing the inventory of medical supplies and office materials.
- Inter and Intra clinic/location communication.
- HIPAA compliance.
- Patient portal.

In a Cloud-based practice management solution, the software is accessed through a browser over the Internet, so continuous Internet availability is crucial. Cloud-based practice management solutions can be customized, although admittedly to a limited extent compared to on-site solutions. However, Cloud-based solutions can effectively compete with on-site solutions regarding functionality and features.

A patient portal is essentially a website on which patients can log in and access most of their medical records. In a patient portal, the information is presented to make it easy for the patient to understand the

nature of his conditions and his treatment. Most Patient Portals also provide some level of interactivity with the healthcare provider.

Patient Portals represent one of the critical advantages of Cloud-based systems over in-house systems. A Patient Portal interfaces with sensitive, private information of individuals, which should be securely available and web-accessible at all times. It is, therefore, best if the responsibility of managing the patient portal is assigned to an entity that has the expertise, the infrastructure, the resources, and experience to develop and achieve high availability, high-security information systems. Most clinics or physician practices do not have this capability, nor is it practically feasible to invest in infrastructure and human resources to undertake such capability. It is, therefore, best to opt for a Cloud-based Patient Portal.

Many practice management systems and EMR systems include ePrescription capability as a part of their overall functionality. An ePrescription system is a computerized system in which the prescription is either entered by the physician/nurse practitioner or generated by the information available to the system. The prescription can be automatically communicated to pharmacies associated with the healthcare provider. Further, ePrescription systems also have inbuilt rules/databases about drug-drug allergies and the appropriateness of each drug in the context of various health conditions.

An ePrescription system brings several benefits (Soman, 2011):

- It eliminates the possibility of a prescription being incorrectly interpreted due to poor handwriting, reducing medical errors.
- It reduces drug-drug allergies and the possibility of the inappropriate drug being administered by viewing the patients' comprehensive medical history.
- It makes ordering refills easier since prior prescriptions can be easily accessed electronically.
- ePrescriptions are also found to increase compliance by patients merely because they are more convenient

A Cloud-based ePrescription system is likely to be much more highly available and secure and thus communicate prescriptions to pharmacies with higher reliability than an in-house system. Secondly, a Cloud-based system is more likely to cooperate with more and more pharmacy chains over time, enhancing the number of pharmacies the ePrescriptions can be sent to. Even if a clinic does not use Cloud-based systems for practice management, it is a brilliant idea to consider Cloud-based systems for data backup and secondary storage. The way most Cloud-based backup systems work is as follows (Soman, 2011). There is software installed on one or more of the computers within the facility (called the backup client) connected to the primary storage. The backup client tracks the changes to the data stored on the primary repository at regular intervals and communicates the changes to the Cloud-based storage space of the service provider.

The backup client encrypts all information before it is transmitted to Cloud storage. Secondly, bandwidth requirements are significantly reduced because the client only communicates the changes in the data since the last backup run, rather than transmitting all the details again.

A notable special case of a data backup system is the Picture Archival and Communication System ('PACS') due to the large sizes of medical images. In administering health care, various images, graphs, pictures, and scans are generated. That includes images from X-Rays, ultrasound machines, MRI and CT scans, endoscopy, mammograms, computed radiography, etc. Even scanned images of paper documents are often required to be stored when legacy paper-based data is digitized via scanning. To ensure

uniformity, a standard format used to store and communicate visual information has been defined—the Digital Imaging and Communications in Medicine (‘DICOM’).

Cloud-based laboratory solutions are available for various functions such as microbiology, histology and cytology processes, Synoptic/Antibiogram reporting, Image/Document capture, Inventory Management, Voice recording, Blood bank. They have all the functionality of on-site solutions.

Cloud-based Radiology systems are similar to PACS systems. These systems support basic Radiology workflows where physicians can register examination requests for existing or new patients and select appropriate billing rules. It is also possible to interface laboratory devices directly to Cloud-based systems. That means that the readings from instruments or captured images are directly uploaded to the Cloud.

Overall, cloud-based healthcare IT systems are easier to get started; distinctly cost-effective when compared to on-site solutions; more convenient, especially for smaller clinics and private physician practices, while allowing doctors to collaborate on any medical data easily and work on the system from anywhere, including from home.

Cloud Computing is a novelty that rapidly showed tremendous opportunities for application in medicine and health care improvement (Archondakis, Pouliakis, Margari, & Karakitsos, 2014; Eugster, Schmid, Binder, & Schmidberger, 2013; Glaser, 2011; Kuo, 2011; Lupse, Vida, & Stoicu-Tivadar, 2012; Mirza & El-Masri, 2013; Moumtzoglou & Kastania, 2014; Patel, 2012; Pouliakis, Archondakis, Karakitsou, & Karakitsos, 2014; Pouliakis, Spathis, et al., 2014; Rosenthal et al., 2010; Waxer, Ninan, Ma, & Dominguez, 2013; Webb, 2012). It is forecasted that there will be an increase in the US cloud computing market for medical images by approximately 27% by 2018 at a Compounded Annual Growth Rate (CAGR). That is mainly due to the growing volume of medical images and the increasing ownership costs for owning Picture Archiving and Communication Systems (PACS) (GlobalData, 2012).

II. Cloud and Quantum Computing

The basic unit of information processing in quantum computing is called the qubit, short for a quantum bit. While a qubit looks similar to a bit, it is fundamentally different. Like a bit, a qubit can be in one of two states, that is, 0 and 1, but it can also exist in what we call a superposition state. That is a state of a linear combination of the states 0 and 1. Devices that perform quantum information processing are known as quantum computers (McMahon, 2008).

Quantum computing could mean entirely new horizons for healthcare, as it might lead to (Meskó, 2019):

1. Supersonic drugs.

Scientists and pharma companies have started experimenting with AI, human organs-on-chips or silico trials to accelerate the process and make drug discovery and development more cost-effective.

2. In silico clinical trials with virtual humans.

Fully simulated clinical trials are not feasible with current technology and understanding of biology. However, quantum computing could help significantly further the building of ‘virtual humans’ and open the door to ‘live’ clinical trials, shortening the time of trials, their quality and completeness. In silico clinical trials will use an individualized computer simulation used in the development or regulatory evaluation of a medical product or device.

3. Full-speed whole-genome analytics and sequencing.

Quantum computing could significantly accelerate sequencing and more comprehensive and quicker analysis of the entire genome. Predictions will be more consistent as quantum computers will consider even more information than traditional computers. Specifically, they could use every piece of genomic data of the health records.

4. Patient as the point of care

Quantum computers will be able to examine enormous amounts of data. Moreover, patients' surveillance through connected sensory systems might render physical hospitals useless. It could also ensure the 'home front' truly making patients the point of care. Another possibility is raising lifestyle prediction to be predictive.

5. An elevated version of PubMed

Quantum computing could offer a decision support system for doctors by skimming through all the studies at once, correlations and causations, and it might stumble upon diagnoses or treatment options doctors have never figured out. At the same endpoint, quantum computers could create an elevated version of PubMed.

6. Quantum uncertainty and the security of medical data.

The use of quantum uncertainty for encryption is one of the most potential applications of quantum computing. It could be used for encrypting messages sent from one location to another, which will not be easily hacked.

Overall, computers have a critical role in the life sciences. However, there are constantly increasing challenges related to scale and complexity (Emani et al., 2021). Quantum computing is the technology that taking advantage of the increased processing power of quantum computers meets these challenges. So far, reports are trying to foresee applying quantum computing in medicine and life sciences (Cheng, Deumens, Freericks, Li, & Sanders, 2020; Emani et al., 2021; Marx, 2021).

Specifically, in pathology laboratories, there are at least three potential applications:

1. Next-Generation Sequencing (NGS). Pathology laboratories have incorporated advanced molecular techniques to identify pathogens (through their genome) and human genetic issues and therefore facilitate targeted therapy. NGS is a technology incorporated in pathology laboratories, which requires the alignment and matching of DNA sequences. Thus, quantum computing is of interest for NGS applications. Some research works have already proposed quantum computing for such applications (Prousalis & Konofaos, 2019).
2. Whole Slide Imaging (WSI). WSI is one of the modern applications in cytology and pathology laboratories (Pouliakis, Archondakis, et al., 2014; Pouliakis, Margari, Karakitsou, Archondakis, & Karakitsos, 2021; Tamposis, Pouliakis, Fezoulidis, & Karakitsos, 2016). WSI produces virtual microscopy slides; their size is relatively large (tenths of thousands of pixels) and depends on the used magnification. Virtual slides are digital representations of real microscopy glass slides and

can be used for archiving, consulting and other diagnoses. The digital size can be multiplied if there is a z-stack, i.e. 3D information and magnification at the 100x level. Thus, a virtual slide reaches the size of hundreds of gigabytes. However, pattern recognition, although feasible, it is prohibitive in terms of time and processing resources. In this context, quantum computing will facilitate advanced image processing algorithms and eventually lead to a recognition of the histological structure, especially in conjunction with the third application of the histopathology laboratory.

3. Artificial Intelligence (AI) for pathology diagnosis and research. Similarly, AI in the pathology and cytopathology laboratory is well known (Fragopoulos et al., 2020; Margari et al., 2018; Pergialiotis et al., 2018; Perroti et al., 2018; Pouliakis, Karakitsou, et al., 2016; Pouliakis et al., 2018; Pouliakis et al., 2019a; Siristatidis & Pouliakis, 2020; Siristatidis et al., 2021; Siristatidis et al., 2016; Vogiatzi, Pouliakis, & Siristatidis, 2019). However, such applications are mainly based on still and small images, i.e. a limited number of images captured from microscopy slides with relatively small dimensions (usually less than 1500x1500 pixels). These images are used to identify histological and cellular structures and extract measurements. Subsequently, these measurements are fed (sometimes with clinical and demographic data) to small scale AI systems responsible for providing a “diagnosis” or better classification. However, modern AI systems, such as convolutional neural networks, are based on images (i.e. they operate directly on image pixels and not on image features). Applying such algorithms on virtual slides requires a lot of computational resources and a lot of data. In this arena, quantum computing comes of help and provides the necessary computational resources and memory to make AI applications on virtual slides and 3D slides a reality.

Although quantum computing is in its infancy, NASA (NASA, 2013), IBM (IBM, 2021) and Google (Google, 2021) are in the process of building quantum computers, while China is also a strong player (NewScientist, 2021). However, quantum computers, before being affordable to everyone, will first be accessible as shared resources.

That is the point that Cloud technology comes into the scene.

IBM made a small quantum computer available in the Cloud in 2016 (IBM, 2016). As a result, anyone having an Internet connection can design and execute quantum circuits on this computer, i.e. sequences of basic steps performing quantum calculations.

Even though it is a relatively non-powerful machine, it is available for experimentation, leading to new applications that we have not yet imagined (Silicon Republic, 2019).

III. Big Data

Big Data is a terminology used to describe a collection of datasets being so broad and complicated that it becomes challenging to process them using the standard and on-hand database management tools or the available traditional data processing software applications. Although there is no single formal definition of Big Data, most definitions seem to associate with four Vs: Volume, Velocity, Variety, and Veracity. Volume relates to the extensive data produced, collected and exchanged; velocity refers to the need for real-time analysis; variety identifies the different forms of data that are difficult to integrate, while veracity emphasizes the issues related to trust and uncertainty. However, not all data that occupy a large volume are considered oversized. Thus, when defining Big Data, the size is not the primary characteristic; the most appropriate characteristic is the number of independent data sources (separate databases). Each has the potential to interact and be interconnected with one or more data sources.

According to the newest market studies (Market Research Future, 2017; Markets and Markets, 2017), the revenue of Big Data by 2020 and 2021 is estimated in the range of 25-35 billion USD. Thus, the Big Data market is continuously increasing. It is a very competitive market, and many stakeholders have presented innovative products and services dealing with Big Data. The Big Data ecosystem has several discrete areas: a) storage and management, including data servers, software, networking, monitoring, administration and data management b) tools and technologies specialized for Big Data analytics that generates insight from collected data c) healthcare intelligence for the organization and d) embedding the Big Data framework into the organization's business intelligence infrastructure (Koumpouros, 2015).

There are several Big Data solutions, either open source or commercial ones. Open platforms have advantages as they come at no cost for software acquisition and permit various tools for data analytics. However, they require significant effort to install and set up by specialists. The Apache Hadoop framework is the pioneering and most-used open platform. Other open-source systems include NoSQL databases: MongoDB and Cassandra, among others. The Hadoop framework with proper scaling can support the analysis of petabytes of data. In this arena, another platform, Red Hat Enterprise Linux, supports Big Data applications in companion with the OpenStack hybrid Cloud. In the commercial product arena, Info Sphere is one of the products offered by IBM, another platform based on the Hadoop system. It includes data warehouse and stream computing software to perform real-time analysis on vast volumes of streamed data. Cisco offers the Cisco Common Big Data Platform based on Cisco's Unified Computing Architecture and concept. Due to the company's networking history, it integrates computing, networking and storage capabilities. Other Big Data platform and services vendors include Cloudera, Hortonworks, Platfora, DataStax, 10Gen, and Amazon, supporters of Hadoop and NoSQL. As well as Hadapt, Platfora, Splunk, Datameer, and Karmasphere.

One of the central Big Data and cloud service providers are Amazon. The leading service is the Elastic MapReduce (EMR), a Hadoop based platform that scales to thousands of nodes per cluster. There is support for easy to use mission-critical, real-time applications, a petabyte-scale warehouse service. Finally, it includes business intelligence tools and can operate on datasets of a few hundred gigabytes to petabytes.

Healthcare is probably one of the leading areas in the Big Data arena because significant amounts of personal and sensitive, health-related data can be continuously collected from patients. In the medical field, those data are collected by different actors in different locations for various purposes and used/viewed differently by each information consumer (Koumpouros, 2015). For the medical specialists to reach the best possible diagnosis and, subsequently, the appropriate therapeutic scenario, accurate and complete information is required; without Big Data, this is not feasible.

Evidence-based medicine (EBM) is another factor that stresses the need for Big Data in healthcare, as it relies on large scale data sets, usually distributed (Beckmann & Lew, 2016; Sniderman, LaChapelle, Rachon, & Furberg, 2013). Physicians and health care management use EBM, and insurance organizations, pave the way for the acceptance of Big Data.

As far as population health management is concerned, there is already an application of Big Data (Wells et al., 2016). Specifically, the application is mainly based on the US Medicare and Medicaid insurance programs. Within this application, data from diverging lines of evidence are used:

- Demographic and contact details along with insurance coverage.
- Insurance claims, submitted by doctors, hospitals, and other providers to Medicare; those data include standardized codes for medical diagnoses and procedures, place of treatment, amounts billed, as well as whether service was provided:

1. in the emergency room
 2. inpatient service
 3. ambulatory service
 4. laboratory
 5. long-term care unit
 6. ancillary service
- Prescribed pharmaceuticals include the drug name and class, a drug code identifier (applied at the national level), drug dosage, dates, and the number of days for drug usage. It is worth noting that this is a separate database linkable to the medical claims and administrative data from Medicare.
 - A questionnaire measures experiences with Medicare health plans, including the health status, satisfaction, and experiences from healthcare services.
 - US Census data are related to the zip code and identify differences in the geographic regions.
 - Data from Dartmouth Atlas describes the supply of healthcare services in a geographical context.
 - The AmeriLINK Data Sourcing system indicates the social and economic status of members.

The processed Medicare data were around 4 million records, and the results of health analytics proved to be very interesting. The aim was to ‘get the right person to the right care at the right time’ Individuals who filled the questionnaire had two times more probability of using a Medicare service. In contrast, increased care coordination was linked with fewer hospital readmissions. Thus, those individuals were more likely to visit a physician’s office than return to the hospital and increase healthcare costs. Improved depression management enabled the reduction of depression symptoms in about 60% of engaged individuals in the program. Finally, Big Data analytics-enabled suggestions for participation in a wellness program.

However, there are still numerous issues in the Big Data arena, especially in healthcare. By 2020, experts predicted that data would be produced at a rate of about 40 trillion gigabytes per day. Current information technology is not capable of storing and processing such large volumes. Also, there is a shortage of skilled personnel to collect, manage and process these data. Furthermore, there is resistance from health providers and administrators, as they do not understand the benefits of Big Data and especially for population health management. Data collected from the medical facilities, systems’ time, and technical diversity seem to be barriers to data collection.

Moreover, medical systems constantly change as they adapt to new technological and scientific advances and emerging organizational and regulatory requirements and newly developed standards. As a sequel, even in a single hospital, several information systems and often a bridge are required to ensure interoperability. Despite the evolution in medical standards, it seems that several efforts are still needed. Within the healthcare facilities, the replacement of existing systems depends on healthcare providers’ willingness and financial capacity. Additional barriers will emerge due to the application of M-Health; whereas data collection will be more intense, individuals are already able to collect them from their own devices.

IV. M-Health

M-Health describes the use of a broad range of telecommunication and multimedia technologies within the wireless care delivery design and can be broadly defined as providing healthcare services via mobile communication devices (Dimitriou et al., 2017; Metelmann & Metelmann, 2017; Rana, 2017). M-Health

establishes healthcare communities in which every stakeholder can participate (O'Connor, Heavin, & O'Donoghue, 2015). However, it disrupts the traditional service model where healthcare information, security, and access is centrally managed, maintained and limited, transforming the health sector and destroying components that are slow to adapt.

M-Health interventions range from simple to complex applications and systems that remotely coordinate and actively manage patient care (Pouliakis, Archondakis, Margari, & Karakitsos, 2016). This context offers an elegant solution to accessing the correct information where and when it is needed within highly fluid, distributed organizations. Moreover, it removes geography and time as barriers to care by establishing connectivity with remote locations and remote workers, creates new points of contact with patients, and changes the frequency and intensity of health care delivery. It also establishes effective new treatment modalities like telehealth, remote patient monitoring, self-care, and home health while blurring the boundaries between professional medical advice and self-care. Overall, M-Health blends three bodies of knowledge: high technology, life sciences, and human factors.

M-Health could also be thought of as the practice of medicine and public health supported by mobile devices. The use of mobile computing and communication devices, such as mobile phones, tablet computers and personal digital assistants (PDAs), by health professionals is rapidly growing. Wireless networks are the answer to the interconnection of ubiquitous devices. However, wireless communications increase security challenges, privacy concerns, and trust issues for the wireless network, mobile devices, connected medical devices and e-health applications (Grami & Schell, 2004). Wireless, mobile nodes is a new challenge in the distributed systems which carry out functions like packet forwarding, routing, and network management (Chlamtac, Conti, & Liu, 2003). Various protocols and algorithms are available for mobile ad-hoc networks (Chlamtac et al., 2003), while the quality of service models for mobile ad-hoc networks and network security are significant challenges to be surveyed (Chlamtac et al., 2003). As a result, different service constraints for various services illustrate the need for an automatic wireless technology option (Janevski, 2009; Kitanov, Monteiro, & Janevski, 2016).

Currently, the generations of mobile phone networks (3G/UMTS, 4G and the predecessor of 5G, i.e., 4.5G) are packet-based architectures (Kastania & Moutzoglou, 2012). Mobile telephony since the 3G technology enabled the seamless delivery of web content to mobile consumers (Wilson, 2006). Users' management involves subscriptions and profiles for different terminals (cell phone, PDA, laptops, desktops) (Hong & Leon-Garcia, 2005). The choice of a cell/mobile device is heavily influenced by the provided mobile services and device capabilities.

Existing cellular and WiFi networks that have, nowadays, merged with the Internet, represent the 4th generation (4G) and the predecessor of 5G (i.e., 4.5G) wireless, mobile Internet networks (Gani, Li, Yang, & Zakaria, 2008). 4G generation of wireless enhanced and replaced the 3G systems, a mobile network, IP-based, providing a connection via always the best available network using seamless roaming and free radio access technologies. In 4G mobile systems, different access technologies are combined, in the best possible way, for various radio environments and service requirements. 4G technologies have already implemented much more extensive data rates supporting full mobility while enabling wireless connection and access to multimedia services with high-quality voice and high-definition video. 4G wireless telecommunication supports smart multimedia providing higher bit rate and broader bandwidth, 3D image technology, streamed HD TV with remote control, video multimedia and advanced multimedia messaging service. Mobile multi media provision requires a modern mobile communication system to make ubiquitous communication using mobile characteristics. High-quality voice, video, and data services can be delivered on a metropolitan using WiFi (IEEE 802.11a/b/g/n) as a transition towards 5G. While

expected to fulfill the goals of 4G technology offering full broadband for all services, Mobile WiMAX is not, nowadays, the technology of choice. In this context, global roaming and open interconnection interfaces are essential functions of 4G communications systems.

According to many researchers, mobile applications ensure seamless mobile services for end-users, anywhere, and on any device. However, the shifts towards more advanced networking systems depend on wireless radio access technologies and networking technologies.

Services adding to 4G include 5G, which is expected to be a more intelligent technology for the whole interconnection world without limits. 5G technology is currently implemented and is the standard of mobile telecom providers; it is synonym with the LTE Advanced (Long Term Evolution) and MIMO (multiple input / multiple outputs) technologies that enable the multiplication of capacity and frequency use along with optimization in the urban and indoor environments to handle multi path effects.

5G is planned to provide additional services and have more advantages related to energy consumption, network coverage, spectrum handling, bandwidth use and allows users to participate in a fully distributed or cellular-controlled fashion. All IP-based services for heterogeneous wireless access technologies, assisted by mobile IP, are provided by 5G mobile communication networks. 5G aims at a higher capacity and simultaneously a higher density of mobile users. Moreover, it supports device-to-device and machine to reliable machine communications (i.e., mobile ad-hoc networks / MANETs). Thus, 5G aims at lower latency than the 4G equipment and lower battery consumption and is an enabling technology for the Internet of things. Nowadays, there is no standard for the deployment of 5G. However, the expected characteristics include:

- Tens of megabits per second, simultaneously for dozens of thousands of users.
- More than 100 megabits per second for metropolitan networks.
- 1 Gb per second, simultaneously available to all users on the same building floor.
- Capacity for hundreds of thousands of simultaneous connections for the implementation of the Internet of Things.
- Spectral efficiency / i.e., more Mbps for the same frequency slot.
- Improved coverage.
- Significantly reduced latency.

MEDICAL APPLICATIONS FOR THE NEXT GENERATION OF MOBILE DEVICES AND NETWORKS

Mobile web services represent the integration of web services between mobile devices without any centralized entities (Srirama, Jarke, Zhu, & Prinz, 2008). Factors influencing mobile hosts are network characteristics, searching capability of the services and computational resources (Srirama, 2006), while collaborative sharing of peer resources is possible for Mobile Hosts in P2P (Srirama, 2006). Mobile Host in JXME JXME allows collaboration, image sharing, and location-based services (Srirama, 2006). Each Mobile Host can provide some services in the wireless network acting, through the cell phone, as both web service client and provider (Srirama, Jarke, & Prinz, 2007). The quality of service (QoS) for the Mobile Host is critical regarding security and scalability.

A mobile phone is a communications device offering wide-area networking capabilities (Rousos, Marsh, & Maglaveria, 2005). Cell phones can serve as control devices for ubiquitous systems and

information service endpoints, focusing on protecting the user's information (Roussos et al., 2005). Many mobile phones interact with other nearby devices due to the availability of wireless networking capabilities (Itani, Kayssi, & Chehab, 2016; Roussos et al., 2005). Visual tag clicking on the camera phone allows user interaction with a mobile service (Toye et al., 2007) while mobile content can be downloaded, in commercially available products scanning visual tags (Toye et al., 2007). Moreover, data rates increase web browsing and offer reduced access times. However, there are constraints associated with small mobile displays and keypads (Toye et al., 2007), while more significant data rates increase energy consumption and complexity of the device.

Overall, the smart Internet phone lets the mobile phone select the best connections (Janevski, 2009). Furthermore, all smartphones (cell phones that include PDA functionality) are equipped with the functionality to access high-speed data through a variety of networks, including those supported by mobile phone networks (3G and 4G+), local networks (WiFi) and personal area networks (Bluetooth and NFC). Applications for the next generation of cell phones will provide localized, real-time services and localized information services. However, confirmation is needed of the services provided by smartphones in a wireless network (Srirama et al., 2007).

Handheld computing has already numerous applications such as:

- Ambulatory medicine (Banitsas, K., Perakis, Koutsouris, Konis, & Tachakra, 2005; Banitsas, K. A., Perakis, Tachakra, & Koutsouris, 2006; Kiselev, Gridnev, Shvartz, Posnenkova, & Dovgalevsky, 2012; Pavlopoulos, Kyriacou, Berler, Dembeyiotis, & Koutsouris, 1998; Rosales Saurer, Mueller-Gorchs, & Kunze, 2009; Zerth, Besser, & Reichert, 2012).
- Diabetes management (Quinn et al., 2011; Ribu et al., 2013; Skrovseth, Arsand, Godtliebsen, & Hartvigsen, 2012; Spat et al., 2013).
- Asthma management (Finkelstein, Hripcsak, & Cabrera, 1998; Gupta, Chang, Anyigbo, & Sabharwal, 2011).
- Control of obesity (Patrick et al., 2009).
- Smoking control (Ghorai, Akter, Khatun, & Ray, 2014; Ybarra, Holtrop, Prescott, & Strong, 2014).
- Seizure management (Pandher & Bhullar, 2014).
- Stress management (Clarke et al., 2014) and
- Treatment of depression (Burns et al., 2011) among others.

In the field of M-Health, most applications are fitness related (43%), followed by health resources (15.0%) and diet/caloric intake (14.3%). In comparison, user engagement has the form of self-monitoring and training (74.8%) (Sama, Eapen, Weinfurt, Shah, & Schulman, 2014). On the other hand, despite the applications that target patients, there are currently limited applications targeting physicians and doctor-patient interactions (Martin, 2012). The pioneering field seems to be radiology consultation for X-rays and mostly Computer Tomography (Choudhri et al., 2012; Choudhri et al., 2013; Johnson et al., 2012; Toomey et al., 2010) and ECG transmission (Vaisanen, Makijarvi, & Silfvast, 2003).

However, the mobile device has emerged recently as a technology gadget capable of collecting biomedical data, either in the form of the mobile phone or as a specialized appliance, usually in the shape of a wrist attached device. This plethora of devices has created a new Quantified Self (QS) (Fawcett, 2015). QC involves ordinary and usually healthy people that record and process aspects of their lives with the help of (usually) self-collected data. This QS movement has attracted the interest of commercial

companies offering products and services (hardware and software). The M-Health applications being of interest to physicians, patients, and the science of individuality include the following.

Mobile MIM (MIM Software, 2017) is a software application for viewing MRI, PET and CT data using mobile devices compatible with the Apples' iPhone series operating system (iPad®, iPhone®, and iPod touch®). MRI, PET, and CT images are transmitted using software, and it is possible to measure the image intensity and distances.

MobiUS™ is an image-based series of products (Mobisante Inc., 2017) supporting ultrasound (US) imaging. That is smartphone and tablet-based and is cheaper than traditional US systems, being equipped with specialized monitors. Moreover, this system supports sharing of images among patients and clinicians.

Gyromaniac (Subversus Interactive, 2011) uses the iPhone gyroscope electronic components to help physicians practice spatial orientation: for example, to assist gastroenterologists during training how to perform a colonoscopy (Iltifat, 2010).

There are also software platforms for continuous wearable, non-obtrusive ECG data (cardiac) monitoring. Such solutions can help cardiologists monitor and manage patients with angina, infarction of the myocardium, cardiac interventions such as stents, pacemakers, and bypass, as well as cardiac failures and ambulatory medicine. Such devices have been in service for gynecologists for fetus monitoring (Medical design, 2013; Su & Chu, 2014). That avoids frequent visits to the outpatient department for follow up, unnecessary waiting time and anxiety for patients. That system also aids proactive management of complications, identifying them with intelligent analysis as and when they occur and addressing them based on evidence.

A recently announced device (Wavelet Health, 2017) incorporates a photoplethysmograph (PPG) sensor; a pulse oximeter illuminating the skin and measuring changes in light absorption; such a device is capable to continuously monitor perfusion of blood to the dermis as well as subcutaneous tissue; therefore, it can detect heart rate as well as blood oxygen levels.

Recent announcements (University of Illinois College of Engineering, 2017) are related to a lab on a chip device that can perform lab-grade medical diagnostics when coupled with a smartphone. Such tests usually require large, specialized and expensive instruments. However, the developed inexpensive microchip incorporates standard technology in the three top categories of medical diagnostics. The microchip promises to perform thousands of already available tests. It is based on the mobile phone camera that is used as a spectrometer. Specifically, the biological sample should be in a fluid form; this is illuminated by the cell phone's white LED flash. Subsequently, the light from the fluidic sample is collected by an optical fiber. After being captured by the phone's internal camera, the use of the software can be evaluated. Such technology enables advanced biological tests in remote areas, often in the developing world, and personalized tests at the individual patient level.

In otolaryngology, some applications can determine reference sound levels; thus, it is feasible to conduct a hearing screening on devices calibrated with a predefined reference noise level (Masalski, Kipiński, Grysiński, & Kręcicki, 2016).

Also, the advanced communication capabilities allow voice and video conferencing features for patient/doctor and doctor/doctor interactions and seamless transmission of captured images and video.

Mobile electroencephalograph (EEG) is another area in mobile devices that may become a commodity. Emotiv Insight Brainware® (see Figure 1) is a five-channel EEG device that can capture brain signals and transmit them via Bluetooth interface to the mobile phone (EMOTIV, 2017). Such commercial and portable EEG devices have already been used to measure auditory potential in children and adults

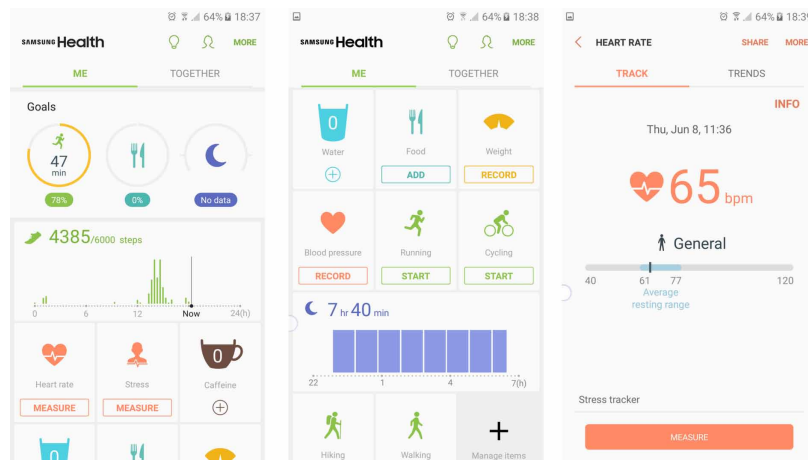
(Barham et al., 2017). They are used to convert brain signals to computer commands, and some identify the mental status and record it for archiving purposes.

Figure 1. A commercial portable EEG device capable of communicating via Bluetooth with the mobile phone



Furthermore, modern high-end mobile phones are coupled with sensors that can measure life signals and communicate with commercial devices that measure health signals such as blood glucose. For instance, some cell phones have integrated heart rate sensors with high accuracy and step counters. They also have applications (Figure 2) that measure and store data to the Cloud, such as exercise and sports activity, heart rate, stress, sleeping duration, consumption of food and liquids, weights and glucose when coupled with appropriate medical devices or when the user wishes to supply such information.

Figure 2. A display of mobile phone applications for the measurement of health and well-being data



Conclusively, the recent advances of mobile telephony have contributed to the conversion of mobile telephones into smartphones; due to the sophisticated operating systems. Especially during the previous five years, hardware components enriching cell phones became available, including more processing power (8 or more processors), high-definition cameras (more than 15Mpixel) and large display resolutions. Moreover, the 4.5G and WiFi connectivity have created an always open, relatively inexpensive communication channel with the Internet. Today, there is no more trend to shrink the telephone; in contrast, mobile phones are becoming more prominent and complete tablets regarding size and weight; they are easy to use and have capabilities similar to computers available five years ago. It seems that mobile devices now have the maturity of computers used in the health sector five years ago.

ISSUES, CONTROVERSIES, PROBLEMS

First, we must recognize that if we design population health efforts solely around patients, we fail to address the enormously significant social determinants of health, including environmental, economic, and cultural factors.

Instead, we need a proactive, holistic, longitudinal, without walls, profoundly personal approach to population health management. That means the approach should include the care of the sick and proactively reach out to hard-to-reach populations. Moreover, the approach should:

- Address the range of psychological, biological and social factors that influence health and wellness.
- Leverage the patient as a source of continuity by engaging him or her as an integral member of the care team.
- Recognize that supporting an individual's lifelong health and well-being cannot be relegated to any particular setting.
- Take into account the personal goals, strengths, and challenges for primary drivers of care management, planning, and decision-making.

While ‘Big Data’ has its place for identifying patterns and gaps in care and predictive analysis, the most relevant data regarding the science of individuality are self-reported data. In this context, the population health management strategies will fail to engage patients, reduce costs, and improve outcomes if implemented without the underpinning of person-centered care. Ultimately, the health of a population has nothing to do with data and technology but with the individuals that make up the population.

In this direction, and due to the sensitivity of the stored and transferred information, data security for all of the associated technologies is of essential importance (Spyra, Buchanan, Cruickshank, & Ekonomou, 2014). In this context, the European Union approved (in April 2016) the General Data Protection Regulation (GDPR), the most significant change in the European legal framework in the last twenty (20) years. The GDPR was expected to directly apply in all member states on May 25, 2018, and heavy fines on non-compliant organizations assure enforcement. However, the implementation of the GDPR, to a large scale, might be a big issue, as information flowing across the EU borders and data storage in non-EU countries could be essential, taking into account that non-EU countries are not obliged to apply the GDPR. As a result, services offered by organizations residing outside the EU could be vital for e-health applications targeting individuals.

FUTURE RESEARCH DIRECTIONS

The future of population health management is tied to the rise of cognitive computing. Cognitive computing is the simulation of human thought processes in a computerized model and uses parallel processing and AI to convert unstructured into structured data, search the medical literature, and find connections among multiple types of evidence; in short, it creates knowledge.

Cognitive computing aims to build automated IT systems capable of solving problems without requiring human assistance. The cognitive computing systems:

- Use natural language processing and machine learning algorithms.
- Mine the data for information.
- Refine the way they search for patterns.

Heretofore, cognitive computing is used in the following AI applications, among others:

- Expert systems.
- Natural language programming.
- Neural networks.
- Robotics.
- Virtual and augmented reality.

CONCLUSION

Population health management (PHM) has been, so far, a discipline that studies and facilitates care delivery across a group of individuals or the general population. In population health management, the life science industry has no motivation to design drugs or devices that are only effective for a distinct

segment. At the same time, the regulatory agencies are entirely risk-averse and are suppressing remarkable innovative and even frugal opportunities to change medicine.

However, the significant outgrowth of the science of individuality and the rising ‘wiki medicine’, the individualized medicine that respects individuality, fully recognizes the individual’s uniqueness. In this regard, it will not be long until digitizing a person unlocks the root cause for what is wrong, creating valuable knowledge that can save or markedly improve the quality of life.

In conjunction with Cloud computing, Big Data and M-Health technologies, Quantum computing offers the resources to deal with the shortcomings of the population health management approach. Specifically, while population health management focuses on what happens on the bed or a doctor’s office., the technologies above facilitate the propagation of the science of individuality by taking the challenges of wellness, prevention and lower cost. Finally, cognitive computing is considered the future of population health management.

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Chapter 3

The Australian National Disability Insurance Scheme During COVID–19: The Case of People With Disabilities From Culturally and Linguistically Diverse Backgrounds

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ABSTRACT

We have learned from COVID-19 to humanize our society and seriously challenge the rising inequalities, racism, and discrimination that exist in our contemporary human world. One of the apparent discriminations in our society is based on the government's approach and treatments towards people with disabilities. This chapter is about the Australian people with disabilities from culturally and linguistically diverse backgrounds and how the Australian National Disability Insurance Scheme has responded to the needs of these people within the Australian society during COVID-19.

INTRODUCTION

The Covid19 has changed our society the way it was normally organized, and we were used to it. The change deepened the existing inequalities in Australian society. It has become clear that people with disabilities and marginalized individuals and communities will bear the most significant impact (Hashmi and his colleagues, 2020). The extent of this impact on people with disabilities will be discussed and analyzed, and suggestions will be offered to improve the lives of these most vulnerable people in society. While the focus is on people with disabilities from culturally and linguistically diverse people in Australia, yet for a deeper understanding of this complex issue, it is important to develop a broader context to include a brief historical background of the development of the Australian National Disability Insurance

DOI: 10.4018/978-1-7998-9198-7.ch003

Scheme as well as discussing theoretical frameworks to shed deeper light in our understanding of this complex issue in human society. Thus, in the first part, our discussions begin with a brief history of the Australian healthcare system.

The primary characteristic of the Australian Healthcare System has been the coexistence of public/private division. Medicare is Australia's compulsory universal health scheme, and all Australian people have equal access to its services. The Australian Federal Government takes the principal responsibility in the provision of health care services. For a complete understanding of this process, see Australia in 2030. What is our path to health for all? (*MJA*, 2021).

Historically, the Australian Governments' policy on people with disabilities has been closely connected to the government's policy on employment. As a result, when rehabilitation services were established in 1948, it was closely linked to the Government policy on employment (Howe 2004). However, in the 1970s, during the administration of Gough Whitlam and Fraser, incrementally, a change occurred. People with a disability could have access to third-party compensation insurance if people were injured or became incapacitated. In 1986, the Hawke government introduced Disability Services Act 1986. The argument was that "people with disabilities should have the same rights as other Australians to realize their capacities for physical, social, emotional and intellectual development" (Cass 1988:15). Since then, and particularly in the 2000s, many not-for-profit organizations involved in providing relevant services for various needs of people with disabilities. These efforts led to the establishment of DisabilityCare based on the recommendations from the Productivity Commission of Australia. Later this was considered the first manifestation of NDIS (Carson & Kerr. 2020).

After introducing Medicare in 1984 in Australia, the National Disability Insurance Scheme (NDIS) is considered the second greatest change in the Australian Healthcare System. Although NDIS has been progressing well during the last few years and providing much-needed service to many people with disabilities, the research indicates that some communities/groups and individuals have not been satisfied with the level of services they have been receiving from NDIS. One of these groups includes people with disabilities from Culturally and Linguistically Diverse Backgrounds. While this chapter focuses on discussing the major issues that these people face in accessing their necessary individual services, it is important to provide a holistic discussion and understanding of disability from various perspectives, including social and market perspectives. NDIS is based on a market approach and includes 'choice', 'market purchase services', 'individualized funding approaches' and 'person-based services'.

Australia is proudly a Multicultural society. Almost 30% (7.6 million of the total Australian population of 25, 694 393 people in 2020) of its population are from four corners of the globe and have settled in Australia. Migrants advanced Australian society in many ways and have made significant contributions in many areas, particularly the economy. Migration Council Australia provides a research-based estimation that by 2050, migration will be contributing \$1,625 billion (1.6 trillion) to Australia's GDP. At the same time, people with disabilities within Culturally and Linguistically Diverse backgrounds are some of the most vulnerable Australians with little or no voice in Australian society. This becomes more pronounced during the Covid19 that will be discussed in more detail in this paper. Also, let's consider the sheer number of people from Culturally and Linguistically Diverse groups. The significance of its population requires urgent attention for the Australian Governments to access their services and be protected from the real risk of Covid19.

Regarding the population of these groups, it is estimated that out of 1 million people with disabilities from these backgrounds, there are over 120,000 people with severe and permanent disabilities (National Ethnic Disability Alliance-NDIS). The significant number of this group and the intensity of their re-

quired services create severe challenges for NDIS to tackle positively and constructively. This paper aims to attract the NDIS Authority and the Australian government's attention to providing services and protections necessary from Covid19 for these most vulnerable groups in Australian society. As Jane Shill and her colleagues (MJA, 2021:55) state: "All Australians have the right to access the resources and environments necessary for long and healthy life. Yet many in our community face multiple barriers in achieving good health and wellbeing." This statement also includes people with disabilities from Culturally and Linguistically Diverse backgrounds. It should also be emphasized here that these services must be provided within the relevant cultural context and competency within NDIS services.

BACKGROUND HISTORY OF NDIS

This section provides brief descriptions of the major challenges and legal processes leading to developing the National Disability Insurance Scheme (NDIS). What has become obvious is that NDIS, as the second most crucial healthcare reform in Australia, has altered many Australians' perceptions of viewing and treating people with disabilities in Australia. This achievement has resulted from the continuous efforts of people with disabilities themselves and their supporters to challenge the existing individual legislations and anti-discrimination acts on people with disabilities within different States in Australia. Some of these Acts date back to the 1980s.

However, the first most significant national act in this area was developed in 1992, the *Disability Discrimination Act 1992* (DDA). It was an act presented by the Parliament of Australia to promote people with disabilities in certain areas. The objects of this act were: "(a) to eliminate, as far as possible, discrimination against persons on the ground of disability in the areas of (i) work, accommodation, education, access to premises, clubs and sport and (ii) the provision of goods, facilities, services and land; and (iii) existing laws; and (iv) the administration of Commonwealth laws and programs; and (b) to ensure, as far as practicable, that persons with disabilities have the same rights to equality before the law as the rest of the community; and (c) to promote recognition and acceptance within the community of the principle that persons with disabilities have the same fundamental rights as the rest of the community", (*Disability Discrimination Acts 1992, no.135*).

This act aimed to standardize the scope of rights offered in various states and territories and implement the Australian government's obligations as a signatory to the International Declaration on the Rights of People with Disabilities. The overall assessment of the act is that it has been reasonably effective in reducing discrimination in employment and education for people with disabilities. Yet, it was not responding to the needs of these people in many areas of their lives. However, in the late 2000s, there were increasing calls from the disability sector to introduce a new mechanism for funding support for people with disabilities. In 2009, the Rudd Government in response to these calls, requested that the Productivity Commission investigate "the feasibility of new approaches, including a social insurance model, for funding and delivering long-term disability care and support for people with severe or profound disabilities however they are acquired" (Buckmaster 2012). On July 31 2011, the Productivity Commission reported: "The current disability report system is underfunded, unfair, fragmented, and inefficient. It gives people with a disability little choice, no certainty of access to appropriate supports and little scope to participate in the community" (Productivity Commission 2011).

Through its research and investigations, the Productivity Commission recommended establishing new disability care and support scheme called the NDIS. All Australians with a significant and ongoing

disability would have access to long-term care and support through this scheme. On the release of the Commission's report, the Gillard Government announced that the government would start work immediately with states and territories on measures that will build the foundations for a National Disability Insurance Scheme. On March 21 2013, the Gillard Government passed the NDIS Bill through Parliament, arguably the second most important health reform, after Medicare.

In discussing the major characteristics of the NDIS, it is sufficing to state that although the NDIS is moving away from blocked funding and charity approach organization to a universal scheme, yet still is somewhat away from the social model of disability based on human rights context. Fawcett & Plath (2012: 14) state that NDIS reflects liberal/market principles rather than human rights perspectives. Within the market principles of care, not all people enjoy the same opportunity. There will be those who desperately require advocacy to make decisions based on their needs through planning, assessment, and choice. This group of people require particular attention and protection that the NDIS should provide for them. That is the area most attracted to social work and human service professionals. They have embedded human rights values and holistic understandings in their education to support society's most vulnerable and disadvantaged people.

HOW IS DISABILITY UNDERSTOOD?

At the outset, it is helpful to state that social change has altered society's view, at least, in the Western World on disability during the last several decades. Before this change, people with disabilities were not considered 'normal' and faced ongoing abuse and gross discrimination. Many people with a disability were institutionalized. They had very little control, if any, over their own lives. Background information in this area is essential to understand how disempowerment and marginalization of disability groups form the historical context for our understanding (see more details of the National Disability Insurance Scheme, 2014:268).

Disability has been the subject of continuous debates in human society. In Western societies, particularly during the late 19th and early 20th Centuries, there were debates on the ideal human society where people with disabilities would not be present. In this context, the focus was on human genetics. That led to the development of eugenics. This field of study was aiming to improve the qualities of the human species. Eugenics scientists believed that people with disabilities are genetically inferior and strongly discouraged from having a child. Belser (2015) describes this as 'forms of eugenic imagination that envision liberation through the denial of bodily and sensory difference'. That led to the development of policies in the United States to force sterilization of so-called "insane" people with disabilities. Another application of this policy relates to US immigration law. These laws were designed in such a way to refuse the entries of people from southern and eastern European countries. In other countries of Europe, such as Nazi Germany, this led to the Holocaust tragedy. Before World War I, European people saw themselves as superior to other people, including blacks. In Scandinavian countries, eugenics also attracted the broad attention of politicians as well as ordinary people. It was in the 1920s and 1930s that this led to antiracist sentiments. However, "eugenic sterilization was an integral part of the social welfare state that emerged in the 1930s and 1940s" (Broberg and Roll-Hansen, 2005). To understand the depth of eugenic influence on people with disabilities and how they have been seen within this context, the author discusses his holistic understanding of disability and critically examines the relevant theories and theoretical perspectives on disability (Abberley, 1987).

DEFINITION OF DISABILITY

The roots of the definitions of disability are closely connected to the way medical establishments understand human bodies and minds in various historical contexts. It is also important to emphasize the importance of who defines what disability is? It is also essential to consider intersectionality, gender, race, sexual orientations, and social class within this context. Since discussions in these areas are beyond the scope of this paper, however, interested people can read Burch and Rambis' book (2014). These authors in the book provide critical analysis of disability and challenge the traditional definitions of disability that are still prevalent in the Twenty-First Century.

Therefore, it becomes clear that the definition of disability as a socially constructed term has been a subject of debate over time and within different cultures. For example, from the sociological perspective, Germov (2014: 264) refers to disability in its broadest context as: "physical or mental limitations, restrictions, or impairments that can be chronic or last for a sustained period ". In the global context, the International Classification of Functioning Disability and Health (ICF) view disability in a broader context to include "impairments, activities limitations and participation restrictions". Within this context, the focus is on the health condition of a person with a disability with his/her social environment and related government and community support services (WHO: Disability and Health, 2015). Based on this definition, the World Health Organisation estimates over one billion people with disabilities living globally, and the number of people with disabilities is rising (op. cit).

In Australia, the main focus of the NDIS is on the functionality of a person with a disability. With this approach, NDIS proposes a narrower definition of disability. That has led to a large gap between the number of people with disabilities that NDIS accepts as its clients and what ABS suggests in its research and findings.

According to the Australian Bureau of Statistics definition, "disability refers to any person with a limitation, restriction, or impairment, which has lasted, or is likely to last, for at least six months and restricts everyday activities". Based on this definition, it is estimated that "nearly 4 million Australians – that is, 20 per cent of the population – fit this description, with 2.6 million of those aged less than 65 years (Begg et al., 2007). This number also has increased from 4 million in 2007 to 4.2 million in 2102. A further 4.7 million had a long-term health condition that did not restrict their everyday activities. For those people with a disability, 3.7 million had a specific limitation or restriction that meant they were limited in the core activities of self-care, mobility, or communication, or restricted in schooling or employment (Australian Bureau of Statistics, 2012). These numbers are in sharp contrast with the total number of 410,000 people with disabilities that the NDIS aims to cover in Australia. This difference becomes even more pronounced when we consider the degree of disability in ABS' survey.

Based on the degree of disability, an ABS survey in 2003 found that 1.2 million individuals had profound core activity limitation, meaning that they sometimes or always required help or supervision with self-care, mobility, or communication. Over one million people also needed assistance with at least one of the following activities: self-care, mobility, communication, health care, housework, property maintenance, paperwork, meal preparation, transport, and cognition. Of these, 0.7 million are under 65 years (Begg et al., 2007:153). These groups may be considered as part of the second tier of NDIS. This distinction is useful and needs to be made in the annual review of the NDIS. It is also worth mentioning that the NDIS should notice the gender differences within the disabled population. Begg et al. (2007), with other scholars in their research, suggest that while men can expect to have five years of living with disability, the figure for women is eight years.

The number of people with disabilities is increasing because of the increasing life expectancy caused by an improvement in many areas, including medical advancement. People live longer, and at the same time, chronic illness is rising too. These changes impact the extent and significance of disability within the nation. As the age and number of people living with a disability increase, the healthcare system is facing new challenges, and at the same time, impairment becomes 'normalized' within society. To deal with these challenges, we need to adopt an inclusive approach in Australia by developing the most relevant health policy in this area. It is in this context that the Australian government has introduced NDIS. The author's analysis of this policy indicates that while the NDIS has moved away, to a certain extent from the dominant medical model, yet there is a long way to go to face the present and upcoming challenges within Australian society fully. To shed more light on these issues, it is important to compare the two models and perspectives on health care viewing people's health with disabilities. The Biomedical Model of Disability is the model that NDIS uses in providing its services.

THE BIOMEDICAL MODEL OF DISABILITY

The biomedical perspective on disability is narrow and only confined to impairment. As a result, the emphasis is on the deficit of individuals, including physical impairments such as, for example, blindness or deafness. Alternatively, emphasis is on the mental deficit, such as epilepsy, as an example. With this approach, the blame has been put on individuals with disabilities to normalize disability based on the deficit abilities of individuals. However, people with disabilities challenge such an approach and understanding of disability. Hunt (1966:146) argued that people with disabilities challenge the prevailing norms of society in five main ways: "as unfortunate, useless, different, oppressed and sick". It becomes apparent that by viewing disability as an individual health issue, then people with disabilities become 'abnormal'. Once this division is established, the obvious practical application would be that people with disabilities become labelled as 'patients'. According to Parsons' (1951), the 'sick role' legitimizes the medicalization of people with disabilities. Thus, the 'sick role' describes people with disabilities as socially responsible, how to act and how they are expected to seek treatments from medical practitioners to be 'repaired' or 'fixed'. That is a medicalized view of disability and is often called the medical model of disability (Albert, 2004).

It is interesting to note while the importance of the body in modern western society has been reported by Turner (1984) in his book *Body and Society*, the body for disabled people is the site of oppression both in form and what is done with it. For example, Sutherland (1981), on the use of sign language by deaf children, notes that "something evil, like wanting-things you do with your hands that you are not supposed to". The problem is primarily a medical one, the solution tends to be the cure and /or rehabilitation, and the outcome is social exclusion. That is carried out, usually by health professionals with the good intention of caring for and protecting people with disabilities.

The most harmful aspect of the medical model of disability is influencing people with disabilities to view themselves from this perspective. Thus, people with disabilities may internalize the negative message that all problems with people with disabilities stem from their so-called 'abnormal' bodies. This internalized oppression can make disabled people less likely to challenge their exclusion from mainstream society (Carson, 2009).

The biomedical model of health and disease is based on three philosophical and theoretical foundations and perspectives: "Rationalism" of Rene Descartes Philosophy, Positivism of August Comte,

and Structural-Functionalism of Talcott Parsons. The biomedical model is based on several principal/assumptions, including the following:

- “Dualistic assumption: the divide between mind and body located at the heart of the biomedical model,
- Reductionist: biological explanations of the disease are sought out from the observed behaviours of the body and the particles associated with the conditions,
- Experiment: knowledge is generated by observation and can be confirmed through a process of experimentation,
- Interventionist: medical knowledge can be applied to ‘repair’ damage or sick biological systems,
- Disease is an affliction of the body and is separate from the psychological and social processes of the mind.
- Every disease has a specific pathologic origin whose treatment can best be accomplished by removing or controlling its distinctive causes.
- The person as a unique individual is not included in the biomedical model” (Engel, 1981).

In the 21st century, the dominant biomedical model of healthcare has been facing a pervasive global challenge. Current health literature indicates that the dominant biomedical model of health care delivery is not sustainable and needs to incorporate a social model more effectively to improve healthcare for billions of people across the globe (Adibi, 2014). The current trend is to push for further recognition of the social model of healthcare within the human rights framework to view all individuals, irrespective of their gender, age, body forms, and mental characteristics, as human beings with equal rights and opportunities within society. These characteristics are discussed within the social model of disability.

SOCIAL MODEL OF DISABILITY

One of the prominent and relevant criticisms of the biomedical model is that this perspective does not consider the strong influence of structural factors in society on the health status of people, including people with disabilities. In explaining this approach, C. Wright Mills, an American critical sociologist, has offered a valuable and meaningful dictum: to understand the difference between ‘personal troubles’ and ‘public issues’ (Mills, 1959). The “personal troubles” are the problems experienced by the individual and related to those limited areas of the social life that directly or indirectly affect a person. Since individual factors cause them, it can just be solved with the desire of the individual to change them.

However, ‘public issues’ are usually caused by the structure of society or the failure of one or more of society’s institutions. Thus, the individual will see that ‘others also share these troubles, and that the solution is not to struggle individually but to join forces to change the situation. With such distinction, disability is not ‘personal trouble’, but it is very clearly a ‘public issue’. The Social Model of Healthcare provides a very different view of disability than the biomedical model within this context.

The Social model of disability was developed in the 1970s within the disability movement in the UK (Albert, 2004). It offered a radical alternative to the individualized medical conception of disability by asserting that people with disabilities were disadvantaged not because of their impairments but due to the limitations imposed on them by social, cultural, economic, political, and environmental barriers. By employing this perspective, disability is not about health or pathology but discrimination and social

exclusion. That, in turn, leads to different policy priorities and choices that governments must consider concerning removing the barriers based on the Human Rights approach.

By employing this approach, the Social Model provides a sharp distinction between impairment and disability. In discussing this distinction, Oliver (2009) points out that impairment is the functional limitations within the individual caused by physical, mental, or sensory impairment. Disability is, then, the loss or limitation of the opportunities that people with disabilities face in their engagements with the community on an equal level with other participants.

It would be helpful to point out that the medical model considers impairment as a given 'natural' property rather than a social product. Abberley (1987) provides a further explanation by stating that: "The general tendency has been that those impairments are not identified as the consequence of acute illness and infection to normal wear and tear on the human body. Any social involvement is presented as secondary or peripheral to the major identified patterns of 'natural causation'". In contrast, the view of the social model of disability is that the causes of impairment are established within the social, psychological, and environmental factors. For example, poverty, car accidents, poor nutrition diets and environmental pollutions can be mentioned in this area. The governments' policies determine all these conditions. Since the main focus of governments' policies in Australia is based on 'cure' and sustaining status quo rather than on prevention, thus there will be little progress to improve the quality of lives of people with disabilities drastically. Today, it has become common knowledge that improvement in public health, prevention in mental health, safe driving, affordable nutritional food and reducing inequality in many areas of life enormously improve the quality of people with disabilities. Even in stem cell medicine, improvements are promising but require more governments' investment in research. All this improvement will shift the focus from genetic to social and environmental factors in reducing the severity of genetic factors.

In this context, disability is understood as a social and political issue rather than a medical one. This definition then leads to critically questioning the value of medical interventions such as attempts to cure impairments or restore 'normal' bodily functioning. Instead, there are obvious needs to seek social and political solutions to challenge the existing discriminations that people with disabilities face in Australian society.

Thus, within this context, people with disabilities are considered oppressed and occupy inferior positions to others who do not have disabilities. In explaining the existence of this situation, Abberley (1987) argues that "these disadvantages are dialectically related to an ideology or groups of ideologies which justify and perpetuate this situation". Abberley further argues that such disadvantages and their supporting ideologies are neither natural nor inevitable.

One of the strong emphases of the Social Model of disability is on human rights perspective, which advocates for the elimination of discrimination that people with disabilities face as Albert (2004) argues that people living with impairment are as entitled as the rest of the population to a fulfilled life and the opportunity to contribute to society. Although disability services have been mainstreamed for several decades yet advocates of disability are pointing to the existence of some form of "social apartheid". For example, Germov (2014) states that. "There remain many symbols, physical and social barriers that create isolation and social exclusion, preventing a normal existence. That is reflected in a range of negative outcomes, including low incomes, poor health, difficulties in establishing intimate relationships and friendships, and weak labour market participation". One of the significant areas that disadvantaging people with disabilities are facing is paid employment. Many people with disabilities are willing to work, but they have less opportunity to work than people who do not have a disability. Begg et al. (2007), in

describing the gap between these two groups, state that the levels of employment of people with disabilities are 53 per cent compared with 81 per cent for people with no disability and even people with severe or profound limitation, the figure is only 30 per cent.

Some scholars developed and introduced Anti-Discriminatory and Anti-Oppressive theories for social work practice to change this discriminatory situation. For example, Nile Thompson (2006) introduced his 8 Steps Process to demonstrate and educate social workers and others to fully understand how discrimination goes through 8 Steps to be presented and used against people with disabilities. For example, in following discussions, Trish Hafford-Letchford and Christine Cocker (2014) expanded their analysis by stating that: "The concepts of anti-discriminatory and anti-oppressive practice have long been embedded in social work, but whereas once these may have offered an alternative critique of individual and societal relations, they have long become part of mainstream thinking and have lost their political edge". However, by acknowledging the contributions of anti-discriminatory and anti-oppressive theories so far, they are focusing on commitment to working with marginalized groups, including people with disabilities, within the context of diversity, equality, and social justice.

It is essential to point out that due to societal changes, the medical model of disability should no longer be sustained as the dominant model of disability in Australian society. One of the distinctive features of this change occurred through the rejection of the medical model of disability by people with disabilities themselves. Primarily they draw on their life experiences and their challenge of the discrimination they face daily. However, gradually, through their need to access resources in society to cope with their living conditions, they received further support from various corners in society, including academic research on social aspects of disabilities and ongoing critiques of the medical model of disability. Furthermore, their health and welfare attracted larger attentions from various sections of society to demand governments' policy change. People with disabilities were experiencing a lack of choice and control in their lives and challenging the embedding assumptions of the medical model of disabilities.

Australian political parties, particularly the Green and Labour parties, supported universal health care and supported the change of the existing disabilities services based on the traditional medical model, leading to continuous discrimination and social isolation of people with disabilities. All these forces aligned and came together when the Labour Party came to power in 2010 and introduced the NDIS. Now the question can be asked here is: does the NDIS has the capacity to meet the needs of people with disability? Moreover, a further question which is the aim of the present paper, is: does the NDIS respond culturally and adequately to the needs of people with disabilities from Culturally and Linguistically Diverse backgrounds. Based on the research, facts, and evidence, our detailed response to these questions will be offered in the following.

NDIS AND PEOPLE WITH DISABILITIES FROM CULTURALLY AND LINGUISTICALLY DIVERSE BACKGROUNDS

This part begins with a brief background introduction of the NDIS and its impact on trial years on people with disabilities. It then focuses on how people with disabilities from Culturally and Linguistically Diverse Backgrounds receiving these services and facing particular barriers. The Federal Labour Government introduced the National Disability Insurance Scheme (NDIS) in 2012. This reform has provided necessary and relevant support for people who have a significant or permanent disability in Australia. The

The Australian National Disability Insurance Scheme During COVID-19

delivery of this reform has been taken up by the National Disability Insurance Agency (NDIA). The first trial of NDIS began on July 1 2013, and some of its major features have been as follows:

- The NDIS is the second-largest reform after Medicare in Australia. It has far-reaching effects throughout the disability services sector and beyond.
- By introducing this reform, the Australian Commonwealth Government is undertaking distinctive responsibility in disability, including expenditure.
- It is estimated that the schemes' annual cost is nearly \$14 billion which is, more than the current annual cost of the Pharmaceutical Benefits Scheme (\$10 billion) and not substantially less than the current annual cost of Medicare (\$18 billion) (Buckmaster, 2013).
- NDIS provides all Australians with disability insurance. It ensures that Australians will have access to necessary services when and if they experience disability.
- It also provides information and referral services to individuals who are affected by disability.
- NDIS has changed disability services from charity-based care into universal care.
- Under this scheme, people with disabilities choose to select their providers and choose their relevant services.
- It is estimated that 410,000 Australians who have a significant and ongoing disability will use NDIS services

The Australian government committed to providing \$1.0 billion over four years to implement the first stage of the NDIS. The scheme was established in four locations and began in 2013-14. Around 10,000 people with disabilities used NDIS services in the first year of its implementation. It was estimated that in 2015, the number of people with disabilities would increase to 20,000. However, as stated earlier, it is estimated that NDIS will provide long term care for 410 000 Australians who have significant and ongoing disabilities (Buckmaster, 2013). The third round of the NDIS started in 2016. In Queensland, and by the end of 2019 will be fully implemented in other parts of Australia. It is also estimated that around 97,000 people in Queensland who have an ongoing disability will be using NDIS services in 2019. The Queensland Government committed in 2012 to provide some \$868 million in several instalments to the scheme by 2019. In this process," the Commonwealth and Queensland Governments on September 25 2015, announced an early transition to the NDIS in Townville, Charters Towers and Palm Island" (Department of Communities, Child Safety and Disability Services).

UPDATE ON THE FUNDING NDIS

In its Annual Report in 2013-14, NDIA distinctively pointed out that the cost will increase as NDIS services continue. This has been the case in each Annual report since then. Considering the scheme's sustainability, the upward projected cost in 2020-21 has been estimated to be \$24.6 billion. Elliott King, in his article, provides more detailed information in this area. King writes: "According to the latest NDIS Quarterly Report between July 1 and December 31 2020, \$10.9 billion in payments were made to participants, supporting around 433,000 people ". It is forecasted that the cost for social services will reach \$33.3 billion by 2024–25 (Portfolio Budget Statements 2021-2022)

There are two primary sources of funds. The first and foremost solid basis of funding NDIS is taxation: increasing the Medicare Levy to 2.5% (King, op cit). The second source is from the savings of social

welfare. Michael Klapdor writes:” The Government will direct around \$1.3 billion in net savings from social welfare payment expenditure towards the National Disability Insurance Scheme (NDIS) Savings Fund”. In summary, although the Productivity Commission from the start of the scheme considered several sources for financing NDIS, the final decision is that the Australian government is the single funder of the NDIS.

Disability advocates and service providers have welcomed the scheme. To understand the degree of their support, the critical points of six reviews on the scheme are presented as follows:

1. In their review, Michele Foster et al. (2012) focused mainly on two central concepts of ‘entitlement and personalization. In analyzing personalization, they write: “while generally personalization initiatives have been positively perceived, their operation has posed unique challenges for front-line workers and traditional models of care” (P.332). They conclude: “Personalization involves reframing financing, governance and service delivery” (P.332). They further argue that there exist the inherent tensions between both entitlements based on need and personalization and asking: “how these inherent tensions would be resolved and how the desired outcome will be ascertained”. (P.334). While they have raised interesting questions for discussions, they are short of providing tangible conclusions of NDIS within the socio-cultural contexts of Australian society.
2. In their article, Barbara Fawcett and Debbie Plath (2013) assess critical features of the National Disability Insurance Scheme and attempt to explore underpinning conceptualizations of ‘disability’, ‘autonomy’, choice’ and ‘assessment’. The first point of their discussion relates to welcoming the provision of care services to people with disabilities and government injection of funds. However, they question the social model of disability that NDIS is presenting. They argue that “details of the proposal sit squarely in line with individualized/medicalized orientations, with care package policies, including ‘cash for care’ reflecting liberal/market rather than human rights perspectives” (Fawcett & Plath 2012). Furthermore, the authors value the focus of NDIS on choice and control. They believe that these have the potential to empower people with disabilities. At the same time, they caution Australian Governments that NDIS must ensure that those many individuals who experience inequity within the intersectional framework must not be further disadvantaged. To ensure this, they suggest that social work and human service professionals can be actively involved in contributing to the scheme’s implementation.
3. In their review, Jenny Green and Jane Mears (2014) focused on the person-centred approach and its potential benefits and disadvantages. They argue that while there are potentially overwhelming benefits, there are also potentially significant losses. In their conclusion, the authors state that “all of the reports reviewed for this paper highlighted, alongside the positive experiences of those already receiving individual support packages, that there is much confusion, misunderstanding and anxiety from providers, employees and people with disability. Implementation inevitably is complex” (Green and Mears, 2014:9). The authors conclude their paper with the following quotation from Cortis et al. 2013).

“Cortis et al. (2013) summarise a way forward to take account of the interests of organizations, employees and people with disabilities. It is referred to as the ‘high road’ strategy (Folbre, 2006). It requires higher costs and investment in the short term to support organizations and individuals through the transition and establishment of person-centeredness. Implemented effectively, it will lead to more sustainable and higher quality service delivery in the immediate and longer terms with ‘better outcomes for people with

disabilities, and a more efficient and cost-effective system of care” (Cortis et al. 2013:43). “We need to follow this high road” (Green and Mears, 2014).

4. Stephanie Backhouse (2017), in her thesis “Who loses out in the NDIS?” provides a detailed discussion on how the NDIS model indicates significant opportunities for people with disabilities who can make decisions on using the required services based on their needs. However, she also analyses how these opportunities are a constraint for the most vulnerable people. Within this context, she points out that those who have supported can access the NDIS, and those with no support will not have access to those services. She concludes that “the original intent of NDIS is compromised by a political discourse of privatization and marketization. As a result, some groups of people with disability may be left behind in a user-led system”.
5. Some other researchers also question the capacity of NDIS to meet its aims for people with disabilities from culturally and linguistically diverse backgrounds. They argue that these people with disabilities are already at risk of disengagement from support systems and risk social exclusion and marginalization (Wadiwel and Cooper, 2013 & Soldatic, Toom, Dowse and Muir, 2014). In this discussion and analysis, the author argues that, at present, the NDIS appears to have little capacity to respond to the complex needs of people with disabilities from CALD backgrounds.
6. Jacqueline Nhu Quynh Pho and her colleagues, in their systematic review (2021), did not engage in discussion on the ideological basis of NDIS. Instead, they have focussed their paper on describing the gaps in support service needs of individuals from culturally and linguistically diverse backgrounds. Their findings can be summarised in three areas: removing barriers to employment, acknowledging this group’s particular health needs, and cultural awareness and competency in providing health and support services to people with disabilities from culturally and linguistically diverse backgrounds.

However, before engaging with the discussions, it is useful to point out that people with disabilities from Culturally and Linguistically Diverse backgrounds are not the only marginalized group having less access to NDIS’s services. It is possible to identify four other distinguished groups of people with disabilities who are the most vulnerable and facing the risk of becoming more marginalized in the NDIS dominant model of care. They include indigenous people with disabilities, people with disabilities living in remote areas of Australia, people with severe and complex disabilities, and people with disabilities in prisons. However, discussions in these areas are beyond the scope of this paper, and the focus is solely on people with disabilities from CALD backgrounds who are facing double discriminations and underutilizing the existing NDIS services. This is also true for Indigenous Australians and how their culture is ignored in health policies that the Australian government develop for these people in their research focussing on this very important point and state: “While Aboriginal and Torres Strait Islander people have long understood the role that culture plays in health and wellbeing, the elucidation of the cultural determinants of health is more recent and ‘still is ignored in Australian governments’ health policies’ (Summer et al., 2021).

THE MARKET APPROACH OF NDIS AND PEOPLE WITH DISABILITIES FROM CULTURALLY AND LINGUISTICALLY DIVERSE BACKGROUNDS

The National Institute of Labour Studies at Flinders University has undertaken two studies, so far, on NDIS. These studies and evaluations are called ‘trial’ and ‘intermediate’ and taken by a Flinders’ academic team. The significant stakeholders have supported these evaluations, including the Department of Social Services, the National Disability Insurance Agency, the Department of Human Services, and the Project’s Steering Committee. These reports are on New South Wales, Victoria, South Australia, Tasmania, Northern Territory and the Australian Capital Territory. In these reports, around 7790 people with disabilities and their family members have been surveyed. In addition, approximately 3,102 disability service providers and their workforces have been surveyed. Researchers also interviewed 123 people with disabilities and their families and carers, 49 service providers, 29 disability organizations and 87 NDIA staff (Mavromaras, Kostas, Mahuteau, Stephane and Moskos, Megan., 2017 NDIS Evaluation).

The findings and conclusion of these reports indicate overall improvements in the area of choice and individual control. The report provides a more detailed picture: almost 50% of participants responded positively by undertaking a closer investigation. That means that they are better off compared to their previous situation, i.e., before joining NDIS. However, the finding also indicates that 15 per cent of participants responded that they are worse off. The remaining populations also noted that their situations had not been changed, so they are about the same (Mavromaras, Mahuteau and Moskos, 2017).

In discussing the majority of 15 per cent of people with disabilities who report that they are worse off, the report points to people with disabilities who were unable to effectively advocate for services on their behalf. People with disabilities from Culturally and Linguistically Diverse backgrounds constitute a significant part of this group. Due to cultural differences, these people have severe difficulties adapting to the new situation and even having more problems with the NDIS’s complex registration process and having access to its services.

In addition to those problems identified in the report, from our research, there are many other significant cultural and adjustment problems that people with disabilities from Culturally and Linguistically Diverse backgrounds are experiencing. Disabilities are no longer a hidden phenomenon within Australian society and are increasingly becoming an ‘accepted and legitimized’ and ‘normalized’ feature. That is mostly due to the establishment of NDIS. Yet, at the same time, many people with disabilities from Culturally and linguistically diverse backgrounds due to their perceptions of ‘disability’ may not consider themselves “disabled”. Therefore, they may not have enrolled in NDIS’s program. An analysis of these situations provides the following detailed reasons:

1. There are different perceptions of “disability” within other ethnic communities within Australian society.
2. ‘Disability’ is considered a deficit of the individual, and its acknowledgement requires the empowerment of individuals within new environments.
3. NDIS’s definitions of “disability” may not have been well understood by many people from a Culturally and linguistically diversified backgrounds.
4. Many people with disabilities might not apply the label to themselves because of the discrimination and stigma associated with it — for example, older people who acquire impairments but do not consider themselves disabled. Since NDIS does not apply to those over 65 years older so this

group is excluded from the outset. That results in people with disabilities not receiving assistance. This issue needs to be further researched and publicly discussed (Harpur, 2016).

5. Many people from the CALD groups and Indigenous Australians or homeless people do not use disabilities services due to their accessibilities (See AMPARO Advocacy Inc.).
6. Some people with disabilities may not consider their disability as permanent as required by the NDIS. This context is still not clear. For example, does periodic severe mental illness can be considered legitimate for the NDIS or not? (Fisher, 2016).
7. Some people from a CALD background who do not have support for using and navigating the system do not register with NDIS. People with multiple and complex support needs are an example of this exclusion. The diversity and complexity of these groups require in-depth study and analysis, which is beyond the scope of this paper.

People with intellectual disabilities and complex support needs are likely to represent a significant proportion of the NDIS's anticipated 410,000 participants (National Disability Insurance Scheme, 2015). These people represent a substantial proportion of the potential NDIS market, not just in terms of numbers but also the extent of the services they need. This paper focuses on people with intellectual disabilities and complex support needs from cultural and linguistically diverse backgrounds within this context. Australia has a unique history that has shaped the diversity of its peoples, their cultures and lifestyles today. Today, Australia's population of over 24.6 million is one of the most culturally and linguistically diverse populations globally. The 2016 Census, while confirming the changing face of Australia, clearly shows that nearly half (49 per cent) of Australians had either been born overseas (first generation Australian) or one or both parents had been born overseas (second generation Australian).

However, the available data on the number of people from Culturally and Linguistically diverse backgrounds living with a disability is currently insufficient. Relying on the country of birth as an indicator of cultural and linguistic diversity is not a sound indicator of identifying cultural and linguistic diversity. However, within this constraint, the 2016 Census shows that one in five Australians now speak a language other than English at home. The number has increased by almost 1 million from 2011 to 4.9 million, 21% of the Australian population of 24.6 million in 2016. The Census also reveals that there are over 300 separately identified languages spoken in Australian homes. The number of people with low English proficiency has also jumped to almost 820,000. This data reveals that Australia is fast-changing and ever-expanding as a culturally diverse nation, and cultural diversity is irreversibly our demographic norm and strength. Diversity also exists in many other areas, including culture, religion, gender, sexuality, and disability.

The successful sustaining of this diversity has relied heavily on the Australian government's inclusive policy for the required services of minorities in Australian society. One such service relates to people with disabilities from Culturally and Linguistically diverse backgrounds. The National Ethnic Disability Alliance (NEDA) is the national peak organization representing the rights and interests of people from a non-English speaking background with a disability, their families, and carers throughout Australia. According to NEDA, one in every four people with a disability is a person of either first or second generation of non-English speaking background (NESB), representing approximately 1 million people across Australia. Of this, over 120,000 people will fall into NDIS's third tier, people with significant care and support needs which NDIS describes as having a permanent and irreversible disability (NEDA).

With such a large population, the NDIA has acknowledged that all sites have lower than expected Culturally and Linguistically diverse backgrounds participants with only 4% with approved plans as of

June 30 2016 (NDIS Quarterly Report to COAG Disability Reform Council June 2016). Even the participation rates from people with disabilities from CALD are much lower in some states, for example, 2.5% in Queensland (NDIS Quarterly Report to COAG Disability Reform Council June 30 2016). A report from AMPARO Advocacy Inc. (2017) by analyzing this situation state that: “The lower levels of participation by people from CALD backgrounds at a National and State level in the NDIS, reflects a system that has been designed and developed with policy, processes and communication and engagement strategies that so far are struggling to meet the needs of CALD communities”.

The report also concludes that by addressing decades of disadvantaged experiences of people with disabilities from CALD groups, now it is the time that “mistakes of the past are avoided, and NDIS incorporates as a matter of priority, genuine and well-resourced access and equity measures into the core business of the NDIS”. Some of these people experience multiple and intense forms of disadvantage. These include more than one form of disability, substance abuse, poverty, mental illness, psychosocial disability, homelessness, ill health, and violence (Churchill, Sotiri and Rowe, 2017).

Large numbers of vulnerable people with complex disabilities from CALD backgrounds have several socio-cultural characteristics that place them at the bottom of the ladder to access the required services from NDIS. Then, NDIS must develop a dedicated communication strategy with the multicultural community to ensure that its services are accessible and understood by all people with disabilities from the CALD community. NDIS also must address the current under-utilization of disability services by people from NESB and or/CALD.

One of the significant factors for underutilization of disability services by people from NESB relates to cultural factors, settlement needs, and the integration process within Australian society. Research indicates that in accessing Australian Government disability services, there are significant differences between people from English Speaking countries and those from NESB.

For example, according to the Productivity Commission Report of 2009, the proportion of people born in a non-English speaking country who use Commonwealth, State and Territory funded accommodation support and employment services are lower than the proportion of people born in an English-speaking country who use these services. The Productivity Commission Report further stated that people with NESB background and with disabilities are approximately four times less likely to receive Accommodation Support Services than people born in English Speaking countries; they are also 2.5 times less likely to receive Community Support Service and Community Access Services 3 times less likely to receive Respite Services and two times less likely to obtain employment services than those who are born in English Speaking countries (Productivity Commission *Report on Government Service* 2009).

Poor access to services, education and employment opportunities means isolation and marginalization for many people from NESB with a disability, their families, and carers. People with an intellectual disability from CALD backgrounds will likely experience multiple forms of discrimination throughout their lives. They are likely experiencing discrimination from the broader community due to their ethnicity and discrimination from both within their cultural group and the broader community due to their disabilities. In particular, people with an intellectual disability will have language and communication difficulties in understanding how services operate and having access to the required services and the existing support services and experience financial vulnerability and reduced capacity to participate in social, economic, political, and political-cultural life in the community. The National Ethnic Disability Alliance (NEDA) clearly describes this situation. It reveals the scope of difficulties by stating that three-quarters of people with disabilities from CALD backgrounds miss out on accessing disability services and supports.

The Federation of Ethnic Communities Councils of Australia surveyed in 2011 under the title of “Engaging people with disability in the multicultural sector. Barriers to accessing services and employment”. The survey was completed by 44 multicultural advocacy organizations and service providers. The majority of these organizations (60 per cent) employed under 50 staff, and 40 per cent of the organizations did not employ people from CALD backgrounds with disabilities. Half of the organizations (22) indicated that over ten people from CALD backgrounds living with a disability access their services every week. Some of the other important findings are as follows:

1. People with disabilities from CALD backgrounds lack awareness of services and their availability. That indicates that some are missing out on services specifically tailored for them. That also shows that lack of accessible information and complex service systems are additional factors impacting the levels of awareness among CALD clients.
2. The second important finding relates to the existence of stigma and fear. Stigma in the community and the issue of disability are still being treated as ‘taboo’. There still exist perceptions within some communities that people with disabilities cannot undertake education or employment. These perceptions exist within some CALD communities and some service provider organizations, which is highly alarming. Another barrier was fear experienced by CALD people with a disability. Their needs would not be understood or accommodated, and staff may not be fully aware of cultural sensitivities. That will result in them turning to their families for care.
3. Other findings of this survey relate to language and communication barriers of people from CALD, accessibility of venues and transport as a significant issue.

Analysis of the present NDIS policy suggests that individuals’ responsibilities are to prove their eligibility for supports funded by NDIS on a case-by-case basis. One of the underlying principles of NDIS on individual choice assumes that NDIS’s participants are knowledgeable and make informed choices. That raises several issues for those whose experience of disability is tied to complex and intractable social disadvantages, such as those from CALD backgrounds. Research shows that people from CALD find it challenging to use and navigate NDIS’s process and system. Thus, the implementation of the NDIS must include strengthening the capacity of individuals to navigate the free market and make informed choices about the services that respond to their requirements, including their cultural needs. It can be concluded that people with disabilities who are already at risk of disengagement from support systems become more marginalized within the existing NDIS context

Based on the existing literature, we recommend that NDIS service providers first and foremost understand and value cultural diversity. It is also essential to understand the individual identity of a person from a CALD background. On this basis then, the providers need to develop appropriate strategies to address additional needs and vulnerabilities arising from people facing double discrimination due to cultural/linguistic differences and disability.

Service providers working with people with intellectual disabilities from CALD backgrounds need to consider their cultural competence strongly. Cultural competence offers a framework to improve service delivery to clients from culturally and linguistically diverse backgrounds. NDIS providers must embed cultural competence within their organizations. There are details on what cultural competence in practice looks like and how to remove some unconscious prejudice. These are available in various manuals that can be adopted by service providers (Directory of key contacts & NHNRC 2005).

Furthermore, the Australian multicultural policy cannot be isolated from discourses of substantive equality and human rights. Just as the multicultural policy must embrace diversity and social inclusion, recognition of multiculturalism is an essential foundation for any human rights framework (Graeme Innes, Race and Disability Discrimination Commissioner).

HOW NDIS HAS BEEN TRAVELLING DURING THE POST-TRIAL PERIOD

People from various sectors of Australian society, including people with disabilities, political parties, governments, medical sectors, and alliance and disability supporters, strongly believe in the NDIS. They believe it is and will be a fabulous scheme. NDIS is delivering reasonable and necessary supports for some, but at the same time, others are missing out. Believe NDIS is not responding properly to many people with disabilities. Covid19 had a different impact on people with disabilities. This has to do with three factors: the first factor is that most people with disabilities have much-reduced access to their routine healthcare; the second reason is that people with disabilities face higher risk; finally, most people with disabilities have fewer resources mitigate the pandemic. Even these conditions have become harder for people with disabilities from Culturally and Linguistically diverse backgrounds (Pijls, BG, Jolani, S, Atherley, A, et al., 2021).

The NDIS Quality and Safeguards Commission undertook a study on the death of people with disabilities. Some of the findings of this study include:

- People under age 65 using disability services were 4.7 times as likely to die compared to the general population under age 65.
- People with a disability had higher rates of potentially avoidable deaths. For example, People with a disability had a crude rate of 240 potentially preventable deaths per 100,000 people, which was 3.6 times as high as the general population after adjusting for age.

Although there is a breakdown of these deaths based on the kind of disease, age and gender, there was no indication relevant to the culture and immigration among NDIS participants. However, eight people who access Australia's National Disability Insurance Scheme have died from Covid-19 since the start of the pandemic (Guardian,2020). This information becomes publicly available through the Disability Royal Commission. It can be inferred from this data that people with disabilities from culturally and linguistically backgrounds occupy the lowest level of social status within Australian society. Furthermore, the NDIS continues to face challenges in accommodating diversity within its culture and services.

Finally, during the Covid19, NDIS has been confronting several issues of its structure and services and serious concerns of its participants. The investigation has been conducted, and a report discussed some of these issues in more detail. A summary of them presented by Doran (2020) include 'frustrations with the administration and bureaucracy of NDIS', 'stable funding support for recipients', 'more health interaction with NDIS staff', 'flexibility for how recipients use NDIS funds', and 'making funding plan easier to understand by all recipients. However, one of the major issues that NDIS faces relates to the Australian government's plan to reassess all NDIS recipients' plans to save costs. The discussion has been turned into a 'public battle', and the government plan has been rejected by opposition political parties as well as NGOs and all organizations and Alliance 20, who are supporting people with disabilities and asking for more improvements in NDIS services

CONCLUSION

After the Australian Medicare System, NDIS is the most significant healthcare reform in Australia in recent time. This reform is costly, with an estimated annual cost of over \$14 billion in 2012. It is designed to provide universal care for people with permanent and severe disabilities in Australia. The prominent characteristic of this reform is that NDIS replaces charity-based schemes which existed for decades in Australia. One of the significant social contributions of the NDIS is that it is reducing the stigma of “disability” and ‘normalizing’ it within Australian society. One of the unintended consequences of this change is reducing the social isolation of people with disabilities. Another characteristic of NDIS relates to its approach as market orientation, emphasizing person-centred approaches, including the support packages aimed at meeting the individual people’s needs. Therefore, based on a liberal/market perspective, NDIS provides individuals with the opportunity to choose their service providers within the context of ‘cash for service’.

In discussing the universal nature of this reform, NDIS provides three tiers of support to people with disabilities in Australia. That includes 1) the provision of information and referral services to those individuals who are experiencing disability; 2) The opportunity of all Australians to access the needed services in case they experience disability due to accidents, and 3) the NDIS aims to provide individualized packages of quality care and support to all Australians with ongoing and significant disability. It is estimated that 410 000 Australians will benefit from the scheme. However, in the 2021-22 Portfolio Budget Statement (PBS) for Social Services, it is forecasted that the cost will reach \$33.3 billion by 2024–25, and the number of participants will exceed over 500,000 people.

The NDIS has received a positive welcome from service providers and people who advocate for people with disabilities in Australia. However, before and during the operation and of the scheme, some scholars and researchers have offered arguments and discussions on various issues relating to the conceptualization of the scheme and its ideological underpinnings. They consider NDIS as a liberal/market perspective and its implementation within governments’ new-liberal social policies. They also highlight the positive experiences of those already receiving individual support packages. However, there is still some uncertainty, misunderstanding and anxiety from providers, employees, and people with disabilities. The overall conclusion of major reports indicated an overall improvement in choice and control advocated by NDIS for every people with a disability. However, research findings also clearly show that about half of the participants are better off than before joining NDIS. About one third indicated that they are about the same, and about 15 per cent indicated that they are worse off.

During the Covid19, NDIS has been confronting several issues of its structure and services and serious concerns of its participants. The investigation has been conducted, and a report discussed some of these issues in more detail. A summary of them presented by Doran (2020) include ‘frustrations with the administration and bureaucracy of NDIS’, ‘stable funding support for recipients’, ‘more health interaction with NDIS staff’, ‘flexibility for how recipients use NDIS funds’, and ‘making funding plan easier to understand by all recipients. However, one of the major issues that NDIS faces relates to the Australian government’s plan to reassess all NDIS recipients’ plans to save costs. The discussion has been turned into a ‘public debate .’ The government plan has been rejected by opposition political parties, NGOs, and all organizations and groups supporting people with disabilities.

However, among the groups worse off, people with disabilities from CALD backgrounds stand out. About 21 per cent of the total population of Australia, 3.4 million, speaks a language other than English at home. Of this estimation, around one million have disabilities, and 120,000 have severe and permanent

disabilities. These people already are at risk of further social exclusion leading to further marginalization. Currently, people with disabilities from CALD backgrounds are underutilizing the NDIS services and have low participation rates. The overall participation rates of people from CALD backgrounds indicate that only 4% had approved plans on June 30 2016. This participation rate differs within the states and is much lower in several states. For example, this rate is about 2.5% in Queensland. This indicates that NDIS needs to seriously investigate this situation and remove discrimination by providing services to people with disabilities from CALD communities.

It is also recommended that NDIS service providers must understand and value cultural diversity within Australian society. On this basis then, the providers need to develop appropriate strategies to address additional needs and vulnerabilities arising from people facing double discrimination due to cultural/linguistic differences and disability. This constructive approach needs governments to sustain some elements of the social model of care for those in serious need. That requires the provision of effective legislative and policy direction to achieve proper and timely government interventions. The pace of change depends not only on the supporters of the social model of care but also on public support mostly achievable through general education. Because of present government policies, there is a strong need to influence public opinion to sustain some social care elements alongside NDIS policies.

Furthermore, people with disabilities from culturally and linguistically diverse backgrounds have faced many barriers to inclusion in the COVID-19 response. More importantly, the many lockdowns within Australia during the Covid19 pandemic proved again that these people with disabilities are worse off and more excluded. The lockdown measures societies have taken during the COVID-19 pandemic have meant people with disabilities are worse off and more excluded. This requires greater attention and support from all Australian governments to strengthen their inclusion policies to include these people.

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Chapter 4

Spreading Stochastic Models Under Ising/Potts Random Fields: Spreading Diseases

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ABSTRACT

Stochastic models have become a powerful necessary statistical tool to estimate parameters where data are represented by regions of interests under uncertain areas. Due to the high dimensionality of the spatial patterns, investigation of the stochastic modeling simulations must be applied based on spatial variability. Models for spreading diseases are given based on whether or not the disease succeeds or fails to appear in the region. Based on this assumption, an Ising/Potts random fields model has to be introduced to analyze the spatial pattern of spreading. In this work, the spatial pattern models for spreading diseases have been analyzed considering Markov random fields auto-models. The Gibbs sampler would be used to simulate example images for various parameter combinations. In this work, a spatial analysis methodology based on Bayesian analysis was introduced, and procedures to solve the problem with spatial variability are described based on spatial model estimation techniques.

INTRODUCTION

The spreading diseases process involves investigations of the interactions between regions at different scales considering spatial homogeneity. Based on the spatial homogeneity, modeling of spatial patterns has to be applied, leading us to analyze specific neighborhood connectivity between areas (Zimeras and Matsinos, 2011; Gerritsen and Caers, 2013). Modeling the spatial neighborhood structure could be achieved by analyzing interactions between sub-patterns considering Markov random fields where the neighbouring local structure is under investigation (Zimeras, 1997; Jansen, 1998).

DOI: 10.4018/978-1-7998-9198-7.ch004

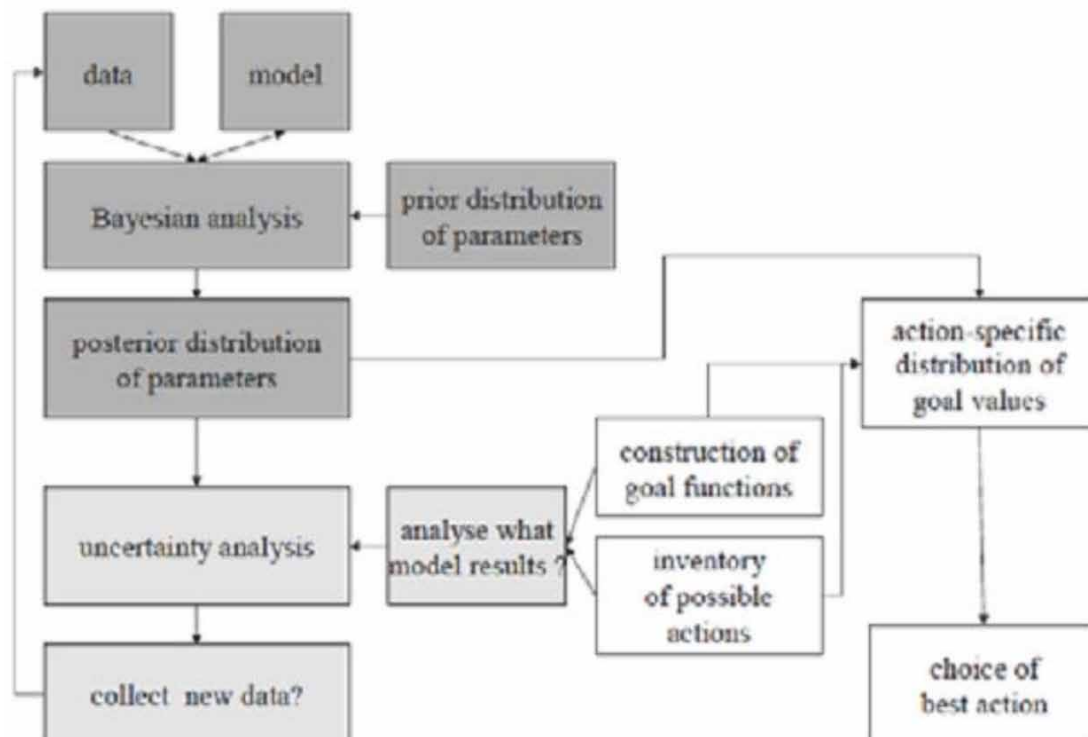
Modeling the spreading process under Markov random fields due to duality (success and fail) for the virus appearing, a specific model must be introduced, leading us to the definition of Ising / Potts random models. These models are based on the spatial connectivity between different regions under homogeneity, considering various variability of spreading. Under the implementation of this variability, uncertain regions have appeared, and modeling of them must be introduced, considering Monte Carlo Markov Chains (MCMC) techniques, especially Gibbs sampler or Metropolis-Hastings methodologies. These techniques are based on the Bayesian analysis where conditional distributions of the parameters in a sub-region given the full parameters of the whole region could be defined.

BAYESIAN UNCERTAINTY

Bayesian statistical methods under uncertainty conditions could be implemented by calculating probabilistic predictions. The procedure has three stages: (1) determination of the prior probability distribution for model parameters, (2) construction of a likelihood function for the statistical model, and (3) derivation of the posterior probability distribution for the parameters by using the Bayes rule to adjust the prior distribution based on the observed data (Katz, 2002).

Statistical estimation techniques can be used to determine the parameters of the distribution. These techniques are helpful to estimate probability distributions from available data or by collecting a large amount of them (Figure 1) (Jansen et al., 1998)

Figure 1. Bayesian statistic uncertainty analysis (Jansen et al., 1998)



Under Bayesian analysis, modeling of the uncertain regions could be illustrated by introducing hidden models due to the high dimensionality of the process (Morgan and Hemion, 1990, Klepper, 1997, Katz, 2002). In confidential information, hidden models could be denoted, and an estimation procedure could be applied based on hidden Markov Models. These models can be used to estimate confidential information based on Markov random fields models where spatial homogeneity between regions is taking place (Zimeras, 1997; Zimeras and Matsinos, 2011; 2012; 2019). The advantage of these models is that they need only the local characteristics between neighboring regions. Models that can explain the spatial patterns considering conditional p.d.f. functions are defined as auto-models (Zimeras, 1997).

Markov Random Fields Modeling

Markov random fields are necessary where local characteristics of the image presentation could be represented by neighborhood connectivity between regions (Besag, 1974; 1986, Cross and Jain, 1983 and Aykroyd et al., 1996; Zimeras, 1997).

Based on this modeling, a two-dimensional space, S , is partitioned into n pixels (discrete or continuous), defining a state-space $\Lambda_i = \{1, 2, \dots, n\}$. Let X_i be a random variable assigned to a pixel x_i and $\mathbf{X} = (X_1, X_2, \dots, X_n)$, be a random variable vector for an image, then an intensity $\mathbf{x} = (x_1, x_2, \dots, x_n)$, with $x_i \in \Lambda$ can be assumed as a realization of $\mathbf{X}$; $p(\dots)$ denote the conditional probability distribution of X_i given the other arguments. The configuration space for the variable $\mathbf{x}$ is denoted by Ω with $\Omega = \prod_{i \in S} \Lambda_i$.

For simplicity, each pixel of the finite lattice can take colors from the set $\Lambda = \{0, 1, 2, \dots, c-1\}$. Site j ($\neq i$) is said to be a neighbor of site i iff the functional form of $p(x_i | x_1, \dots, x_{i-1}, x_{i+1}, \dots, x_n)$ is defined upon the variables x_j

$$p(x_i | x_1, \dots, x_{i-1}, x_{i+1}, \dots, x_n) = p(x_i | x_{\partial i})$$

where ∂i is the set of pixels which are neighbours of pixel i and $x_{\partial i}$ is the set of values of pixels which are neighbors of pixel i (Zimeras and Georgiakodis, 2005; Zimeras, 2006)

A neighborhood system $N = \{N_i, \forall i \in S\}$ is a collection of subsets of S . The symmetry property is based on the following

- (i) $i \notin N_i$ (a site is not part of its neighborhood)
- (ii) $j \in N_i \Leftrightarrow i \in N_j$ (i is in the neighborhood of j if and only if j is in the neighborhood of i)

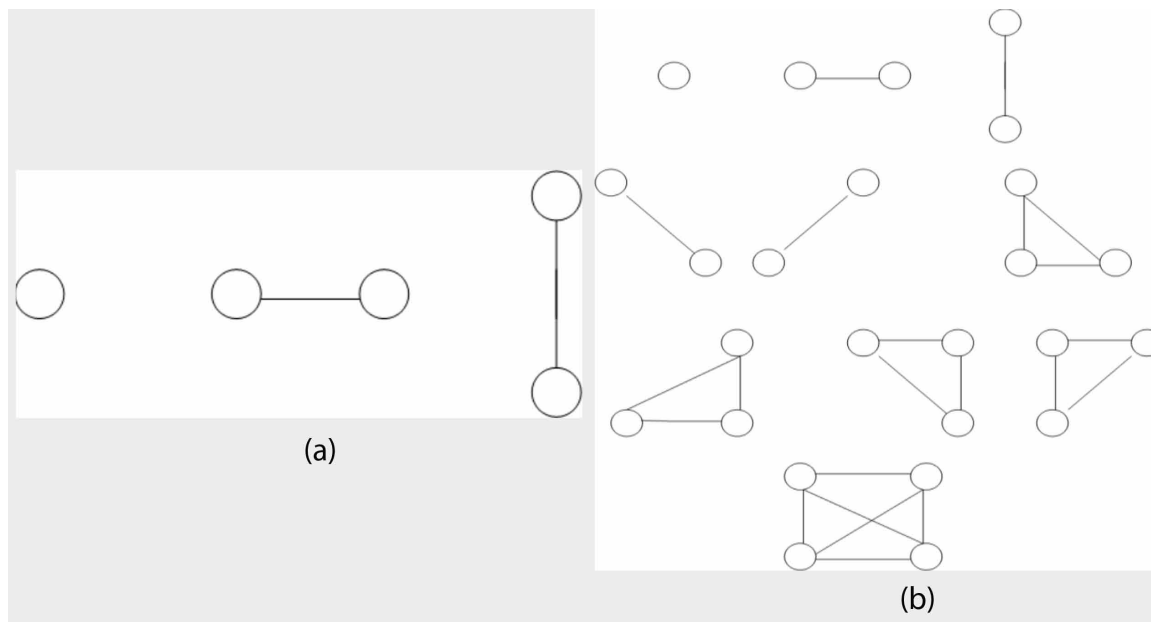
The most usable neighbourhood system in image analysis is the first-order neighbours of a pixel (four neighbouring pixels) (Figure 2 a) and second-order neighbours (including the four corner pixels) (Figure 2).

Figure 2. First-order neighbours (a); second-order neighbours (b)

	$X_{i-1,j}$		$X_{i-1,j-1}$	$X_{i,j-1}$	$X_{i-1,j+1}$
$X_{i-1,j}$	$X_{i,j}$	$X_{i+1,j}$	$X_{i,j-1}$	$X_{i,j}$	$X_{i,j+1}$
	$X_{i+1,j}$		$X_{i+1,j-1}$	$X_{i+1,j}$	$X_{i+1,j+1}$
(a)			(b)		

A clique C is a subset of S for which every pair of sites is neighbors. Single pixels are also considering cliques. All cliques on a lattice are called C . Cliques are important when considering the equivalence between MRFs and the Gibbs distribution. Figure 3a illustrates the set of cliques for the first order or nearest-neighbors system with form: $\{(i, j)\}$, $\{(i-1, j), (i, j)\}$, $\{(i, j-1), (i, j)\}$. Similar types of clique sets for the second-order system are given in Figure 3.

Figure 3. Clique type for first-order neighbors system (a) and clique type for second-order neighbors system (b)



A Markov random field (M.r.f.) is a joint probability density on the set of all possible coloring values $\mathbf{X}$ on a finite lattice D subject to the following conditions (Besag 1974, 1986; Cross and Jain, 1983)

1. $p(\mathbf{x}) > 0$ for all $\mathbf{x} \in S$. (Positivity).
2. $p(x_{ij} | \text{all points } (i,j)) = p(x_{ij} | \text{neighbours})$. (Markovianity).
3. $p(x_{ij} | \text{neighbours } (i,j))$ depends only on the configuration of the neighbours (Homogeneity).

The probabilities on condition (2) are called local characteristics, which can be expressed as $p(x_i | x_j, i \neq j) = p(x_i | x_{\partial i})$ denoting a Gibbs distribution; $p(\mathbf{x})$ is a jpdf of $X_i \in S$ under any neighborhood model $\mathbb{I}$. Under the Hammersley-Clifford theorem (Hammersley and Clifford, 1971; Besag, 1974; Kindermann and Snell, 1980), an MRF can equivalently be characterized by a Gibbs distribution. Then Gibbs distribution can be expressed based on the following form:

$$p(\mathbf{x}) = \frac{1}{Z} \exp \left\{ -\frac{1}{T} [U(\mathbf{x})] \right\} = \frac{1}{Z} \exp \left\{ -\frac{1}{T} \left[\sum_{c \in C} V_c(x_c) \right] \right\}$$

where C are all the potential cliques, Z is the normalized constant/partitions function, T is the temperature with $T=1$, and $U(\mathbf{x})$ is the energy function with (Geman and Geman, 1984)

$$U(\mathbf{x}) = \sum_{c \in C} V_c(x_c)$$

Auto-models are a particular subclass of Markov random fields introduced in Besag (1974) and further studied in Cross and Jain (1983), Besag (1974; 1986) and Aykroyd et al. (1996). The energy function based on these models is depending only upon the cliques no more than two sites which are called second-order energy:

$$U(\mathbf{x}) = \sum_{i \in S} V_1(x_i) + \sum_{i \in S} \sum_{j \in S} V_2(x_i, x_j) = \sum_{1 \leq i \leq S} x_i G_i(x_i) + \sum_{1 \leq i < j \leq S} x_i x_j G(x_i, x_j)$$

where $G_i(\cdot)$ are arbitrary functions. The above models are called auto-models (Besag, 1974). The family of auto-models can be generated based on the assumption (Besag, 1974) that the probability structure of the pixels given the nearest neighborhood connectivity could be expressed as a general exponential family distribution.

An auto-model is defined as an auto-logistic model (Besag, 1974; Zimeras, 2006), if the x_i are taking values concerning the common state $\Lambda = \{0, 1\}$ (or $\Lambda = \{-1, +1\}$) with corresponding energy function

$$U(\mathbf{x}) = \sum_{1 \leq i \leq S} a_i x_i + \sum_{1 \leq i < j \leq S} \beta_{ij} x_i x_j$$

where $\beta_{ij} = \beta_{ji}$ and can be defined as spatial interaction coefficient. The conditional probability for the auto-logistic model, after the consideration of equation 1, is given by:

$$p(x_i | x_{\partial i}) = \frac{\exp\left\{x_i \left(a_i + \sum_j \beta_{ij} x_i x_j\right)\right\}}{1 + \exp\left\{\left(a_i + \sum_j \beta_{ij} x_i x_j\right)\right\}}$$

When N is the nearest-neighbourhood system on the lattice (4 neighbours on a 2D lattice system) and $\beta_{ij} = \beta_{ji} = \beta$ (isotropic auto-logistic MRF), this is reduced to the Ising model (Ising, 1925). A brief history of this model is discussed in Kinderman and Snell (1980). The classical Ising model was used as an ideal model of a ferromagnetic material (spin up [+1] and spin down [-1]) with a general energy function

$$U(x) = \frac{1}{kT} \left[-m \sum_i B_i x_i + \sum_i \sum_j J_{ij} x_i x_j \right]$$

where J_{ij} is the pairwise “exchange interaction” between sites i, j and h_i is the “external magnetic field” on site i . The value k is the Boltzmann’s constant, a fundamental constant in physics. Special cases where $B_i = B$ and $J_{ij} = J$, then the energy function is given by

$$U(x) = -\frac{1}{kT} \left[-mB \sum_i x_i + J \sum_i \sum_j x_i x_j \right]$$

The second term represents the interaction energy of the spins. Due to the nearest neighborhood structure, only near spin interacts. J is a matter constant. If $J > 0$, then spins with the same direction contribute low energy and hence high probability (same directions – ferromagnet). If $J < 0$ we have antiferromagnetism. The continuous $T > 0$ represents absolute temperature, and k is the Boltzmann factor. The first sum represents a constant external field with intensity B . The constant $m > 0$ depends on the material. This term becomes minimal if all spins are parallel to the external field. Considering the general notation of the auto-models, the energy function for the Ising model becomes:

$$U(\mathbf{x}) = -\frac{a}{kT} \sum_{i \in S} x_i - \frac{\beta}{kT} \sum_{\langle i, j \rangle \in S} x_i x_j = -\frac{1}{kT} \left[a \sum_{i \in S} x_i + \beta \sum_{\langle i, j \rangle \in S} x_i x_j \right]$$

where $\langle i, j \rangle$ denotes the nearest neighbours pairs, T represents the temperatures, the external magnetic field strength, and the coupling strength. The model is attractive $\beta > 0$ and repulsive if $\beta < 0$. The auto-logistic model and the Ising model are equivalent to the transformation $\{0, 1\} \rightarrow \{-1, +1\} \Rightarrow x_i = 2x_i - 1$. The auto-logistic (Ising model) is a special case of auto-binomial with $a_i = a$ vertical direction and $\beta_i = \beta_h$ horizontal direction. Then Gibbs distribution for the Ising model can be expressed based on the following form:

$$p(x) = \frac{1}{Z} \exp \left\{ -\frac{1}{kT} [U(x)] \right\} = \frac{1}{Z} \exp \left\{ -\frac{1}{kT} \left[\sum_{c \in C} V_c(x_c) \right] \right\}$$

The generalization of the auto-logistic model to more than two states is called multi-level logistic (MLL), also known as the Potts model (Potts, 1952; Wu, 1982; Graner and Glazier, 1992). In general, spins in a Potts model can take any of c different colours values, running from 1 through c ; $c = 2$ is mapped to Ising. The general energy function is given by

$$U(x) = -\frac{\alpha}{kT} \sum_{i \in S} x_i - \frac{\beta}{kT} \sum_{\langle i, j \rangle \in S} I(x_i, x_j) = -\frac{1}{kT} \left[\sum_{i \in S} x_i - \beta \sum_{\langle i, j \rangle \in S} I(x_i, x_j) \right]$$

where $I(\cdot)$ is the indicator function, $I(x_i = x_j) = 1$, if $x_i = x_j$ is true, otherwise $I(x_i = x_j) = 0$.

The Gibbs distribution for the Potts model is given by

$$p(x) = \frac{1}{Z} \exp \left\{ -\frac{1}{kT} [U(x)] \right\} = \frac{1}{Z} \exp \left\{ -\frac{1}{kT} \left[\sum_{c \in C} V_c(x_c) \right] \right\} = \frac{1}{Z} \exp \left\{ -\beta \left[\sum_{\langle i, j \rangle \in S} I(x_i = x_j) \right] \right\}$$

where $I(\cdot)$ is the indicator function and $\beta = 1/kT$. Generalization of the process is the q -Potts model (or c -Potts model), where different q (c -colours) could be achieved considering homogeneous interactions between pixels. In this case, the general energy function is given by

$$U(x) = -\frac{\alpha}{kT} \sum_{i \in S} x_i - \frac{\beta}{kT} \sum_{\langle i, j \rangle \in S} [2I(x_i, x_j) - 1]$$

and Gibbs distribution for the q -Potts (c -Potts)

$$p(x) = \frac{1}{Z} \exp \left\{ -\frac{1}{kT} [U(x)] \right\} = \frac{1}{Z} \exp \left\{ -\frac{1}{kT} \left[\sum_{c \in C} V_c(x_c) \right] \right\} = \frac{1}{Z} \exp \left\{ -\beta \left[\sum_{\langle i, j \rangle \in S} \{2I(x_i = x_j) - 1\} \right] \right\}$$

where $I(\cdot)$ is the indicator function and $\beta = 1/kT$.

MCMC Simulations

Due to the high dimensionality of the space state, it is impractical to sample from it by direct computation of the probabilities. Various researchers have studied Markov chain Monte Carlo (MCMC) methods as an alternative to exact probability computation.

The general method is to construct a Markov chain with the required probability as its equilibrium distribution. Provided the chain is aperiodic and irreducible, convergence to the equilibrium distribution is guaranteed (Smith and Roberts, 1993). Then realizations of the Markov chain form a pseudo-sample from the required distribution. This pseudo-sample can then be used to estimate various statistical measures of the image (Green and Han, 1992). In particular, our interest is concentrated on the distribution $p(x)$ using a particular realization $X^1, X^2, \dots, X^N$ on the Markov chain with transition probability $p(x \rightarrow x')$. Typically asymptotic results include:

$$X^t \xrightarrow[t \rightarrow \infty]{d} X \sim p(x) ; \quad \frac{1}{t} \sum_{i=1}^t f(x^i) \xrightarrow[t \rightarrow \infty]{} E_p \{f(x)\}$$

where the expectation $E_p \{f(x)\}$ is to be estimated. The corresponding empirical average will be used, namely:

$$\bar{f}_N = \frac{1}{N} \sum_{t=1}^N f(x^{(t)})$$

Based on the previous MCMC process, the Metropolis-Hastings algorithm (Metropolis et al., 1953; Hastings, 1970) is proposed for the realizations from Ising / Potts models. The following steps give the algorithm:

Step 1. Pick a random site and calculate its energy

Step 2. Pick a random number $x \in (0; 1)$

```

For all sites, do
  If  $\Delta U < 0$  or  $x < e^{-\frac{\Delta U}{kT}}$  then
    Change site
  else
    Do not change the site
end
end
    
```

In particular, considering the approximate p.d.f $p(x)$ for Ising model given by Gibbs form

$$p(x) = \frac{1}{Z} \exp \{-\beta U(x)\}$$

where $\beta = 1/kT$ and Z is the partition function. Under the acceptance ratio

$$\frac{p(x)}{p(x')} = \frac{e^{-\beta U(x)}}{e^{-\beta U(x')}} = e^{-\beta [U(x) - U(x')]}$$

with form:

$$a(x, x') = \begin{cases} 1, & \text{if } U(x') < U(x) \\ \frac{p(x)}{p(x')} = \frac{e^{-\beta U(x)}}{e^{-\beta U(x')}} = e^{-\beta [U(x) - U(x')]}, & \text{otherwise} \end{cases}$$

the following steps give the Metropolis algorithm:

Step 1. Start with a starting value $\mathbf{x}=(x_i) \in C, i=1,2,\dots,N^2$

Step 2. Select a pixel at random from $\mathbf{x}$ (as x_n)

Step 3. Calculate the energy $U(\mathbf{x})$

Step 4. Propose a new configuration $\mathbf{x}' = (x_1, x_2, \dots, -x_i, x_{i+1}, \dots, x_{N^2})$ (under the pixel conditions -1 and 1 in $\mathbf{x}$)

Step 5. Compute $U(\mathbf{x}')$

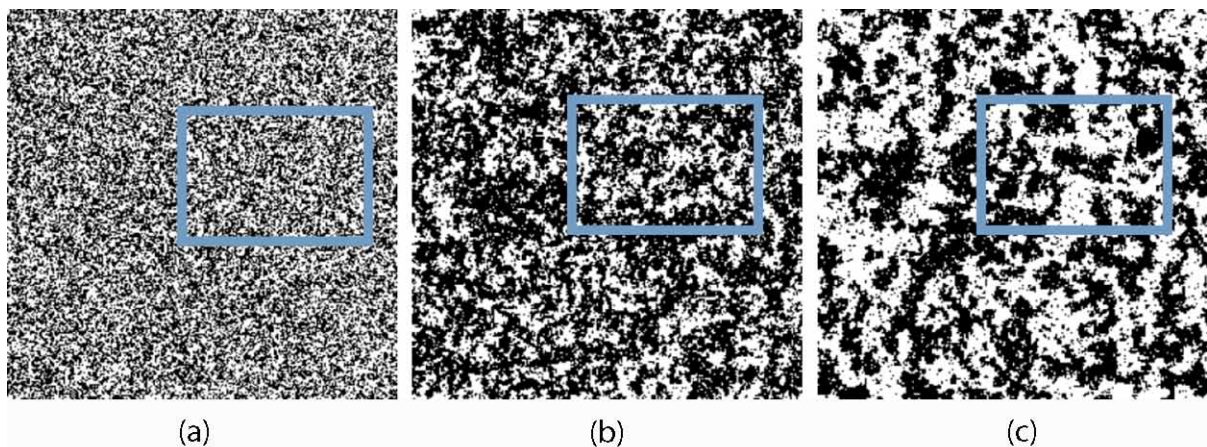
Step 6. If $U(\mathbf{x}') < U(\mathbf{x})$, move to $\mathbf{x}$

Step 7. If $U(\mathbf{x}') > U(\mathbf{x})$, move to $\mathbf{x}'$ with probability $p(\mathbf{x}') = e^{-\beta[U(\mathbf{x}') - U(\mathbf{x})]}$

After an initial transient period, a realization from the required probability distribution has occurred. In practice, it is essential to monitor convergence to the equilibrium distribution. For a discussion of convergence, see Geman and Han (1992) and Sokal (1989).

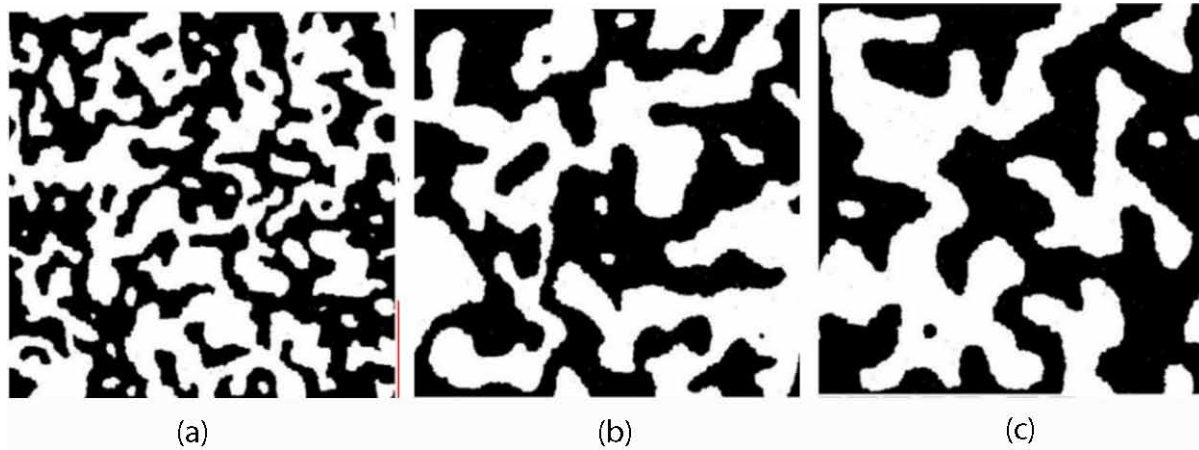
Models for spreading diseases are given based on whether or not the disease succeeds or fails to appear in the region. For this reason, a model based on the Ising random field for the process could be proposed, with white patches representing success and black meaning failure. Under uncertain conditions, the proposed random field model could achieve realizations based on spatial connectivity; Figure 4 illustrates different realizations given specific windows of interest. From the results, it is clear that as the temperature (T) increases, the regions with white pixels (spreading disease) are getting bigger (The values for $K=1$; the values of α are the magnetic fields). One hundred iterations achieve the convergence for equilibrium distribution for a-realization, 300 iterations for b-realization and 500 iterations for c-realization (Figure 4).

Figure 4. Realizations of Ising model considering a. Temp=7.21, field=0.16, $\beta=0.5$; b. Temp=2.67, field=-0.07; $\beta=1.5$. c. Temp=2.26, field=0; $\beta=1.8$. White pixels appears the disease and black is the background



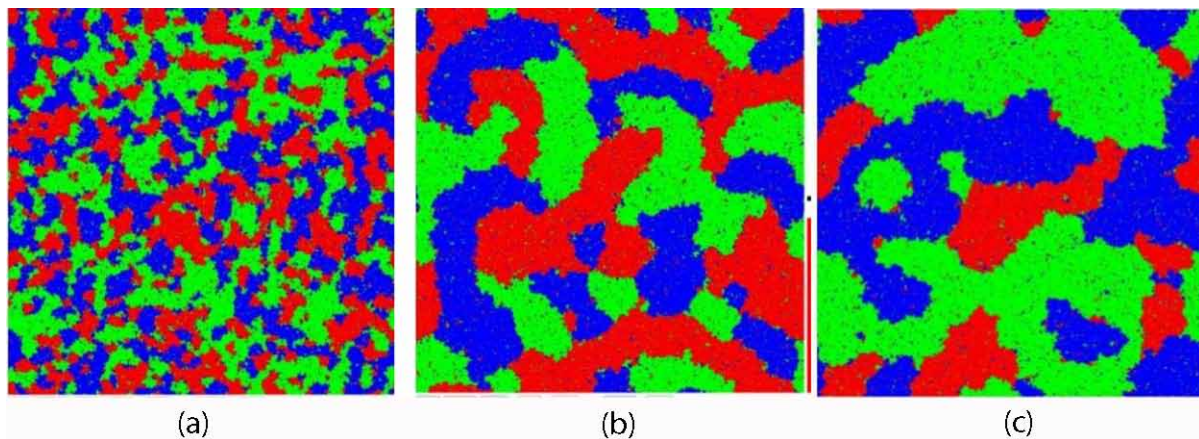
Alternative simulations of the Ising model with $T=1$, $\alpha=1$, and $\beta = 1$ (a. iter=50;b. iter=200; c. iter=500) are illustrated in Figure 5. From the resulting realizations, it is clear that as the number of iterations increases, the homogeneous regions are achieved more clearly.

Figure 5. Realizations of Ising model considering $T=1$, $\alpha=1$ and $\beta = 1$ a. iter=50;b. iter=200; c. iter=500



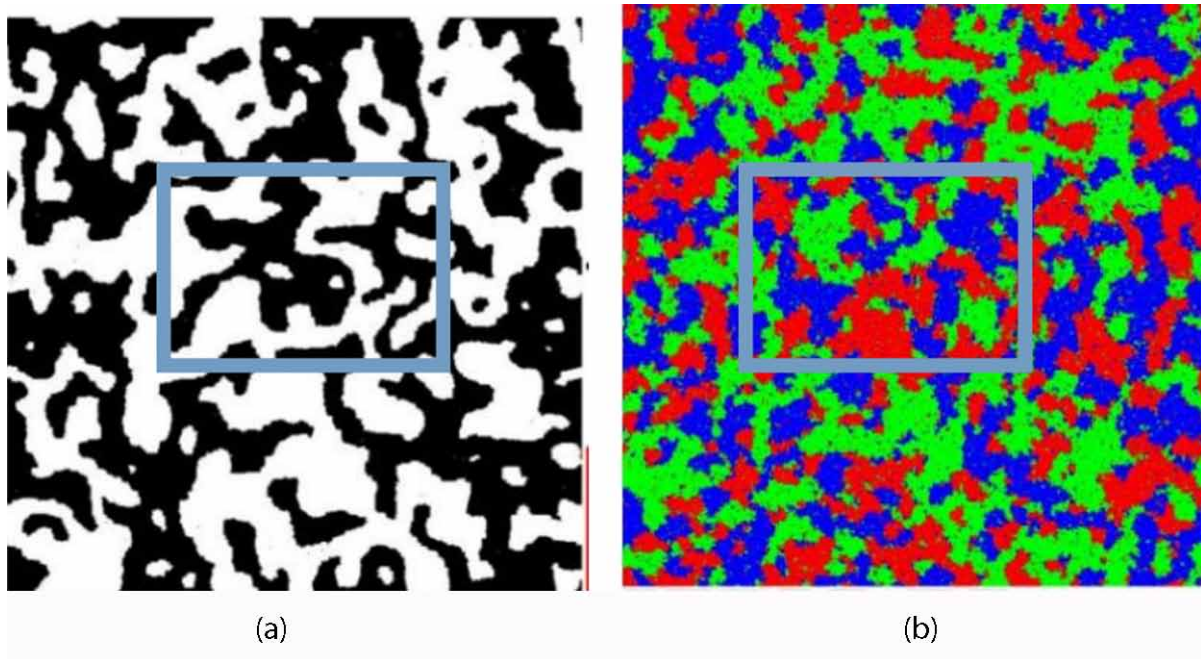
Alternative simulations of the Potts model (with 3 colors: blue=background; red= virus1; green =virus2) with $T=1$, $\alpha=1$ and $\beta = 1$ (a. iter=50;b. iter=200; c. iter=500) are illustrated in Figure 5. Based on this model (3-Potts model), regions with diseases could be spitted into different sub-regions introducing different stages of the spreading process; for example, one sub-region could represent the illness area, and the other sub-regions could be represented the vaccine area.

Figure 6. Realizations of Ising model considering $T=1$, $\alpha=1$ and $\beta = 1$ a. iter=50;b. iter=200; c. iter=500



Realizations could present better results under the uncertain neighbourhood connectivity (window of interest) by Ising / Potts model in Figure 7. These results show that homogeneous regions in the Ising model (white regions) are divided in the Potts model with red and green regions.

Figure 7. Realizations a. Ising mode; b. 3-Potts model



CONCLUSION

Under the spreading diseases process, spatial patterns must be analyzed, and modeling based on spatial models could be proposed by investigating neighborhood structure between regions. Considering the spatial structure, homogeneous connectivity of the regions of interest must be inquired considering Markov random fields models.

Models based on Markov random fields could be proposed to reconstruct patterns with success and fail regions considering the Ising / Potts mode (Cross and Jain, 1983; Hamersley and Clifford, 1971; Zimeras, 2006). Due to the spreading process hiding information leads us to uncertainty conditions. Uncertainty is a situation where a spatial homogeneity is under dispute. Especially where regions of interests are unclear based on inhomogeneity and neighborhood structure leads us to various spatial patterns (Zimeras and Matsinos, 2012; 2016; 2019). To overcome this situation, estimation based on spatial models could be introduced and patterns reconstructions would be illustrated based on MCMC methods, especially with the Metropolis-Hastings algorithm.

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Chapter 5

The COVID–19 Pandemic and Relevant Concerns for Pediatric Neurologists

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ABSTRACT

Novel coronavirus SARS-CoV-2 is being speculated to have a profound effect on the neurological health of children. This chapter addresses the risk of neurological symptoms in children susceptible to COVID-19, which might help pediatric neurologists. As existing research has been mainly focused on adults, this chapter is a compilation of past and present data to understand better the diseases associated with pediatric neurology and COVID-19 and its repercussions. Consequently, this chapter aims to enlighten the level of alertness in pediatric specialists to assess potential neurological involvement of this virus and its probable long-term neuropsychiatric and medical consequences.

INTRODUCTION

SARS-CoV-2, which belongs to the Coronaviridae family (Sahu, Mishra, & Lal, 2020), has been ravaging the world to date. This virus gets transmitted via respiratory droplets (L. Luo et al., 2020) or aerosols (Santarpia et al., 2020) from an infected person upon coming near them. Infection is initiated through the respiratory route. Upon reaching the pneumocyte cells in the lungs using host protein receptors, a cytokine storm is triggered, which infiltrates into the blood and gets carried to other vital organs like the kidney, brain, heart, intestine, gonads etc. (Hojyo et al., 2020) along with neurological involvement affecting up to ~36% of patients (Baig, Khaleeq, Ali, & Syeda, 2020; Paterson et al., 2020; Wu et al., 2020).

Data from previous related coronavirus infections like Severe Acute Respiratory Syndrome (SARS, 2002) and Middle East Respiratory Syndrome (MERS, 2012) implies that all three coronaviruses might

DOI: 10.4018/978-1-7998-9198-7.ch005

have some neurological consequences (Bohmwald, Gálvez, Ríos, & Kalergis, 2018). Variations in the relative severity and amount of neurologic disparity caused by coronaviruses can hamper our overall understanding of COVID-19 (Koralnik & Tyler, 2020). Due to limited information, the likelihood of SARS-CoV-2 neuroinvasion cannot be negated (Li et al., 2020). The implications from these studies highlight the requirement to consider possible neurological involvement in neonates and children affected with COVID-19 in relevance to neurobiological development and the healthcare system.

This chapter highlights various neurological symptoms and disorders caused by COVID-19 infection in children, as reported by recent case studies. The factors leading to such neuronal damage are discussed in context to SARS-CoV-2 pathophysiology. It also emphasizes on the probable link between multisystem inflammatory syndrome in children (MIS-C) and subsequent neuronal impairment. The impact of the pandemic on the mental health status of children and new mothers has been highlighted too. Overall, the chapter foretells the pivotal role of pediatric neurologists in our fight against this invisible enemy.

BACKGROUND

In Wuhan, China, four cases of pneumonia of unknown origin were reported on December 29, 2019 (She et al., 2020; Zhu et al., 2020). On January 12, 2020, the cause of the pneumonia was detected by next-generation sequence analysis of the tissue samples, which was previously thought to be unlinked with infection in humans (Zhu et al., 2020). This strain was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and accordingly named by the International Committee on Taxonomy of Viruses (ICTV). After that, the spread of this virus was rapid worldwide, and on March 11, 2020, World Health Organization (WHO) declared it a global pandemic (Cucinotta & Vanelli, 2020).

The continuation of the COVID-19 pandemic has implied some exciting trends in the acquired data. Primarily to date, the increase in the number of active cases and death tolls in comparison to adults is less frequent in infants and children (Götzinger et al., 2020; Shekerdemian et al., 2020). It has also been reported that severe illness in children is significant, with prior comorbidities being an important contributing factor (Remppis et al., 2021). Several hypotheses including age-dependent qualitative and quantitative variations in immune responses (Bajaj et al., 2021), previous exposure to coronaviruses leading to neutralizing antibody response (Dijkman et al., 2008; Dispinseri et al., 2021; Leung et al., 2009), lower prevalence of existing comorbidities (Zhou et al., n.d.), probability of less Angiotensin-Converting Enzyme 2 (ACE2) receptors with low affinity (Y. Luo et al., n.d.), are all in support of the notion why COVID-19 is less frequent in children as compared to adults. Still, these are not competent enough to justify the existing data. Notably, the current scenario portrays an alarming call for healthcare professionals dealing with the pediatric population because these children are at risk of sustaining and spreading the virus despite being asymptomatic most of the time.

In children, respiratory symptoms and multisystem inflammatory syndrome (MIS) have been reported in the scientific literature in association with neurological symptoms in the case of COVID-19 (Dufort et al., 2020; Larovere et al., 2021). Additionally, chronic and pronounced inflammatory responses and cytokine storms can indirectly damage the Central Nervous System (CNS) (Ong, Go, Wang, Cheah, & Halliwell, 2021). A meta-analysis has reported 27.1% neurological manifestations in children with MIS (Nepal et al., 2021). In the United States, 28% of pediatric patients with COVID-19 have developed headaches (COVID, Team, ..., & 2020, n.d.). In New York, 31-47% of children assessed with MIS-C have reported neurological symptoms, including encephalopathy and alterations in their mental status

(Dufort et al., 2020). Other uncommon neurological manifestations of MIS-C has also been reported by another study group in the United Kingdom which includes anosmia, seizures, cerebellar ataxia, global proximal muscle weakness and bulbar palsy, along with signal changes in the splenium of the corpus callosum detected by neuroimaging (O Abdel-Mannan, Eyre, Löbel, ..., & 2020, n.d.). Similarly, in Northern Iran, 29% of children admitted to the Intensive care unit (ICU) have reported neurologic problems in parallel with other symptoms (Shahbaznejad et al., 2021). Interestingly, a case report of a 6-year old patient with Fisher-Evans syndrome and COVID-19 has reported Acute disseminated encephalomyelitis (ADEM) post COVID with a positive response towards therapy practiced Fisher-Evans syndrome (Manzo et al., 2021). Another recent case report of a 34-month-old child in Iran with COVID-19 has been detected with encephalitis (Cheraghali et al., 2021). Conclusively, as COVID-19 is a respiratory virus, neurological symptoms may go unrecognized during or after a diseased condition, obscuring any neurological findings during the current pandemic.

COVID-19 AND NEUROLOGICAL MANIFESTATIONS

We have reported recent case studies associated with COVID-19 with various neurological diseases and symptoms in Table 1.

Table 1. Summary table of published case reports

S.No	Cases	Observations	References
1.	A 9-month boy without any history of comorbidities with COVID-19 positive	Progression towards acute necrotizing encephalopathy (ANE)	(Lazarte-Rantes, Guevara-Castañón, Romero, & Guillén-Pinto, 2021)
2.	In a rare case of 8 year old previous healthy girl with earlier history of seizures and encephalopathy with SARS-CoV-2 infection	a) Acute fulminant cerebral edema (AFCE) b) RT-PCR came negative for Cerebrospinal fluid (CSF), blood, brain tissue and bilateral lungs.	(Ninan et al., 2021)
3.	A seven-year-old boy with no specific medical history tested positive for COVID-19	a) Absence of SARS-CoV-2 in CSF and brain parenchyma b) Loss of brain grey-white differentiation c) Multiple organs failure d) Brain death	(Kim et al., 2021)
4.	A 10-year-old girl with a COVID-19 infection.	a) Evidence of ischemic stroke	(Khosravi, Moradveisi, Abedini, Behzadi, & Karimi, 2021)
5.	A 9-day old boy with COVID-19 on sixth day had seizures	a) Intracranial imaging defects b) Encephalitis	(Martin, Felker, & Radhakrishnan, 2021)
6.	A 6 year old COVID-19 positive boy	a) Axonal Guillain-Barre syndrome (GBS) b) Acute motor axonal neuropathy	(N, ME, G, & E, 2021)
7.	A 16-year-old schoolgirl with COVID-19 infection	A severe case of associated encephalopathy with fewer symptoms of respiratory problems upon infection	(Gaughan et al., 2021)
8.	A 10-year boy and 11-year girl with MIS in connection with COVID-19	A splenic lesion with rapid recovery from encephalopathy	(Bektaş, Akçay, Boydağ, & Şevketoğlu, 2021)
9.	A 6-year-old patient with sickle cell anemia and cerebral vasculopathy with RT-PCR positive only in case of nasopharyngeal swab and blood.	Defects in craniofacial nerves	
10.	An 18-day old pre-term girl with COVID-19 infection	a) Lethargy b) Absence of alert state c) Decreased muscle tone d) Absence of proper breathing	(Nicola et al., 2020)

FACTORS AFFECTING SARS-COV-2 MEDIATED NEURONAL DAMAGE

According to recent literature availability, coronaviruses can induce neurotoxicity via direct or indirect mechanisms.

i. Induction of Endovascular Damages

Coronaviruses can enter the nervous system by invading the leukocytes present in blood circulation and can damage the brain parenchyma (YF et al., 2003). Though the mechanism behind such infection is still under speculation, the role of monocytes/macrophages in neuronal penetration is strongly supported to date (P.-M. A et al., 2020). The infected monocyte/macrophage can cross the blood-brain barrier and differentiate into perivascular microglia (DA & RS, 2005). Subsequent replication of the virus in microglia can lead to neurodegeneration via triggering the inflammatory cytokines leading to seizures in patients (Talbot, Desforages, Brison, & Jacomy, 2011). Coronaviruses can also induce seizures by infecting oligodendrocytes and astrocytes (AA, K, & S, 2005; BC, EM, N, & KV, 2004). SARS-CoV-2 can also attack the brain microvascular endothelial cells (BMVECs), leading to inflammation and causing encephalitis and meningitis (SK et al., 2011). Conclusively, endovasculture damage upon entry into the CNS can be directly related to neuronal degeneration.

ii. Disruption of Nerve Structures

The entry of neurotropic viruses into the CNS via neuronal pathways plays a pivotal role in their pathophysiology. Motor proteins can mediate infection to either sensory or motor nerve endings, dynein and kinesins, respectively (Lavi & Weiss, 1989). Upon reaching the sensory neurons, coronaviruses can mediate direct connections between the peripheral and CNS to penetrate the brain tissues (Wu et al., 2020). Motor neurons at Neuromuscular junctions (NMJs) are a specialized gateway of entry for viruses into the CNS (KO & NY, 2003). Viral particles can enter motor neuronal axons in the NMJ by binding to unknown receptors or neural cell adhesion molecules (NCAMs) (Bender & Weiss, 2010). In motor neuron infection, 1% of coronavirus invasions are responsible for causing motor dysfunction and paralysis (Turgay, Emine, Ozlem, Muhammet, & Haydar, 2015). The olfactory system also confers direct entry of coronaviruses into the CNS (I, Y, T, & Y, 2005), probably after the intranasal infection (Desforages, Coupanec, Stodola, Meessen-Pinard, & Talbot, 2014). Notably, human coronavirus via the olfactory bulb can enter the entire brain and CNS leading to inflammation and demyelination, as reported in several studies (Desforages et al., 2014; EA, A, ME, PK, & H, 2004). Thus, invasion of sensory nerve endings, motor neurons and olfactory neurons by coronavirus infections can damage various nerve structures.

iii. Cytokine Storm and Neuronal Inflammation

Coronaviruses can also cause immune-mediated CNS anomalies (TE & MP, 2010). In this context, “cytokine storm” can initiate a surge in inflammatory factors after the viral infection leading to disruption of the blood-brain barrier (CC, TE, & SA, 2006). Locally produced chemokines and cytokines in the CNS can interrupt the blood-brain barrier and reduce the stability of tight junctions (Weiss & Leibowitz, 2011). Notably, an increase in the expression of chemokine monocyte chemoattractant protein-1 (MCP-1, CCL2) during coronavirus infections has led to disruption of tight junctions (CY et al., 2005). Traces of

increased levels of different cytokines have been detected in SARS-CoV-2 infected cerebrospinal fluids in connection with acute encephalopathy (Wu et al., 2020). The cytokine storm has been reported to be one of the leading causes of death in COVID patients by inducing neuronal dysfunction and multiple organ failure due to overproduction of inflammatory cytokines (IFN α , IL1 β , IL6, IL12, TNF α , etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, etc.) (R & S, 2017; T. V & F, 2008a). Coronavirus mediated infections can lead to an elevation in the production of inflammatory cytokines and activation of microglia (Chiara et al., 2012). Interestingly, glial activation can function as a double-edged sword; both antiviral and, in case of its long term activation, can also lead to neurological impairment (G et al., 2020). Though the mechanism behind the involvement of inflammatory molecules in inducing neurological disorders is still under speculation, the presence of complex innate and adaptive immune responses have been observed in various animal studies (AN, S, JB, J, & LA, 2005). Viral infection in the CNS requires penetration of immune cells which can promote immune invasion leading to neurological disorders (Bergmann, Lane, & Stohlman, 2006). Hence, unregulated expression of various cytokines can be dangerous and lead to neurotoxicity.

iv. Neuronal Oxidative Stress Pathology

High levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) generation due to various factors, as well as viral infections in airways, can be associated with oxidative stress causing cellular damage (Ntyonga-Pono, 2020). Inflammatory cell recruitment at the site of infection can be a pivotal causal factor in the dysregulation of ROS/RNS generation induced by several respiratory viruses. Increased production of ROS and RNS can have an impact on superoxide (O $^{2-}$) and nitric oxide (NO) production, which are therein generated during the inflammatory processes (M et al., 2007). Both ROS and nitric oxide synthase (NOS) can cause inflammation by affecting the integrity of neuronal gray and white matter of the brain by dysregulation of arachidonic acid (AA) and docosahexaenoic acid (DHA) (Horner et al., 2015). Infiltration of NADPH oxidase-expressing phagocytic cells in virally infected tissues and humoral reactions involving xanthine oxidase (XO) has been associated with O $^{2-}$ and ROS (Drummond, Selemidis, Griendling, & Sobey, 2011). Certain neurological disorders in coronavirus infections have been linked with the production of ROS, NOS and Malondialdehyde (MDA) (Desforges et al., 2014). It has also been observed that neurotrophic viral infections can lead to mitochondrial impairment accompanied by alleviation in the activity of antioxidant enzymes (CS et al., 2014).

Additionally, carbonylated proteins produced by coronavirus infection can also cause DNA damage in brain tissues (Horner et al., 2015). Another molecule involved in coronavirus mediated oxidative stress is the inducible synthase of nitric oxides (iNOS), which plays a prominent role in neurological dysfunction (RM, A, M, & MI, 2003). For example, pharmacologic or genetic inhibition of iNOS in mice was parallel to reduced tissue damage during viral infection, where the role of oxidative damage can also be important (W et al., 2009). During viral infections, properly coordinated oxidative responses can limit their replication via multiple unknown mechanisms (RM et al., 2003). However, it can pose a threat to the host (RM et al., 2003; W et al., 2009). Glutathione (GSH), a small thiol, is a cytosolic antioxidant protein that plays a critical role in scavenging ROS and NOS; conversely which might act as the main target of viral infections (C. J et al., 2003). But oxidation of GSH to GSH disulfide and its subsequent reduction by a specific enzyme, glutathione reductase, can have detrimental effects as its concentration increases during viral infections (CW et al., 2017; C. J et al., 2003). Hence, this can further damage the balance between oxidative and anti-oxidative capacity. Conclusively, coronaviruses disrupt both host

functions and the antioxidant defences of neuronal cells, which might prevent normal brain performance through mechanisms yet to be deduced.

v. Neuronal Apoptosis

There are two known apoptotic pathways, namely, intrinsic and extrinsic apoptosis (S, 2003). The inherent path related to mitochondrial distress, such as DNA damage or oxidative stress, results in cytochrome C release, leading to apoptosome production and after that activation of caspase-9, caspase-3, and caspase-7. Accordingly, in the extrinsic pathway, activation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and Fas lead to stimulation of pro-caspase and caspase-8 and caspase-10, which can ultimately activate caspase-3 and caspase-7 (S. J, FV, & J, 2000). Excessive apoptosis has been reported in aggravating neurodegenerative disorder (MP, 2000). Oxidative stress and inflammation triggered by coronaviruses can be causal factors for apoptosis (Orzalli & Kagan, 2017). Cell death followed by viral infection has been reported to cause multiple organ failure (Yan et al., 2004). The mechanism behind cell death in coronavirus mediated neuronal infection is still not apparent yet. But it is speculated that impairment related to lipid metabolism, reduction in mitochondrial β -oxidation and modulation in the redox state can be responsible for coronavirus-induced neural dysfunction and death (Shi et al., 2014). An increase in Bax, an apoptotic protein, and a decrease in Bcl2, an anti-apoptotic protein, have been observed in COVID-19 infection (Rockx et al., 2020). Coronaviruses can induce intrinsic and extrinsic apoptotic pathways by some unknown mechanism causing mitochondrial dysfunction upon generation of ROS (Gurwitz, 2020). Alternatively, it can be proposed that as the virus's proliferation occurs in the lung cells, it might trigger inflammatory responses leading to alveolar disorders that cause hypoxia in the CNS and apoptosis of brain cell mitochondria (Wu et al., 2020). Acid deposition in the brain may cause cerebral vasodilation, swelling of brain cells and even headache due to ischemia and congestion (L et al., 2020). RNA viruses are known to mediate extrinsic apoptosis by the activation of Fas systems. As the brain cells also express Fas receptors, cell death in neurons of COVID-19 infected patients can occur through detrimental inflammation (Cowley & Weiss, 2010). As discussed earlier, the pathophysiology of severe coronavirus infections has been linked to systemic inflammation, which might cause neuronal death in infected patients by the extrinsic apoptotic pathway (Dandekar & Perlman, 2005).

Additionally, the involvement of coronavirus mediated infection of macrophages, microglia and astrocytes in the CNS can also play a pivotal role in elevating the inflammation in the brain. Inflammatory factors such as IL6, IL12, IL15 and $\text{TNF}\alpha$ are observed to be increased during coronavirus infections, which can also activate Fas receptor (T. V & F, 2008b), leading to induction of apoptosis. Another critical molecule is Angiotensin-converting enzyme 2 (ACE2), linked with a high mortality rate in COVID-19 patients. ACE2 plays a crucial role in respiratory and neurological diseases (Cole-Jeffrey, Liu, Kato-vich, Raizada, & Shenoy, 2015). Some previous studies have shown that ACE2 can prevent cell death in cardiac and pulmonary systems. This protein can inhibit apoptosis and autophagy-related signaling pathways and avoid cell death in various organs (S. A & G, 2020; Cole-Jeffrey et al., 2015). Although many of these mechanisms have not been well characterized in COVID-19, further studies can unravel their molecular signaling.

MIS-C and Neuronal Dysfunction

MIS-C has been reported in children in relevance to infection with SARS-CoV-2. MIS-C is characterized by prolonged fever, increase in inflammatory molecules with multiple organ failure (E et al., 2020). A rare case of a 2-year-old COVID-19 infected boy with encephalopathy along with MIS-C was reported recently (Abel et al., 2020). Another case study included two fully vaccinated six-year-old and a nine-year-old boy with MIS-C and elevated intracranial pressure (ICP) (Baccarella et al., 2021). A 14-year-old girl with MIS-C has also been diagnosed with idiopathic intracranial hypertension and pseudotumor cerebri (LD, GT, VL, & RA, 2020). Similarly, a case series of 4 children with MIS-C accompanied encephalopathy, headache, brainstem and cerebellum signs, muscle weakness and hyporeflexia (Omar Abdel-Mannan et al., 2020). A transcriptome-wide study with pediatric patients affected by COVID-19 has implied the relation between downregulation of NK cells and cytotoxic T cell with MIS-C (ND et al., 2021). Hence, long-term follow-ups are required for better insights into MIS-C and its sequelae.

Mental Health: Children and New Mothers

The problem among children due to COVID-19 has become a common global crisis leading to more pressure on these young minds due to the uncertainty looming over their future. The pandemic has altered mental health balance in many children. Suicidal attempts among the child population have also increased manifold (MS, 2021). Children during this pandemic are battling with sadness, loneliness and a sense of isolation. A retrospective study report of children in the age group 8 to 13 from the Windsor-Essex region of Southwestern Ontario has suggested more psychological stress among them than pre-pandemic time (M. A et al., 2021). In another longitudinal study with age groups; 7-10 and 13-15 years, due to the absence of any structured routine with less exposure to nature etc., were associated with psychopathological disorders (ML et al., 2021). In another study with 38 pediatric COVID-19 patients from Wuhan Children's Hospital, the anxiety rate was nearly double compared to normal children after recovery from the disease (Liu, Liu, Rodriguez, Zhang, & Zhang, 2021). Insufficient access to food sources was also an attribute in deteriorating children's mental health (JM et al., 2021).

Similarly, a high prevalence of anxiety and depression was observed (S. V et al., 2021). In Beijing, China, poor mental health in breastfeeding women were associated with COVID-19 (Z, MY, M, J, & JY, 2021). In a cross-sectional study with breastfeeding women from Australia and New Zealand, both positive and negative impacts of the pandemic were found (VS et al., 2021). Maternal anti-stress medication can harm children, which needs attention from the therapeutic aspect (O et al., 2021). Hence, proper counselling and emotional support from the family can be fruitful in coping up with this challenging time.

SOLUTIONS AND RECOMMENDATIONS

Pediatric bio-specimens are of utmost importance for unravelling questions related to viral transmission by children, differences in viral susceptibility between pediatric and adult and subsequently their immune responses, the effect of maternal SARS-CoV-2 infection on fetal development and factors responsible for MIS-C. The successful establishment of a pediatric biorepository is not only crucial for deducing disease pathogenesis but will also play a pivotal role in future treatment and vaccination strategies. The inclusion of home-based physical and cognitive training to improve the overall health of both children

and mothers during the COVID-19 pandemic should also be considered. An utmost need of the hour is to recruit psychologists with the appropriate technical skills to support school communities during periods of school closure to ensure virtual counseling and consultation to both parents and their wards. Scientifically we have to develop some psycho-spiritual process in both the mother and the child to deal with such a devastating situation. Expansion of food programs to the weaker section of the society should also be discussed. An increase in the sample size of the studies will further empower the statistical analyses of the data.

FUTURE RESEARCH DIRECTIONS

Due to the retrospective designing of most of the studies, more prospective studies are required to confirm the observations for better evaluation of the patients' neurocognitive and functional impact. Big Data leverage this pandemic situation, while Artificial Intelligence (AI) can be utilized to identify the disease hotspots, predict future outbreaks, monitor cases, record maintenance and management of the disease by providing resources at various levels, and facilitate training health care personals.

CONCLUSION

The whole chapter has provided a comprehensive glance towards various neurological aspects associated with COVID-19 and MIS in children. This marks the essentiality surrounding closely monitoring neurological symptoms, ready-made programs to assess any vital signs with steps towards early recognition. The stigma associated with this pandemic has increased social, economic, and peer pressure among children, requiring proper handling and attention from their parents. The importance of neurological and psychiatric long-term follow-up is also highlighted for assessing the disease pathophysiology in context to MIS-C.

ACKNOWLEDGMENT

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Chapter 6

Innovative Learning Technologies for Children With Autism and Special Educational Needs During COVID-19

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ABSTRACT

The internet and the latest technological developments promise new and innovative work and learning environments and capabilities. The COVID-19 pandemic has radically changed the way people work, communicate, and learn. Many traditional infrastructures, such as the internet, have been tested to the fullest extent. Education has faced the most significant challenge as it had to serve people with different needs and backgrounds. Cheap technology solutions combined with increased computing and storage capabilities enable the education system to cope on time. Nevertheless, the need to adequately serve special population groups remains a challenge. The chapter presents an example of a methodological approach to designing an effective solution employing game-based learning techniques for children with autism or other learning difficulties. The latest pedagogical approaches are combined with appropriate gamification techniques to produce the desired outcome. It concludes by presenting critical issues in designing game-based learning applications for children with special educational needs.

INTRODUCTION

The Role of Internet use in Education During the COVID-19 Era

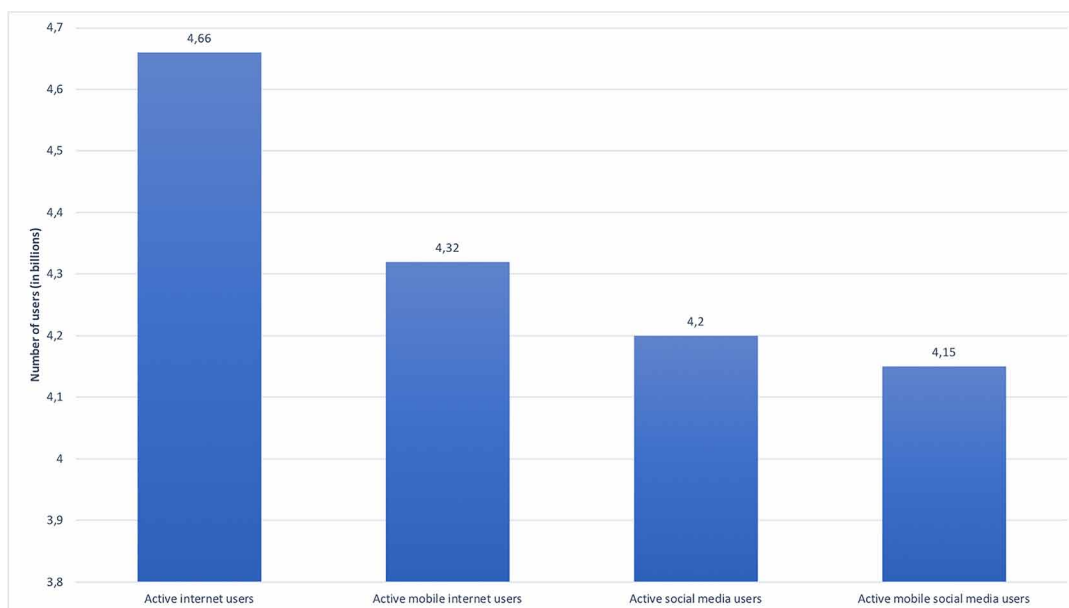
It is striking that in 2021, there are around 4.66 billion active internet users around the world (“Digital 2021: Global Overview Report — DataReportal – Global Digital Insights”, 2021). With a growth rate of 7.3%, active internet users are growing seven times faster than the global population. In other words,

DOI: 10.4018/978-1-7998-9198-7.ch006

more than half of the population worldwide (59.5%) are active internet users. An important finding is that 92.6% of this population (4.32 billion people) accessed the Internet via their mobile devices. The figure below presents the global digital population at the beginning of 2021.

Figure 1. Active Internet users as of January 2021

Source: “Internet users in the world 2021 | Statista”, 2021



According to the latest findings, 65.6% of the entire world’s population has internet access, with Asia keeping the reins of internet users (see Table 1). On the other hand, Africa has the fastest growing online population (“World Internet Users Statistics and 2021 World Population Stats”, 2021).

Table 1. World internet usage and population statistics (2021 year-q1 estimates)

World Regions	Population % of world	Internet Users Penetration Rate (% of the population)	Growth 2000-2021	Internet World %
Asia	54.9%	63.8%	2,316.5%	53.4%
Europe	10.6%	88.2%	601,3%	14.3%
Africa	17.4%	43.2%	13,058%	11.5%
Latin America / Carib.	8.4%	75.6%	2,658.5%	9.6%
North America	4.7%	93.9%	221.9%	6.7%
Middle East	3.4%	74.9%	5,953.6%	3.9%
Oceania / Australia	0.6%	69.9%	298.7%	0.6%
World Total	100.0%	65.6%	1,331.9%	100.0%

Nowadays, users are using their mobile phones to access the Internet. That is translated to 50.2% of overall web traffic coming from mobile phones. This number is higher even from the traffic coming from laptops/computers (47.1%) and tablets (2.6%). The Internet is a wealth of prospects, with so many internet users being distributed over the globe. Education is one of the most critical domains affected by the spread of the Internet.

The coronavirus pandemic changed Internet statistics a lot. The virus pushed people to their devices for work, connect, play and learn. On the other hand, students were disproportionately affected by covid-related school closures, as not all children had the opportunities, equipment, or access to continue learning during the pandemic. According to Human Rights Watch (“Years Don’t Wait for Them”, 2021), the significant dependence on online learning exacerbated the existing unequal distribution of educational support. Many governments lacked the regulations, funding, and infrastructure needed to implement online learning in a way that assured that all children had an equitable opportunity to participate. Following the pandemic, most experts now think that the education sector will adopt some blended learning in the following years. Teachers will be able to use the digital insights provided by virtual learning while still providing the formative learning that is best transmitted through in-person instruction. The “new normal” has brought Internet infrastructure under enormous pressure, increasing global peak traffic by 47%. Internet capacity and reliability were highly tested. Governments and service providers undertook a slew of emergency steps to keep the Internet running smoothly. Flexible spectrum use, additional spectrum release, enhanced international and domestic capacity, subsidized broadband services, and free access to online resources were some of the measures taken by the key players. People suddenly became reliant on services that allow them to work and learning from home. The Internet, in general, proved to be durable enough to handle the traffic surges. However, because countries have various levels of digital readiness, it is evident that this resilience has not been consistent over the world.

Due to the pandemic, several technologies that had been on the verge of becoming popular have been catapulted into the spotlight. 5G connection, the Internet of Things (IoT) and blockchain are all beginning to play significant roles in education. Unified Communication (UC) software, like Zoom, MS Teams, and others, will play an ever-increasing role in delivering educational materials and assessments. Fast upload and download speeds are necessary to introduce new learning mediums such as Virtual Reality and Augmented Reality. Thus, 5G technologies are becoming a must to overcome the limits placed on devices. In conclusion, in 2021, technological advancements are expected to transform educational environments.

According to a recent study (“Student Experiences with Connectivity and Technology in the Pandemic”, 2021), undergraduate students were highly affected by the available technology and connectivity during the pandemic. Some general vital findings are presented below:

- Students with precarious housing arrangements struggle the most with reliable internet access.
- Students have few options for internet access when they are not at home, and even then, they may have to be resourceful.
- Although most students have a laptop, not all devices can handle the rigors of remote learning.
- Most students opt to troubleshoot device issues on their own.

Technological Advancements in Education

Information and Communication Technologies (ICTs) are considered a means to bridge the gap between different groups of people, such as people with special educational needs. Recent research has argued that ICTs and assistive technologies are offering new opportunities, especially to people with special educational needs (“ICTs and Assistive Technology in Education: Paving the Way for the Integration and Inclusion of People with Disabilities | Telecentre”, 2020; Williams, Jamali & Nicholas, 2006). Most studies agree that ICTs can provide people with disabilities equal opportunities in learning, facilitate their daily lives, maximize their independence and promote self-protection (ITU, 2013). The integration of ICT in special education deals with various issues such as assistive technology, web applications, assistive communication systems, etc. (Koumpouros & Kafazis, 2019). Although the use of ICTs has been recognized for at least three decades, a growth of educational programs to support children with special educational and communication needs, exploiting new technologies, are emerging in the last years (Light, McNaughton & Caron, 2019). Game-based learning (GBL) is one of the innovations based on modern learning theories and pedagogical principles and is characterized as a reliable and effective tool of the educational process. Its use is increasing and is the subject of growing research interest (“The Importance of Game-Based Learning in Modern Education”, 2020).

Our era is characterized by the rapid development of achievements in informatics and its applications in all sectors. For example, Virtual Reality (VR), Augmented Reality (AR), and Mixed Reality (MR) has emerged as the most popular options in education. Virtual Reality provides an entirely artificial environment, while in Augmented Reality, virtual objects overlay on real-world environments. Finally, in Mixed Reality, the user can interact with both the real world and the virtual environment since the two worlds are appropriately combined.

Virtual Reality provides an artificial digital environment (sounds, sights and feels) that completely replaces the real world. Special headsets are needed to immerse users in virtual Reality, generating high-quality virtual experiences. A variety of different devices in the form of a head-mounted display (HMD) or headset can support VR. They are either connected to a powerful PC or supported by a mobile phone or standalone devices. The most popular PC-based ones are HTC Vive (“VIVE United States | Next-level VR Headsets and Apps”, 2021), Playstation VR (“PlayStation VR | Live the game in incredible virtual reality worlds | PlayStation”, 2021), and Oculus Quest (“Refurbished Oculus Headsets | Used Oculus Quest VR Headsets | Oculus”, 2021). The Samsung Gear VR (“Samsung Gear VR with Controller”, 2021) and the Google Cardboard (“Google Cardboard – Google VR”, 2021) are standalone headsets that use a smartphone to enjoy VR. Finally, using Facebook’s Oculus Quest 2, virtual experiences can be created without the need for a computer or a smartphone (“Oculus Quest 2: Our Most Advanced New All-in-One VR Headset | Oculus”, 2021). In the same direction, 360-degree immersive videos may be used as a kind of virtual Reality. Many affordable models can support immersive videos, like the GoPro Max (“MAX 6K Waterproof 360-Degree Action Camera | GoPro”, 2021), the Vuse VR (“Home Page | Vuze Camera”, 2021), the Ricoh Theta V (“RICOH THETA V”, 2021) and many others. Virtual reality learning content has the potential to improve education by making learning more immersive and engaging.

In **Augmented Reality**, the user interface is complemented and shaped by augmented information that is interactive and three-dimensional. Using a simple smartphone or tablet, a user can run AR applications. The device’s camera is used to capture the real world, and virtual objects are then overlaid to see them on their screen. Using customized smart glasses or headsets to create AR experiences is

another option (“Glass”, 2021). These AR glasses and headsets, unlike VR headsets, do not immerse users in a virtual environment but rather add digital elements to the real world.

In the third pillar, **Mixed Reality or Hybrid Reality**, virtual content is overlaid on the real environment but is also anchored to and interacts with that environment. That means that the user can interact with the real world. MR is a sort of AR but is more immersive and interactive. To experience MR, someone may use holographic devices like the Microsoft HoloLens 2 (“Microsoft HoloLens | Mixed Reality Technology for Business”, 2021) or immersive devices, like the windows MR headsets from Acer (“Windows Mixed Reality Headset”, 2021) and HP (“Mixed Reality Headset / Augmented Reality (AR) Headset | HP® Store”, 2021). Unlike virtual reality, mixed reality allows students to see the real world and holograms, providing more immersive learning experiences.

Based on the above analysis, it is apparent that the availability of Internet services and the integration of various applications in smart devices (e.g. smartphones and tablets) lead to continuous improvement and the emergence of innovative educational applications with multiple and different acceptors.

Pedagogical Approaches in Learning

According to the literature, several pedagogical approaches have been recorded that take advantage of appropriate technological innovations for educational applications. Game-based learning, situated learning, constructivism and exploratory learning are some of the most important ones. More details are presented below.

Game-based Learning: Game-Based Learning (GBL) describes an environment where game content and the game itself enhance knowledge and skills acquisition. In contrast, game activities include problem-solving and challenges for players/learners giving a sense of accomplishment (Kirriemuir & McFarlane, 2004; McFarlane, Sparrowhawk & Heald, 2002; Prensky, 2001). GBL can provide cognitive development, promote the educational process, and cultivate the user’s skills in a virtual environment through simulation. It is essentially a fun educational tool that provides interactive learning experiences, active participation, engagement and easy recall. Games can be employed in various learning contexts, from behavior modification and rote learning to deep learning in complicated domains. GBL can be simple enough or combined effectively with VR, AR and MR technologies and applications. For example, practicing students to combine AR with Reality in their games will enable them to apply something similar straightforwardly in real life (Brom, Sisler, & Slavik, 2010). With the help of digital technology, students learn to get into their games in specific roles.

Situated Learning: According to Stein (1998), situated learning is a matter of creating meaning from the actual activities of daily living where learning occurs relative to the teaching environment. Through the combination of situated learning (Dunleavy et al., 2009) and play, the student is helped to transfer the real world into the classroom and integrate their personal experiences with Reality. Situated learning occurs in the context of the experience and emphasizes relationships and interactions with others to understand. It is heavily reliant on collaborative activities (Santos, 2010).

Constructivism: Constructivism argues that learning is a process that presupposes knowledge acquisition by the student’s self-action (Bruner, 1990). Several modern learning theories come from the philosophical framework of constructivism, including problem-based learning, situated learning, and game-based learning. Innovative technological solutions, like AR, can be implemented to allow students to actively experience digital content and integrate new information into their existing knowledge base

in a personalized discovery path. Students using AR learn to delve into various theoretical concepts and invent more flexible ways of doing their work (Bower et al., 2014).

Exploratory learning: With instructional and peer-based support, students learn by exploring settings, Reality, and lived and virtual experiences. This way of thinking about learning is founded on the assumption that learning patterns can be usefully transferred to different settings through meta-reflection. The method recognizes the cognitive process that allows people to utilize their imagination and creativity to extract meaning from facts and draw lessons from interactions. Multimedia content, interactions, and textual engagement can aid in the learning process (de Freitas & Griffiths, 2009).

Children with Autism and Special Educational Needs

Children with autistic spectrum disorder (ASD) comprise an exceptional group with much individuality. The term autism comes from the Greek word “self”, which is interpreted as the introspection of the child into himself. Autism is a pervasive neurodevelopmental disorder of the brain. It is one of the most severe developmental disorders and is considered a syndrome. Wolfe & Neisworth (2005) define autism as a developmental disorder characterized by difficulty in communication and social relations and the occurrence of atypical behaviors, such as abnormal responses to sensation, routines and similarities, and repetition movements. Autism is included in pervasive developmental disorders, including Asperger’s syndrome, Rett’s disorder, childhood disorganization disorder, and non-specific generalized disorder. It affects all areas of a person’s interaction with their environment and results in failure of the socialization process. It appears at all levels of the intelligence index but is accompanied by generalized learning difficulties. As for their social relationships, they face problems, and they avoid eye contact with others. Most of the time, they want to be isolated. Additionally, they have unusual sensory interests. As far as communication is concerned, pictures have been proved very effective to this population and are one of the basic approaches for many years now (Aarons & Gittens, 2002; Iacono, Trembath & Erickson, 2016).

The education of children with autism must consider their individualities and the learning difficulties they may face, such as communication difficulties, to improve the educational process. As already mentioned, children with ASD suffer a wide range of learning difficulties that may differ from child to child. Several methodologies have been proposed in the past to satisfy the needs of persons with learning difficulties. For example, in 1972, Margaret Walker, a Speech therapist, designed Makaton in response to the needs of deaf adults with severe learning disabilities (Walker, 1973; Cornforth, Johnson & Walker, 2009). That method provides a means of communication and helps children with a wide range of developmental difficulties in communication. Andrew Bondy and Lori Frost developed the Picture Exchange and Communication System (PECS) method as an alternative communication intervention designed for children with autism (Bondy & Frost, 2001). It is a communication system through the exchange of images or symbols so that children who cannot speak can express their needs. TEACCH was founded in 1971 by psychiatrist Eric Schopler and is a structured educational program designed specifically for children with autism (Mesibov et al., 2004). It is based on behavioral therapy using the material to help children with autism perceive and train new knowledge and become autonomous.

According to the Applied Behavioral Analysis (ABA), appropriate behaviors and goals can be taught through a system of rewards and consequences. To this end, an essential element in any kind of intervention in autism is the use of amplifiers/rewards (“The Effectiveness of ABA Therapy for Autism - New Focus Academy”, 2020). Amplifiers help children progress as they are mainly used to change behavior. Their use should be assured, and they should be delivered immediately after the desired behavior. Their

duration should not be extended, and the child must not have free access. Once the child has achieved the desired results, their use should be gradually reduced until they are completely stopped so that children do not become dependent on them. Amplifiers coincide with the child's interests and are divided into primary (material amplifier, social enhancers) and secondary (privileges, tokens). Primaries emphasize the needs of the children while the secondary ones need to be followed by some learning, which is often done through the primary enhancers, in order to be effective.

CASE STUDY OF AN INNOVATIVE GAME-BASED SOLUTION

The current chapter presents a game-based solution that facilitates children with autism or other developmental disabilities in reading. The design and development phases followed a highly user-centric approach (Koumpouros, 2020; Koumpouros, 2021). A multidisciplinary team was formed at the beginning of the project to guarantee the desired outcome. A computer engineer with expertise in e-learning and autism was guiding the whole process. A teacher with expertise in special education, a speech therapist and a psychologist, with many years of experience in children with autism and other developmental disabilities, composed the last team. Moreover, two high-functioning children in the autism spectrum and their parents were actively involved and participated in the design team.

Four main phases of the user-centered design (UCD) process were followed, as presented below:

- *Phase 1 (Specify the context of use):* Identify the people who will use the product, what they will use it for, and under what conditions they will use it.
- *Phase 2 (Specify requirements):* Identify any user goals that must be met for the product to be successful.
- *Phase 3 (Create design solutions):* This part starts by building a rough concept and concludes with the complete design.
- *Phase 4 (Evaluate designs):* Evaluation takes place through usability testing with actual users.

The current research combines UCD with the benefits of GBL to produce a game that could satisfy the needs of children with autism or other learning difficulties. The wide range of individualities in the targeted population makes it even harder to build a generic solution.

The application was developed with the Unity Game Engine ("Unity Technologies", 2021), which provides a rich environment for creating interactive executable applications that include digital animation. Unity is widely used to create impressive applications with rich content such as videos, graphics, and animations quickly and straightforwardly. Our decision was based on the fact that: (i) it is a free open source platform and has a very supportive community, (ii) it offers the ability to export games to a variety of supported devices, (iii) it allows fast and straightforward animation design, (iv) it is programmable in three different languages (c #, javascript and boo).

The final game contains three levels of difficulty based on appropriate supporting material. The difficulty is based on different axes, like the complexity of the sentences, the length of the sentences and other parameters that can be combined (e.g. available time, etc.). It is played in a cheerful two-dimensional space with not too vivid colors in graphics to make it easier for children to adapt. It simulates real-world elements and depicts fantastic objects that evolve as the game progresses. At each level, the user is in a

different environment in which words hover depending on the level of difficulty and must gather them, jumping and moving forward and backwards (see Figure 2).

Figure 2. Trying to put the collected words in the correct order to make the sentence



The latest pedagogical methodologies have been adopted to satisfy the needs of the intended target group. The character played by the player, having collected all the floating words, encounters an obstacle amplifier. This obstacle does not allow the player to move forward, and the way to go is to synthesize the requested sentence from the available words. The obstacle/barrier is at the same time an amplifier, as it is a virtual stimulus for children and belongs to one of the secondary amplifiers. It lasts until the obstacle is exceeded and is used for short periods. Each level may have a different amplifier barrier. After the successful composition of the sentence, the reading of the sentence is heard, and a user-oriented animation is displayed, and the reward is being heard. Then, a path is created, and the player can continue to the following sentence (Figure 3).

The goal is for the player to assimilate the reading mechanism while playing. In this way, the children learn new sentences and enhance phonological awareness while at the same time connecting the listening of a sentence with its written recording.

At the beginning of the game, the player can choose a character (see Figure 4). Since the words in the figures are in Greek, the corresponding English translations are presented for the convenience of the reader. Additionally, the “Settings/Ρυθμίσεις” and “Choose Amplifier/Διάλεξε ενισχυτή” options are presented along with a button “Play/Παίξε” to start the game.

Pressing the “Choose Amplifier/Διάλεξε ενισχυτή” button from the home menu displays the animation selection screen to the player. The player can select an amplifier/animation to play after each successful sentence finding on this screen. They can choose from the 13 animations that exist or add a

new one. The “Settings” button displays the settings screen (Figure 5), where the educator (teacher or parent) has the following options:

- **Additional settings/Επιπλέον ρυθμίσεις:** It concerns more substantial settings, such as level selection and other controls for more personalization.
- **Sentences/Προτάσεις:** The user can manage the existing sentences or add a new sentence at any level they want.
- **Rewards/Επιβραβεύσεις:** Through this option, the user can select from the list or add a new reward that will be displayed and heard upon success.
- **Progress/Πρόοδος:** This option provides a detailed record of the actions of every player (i.e. chosen character, number of games and sentences played, detailed data of timings and mistakes made by the player during each game) to the educator.

Figure 3. The path appears after having found the correct sentence



Figure 4. Home screen

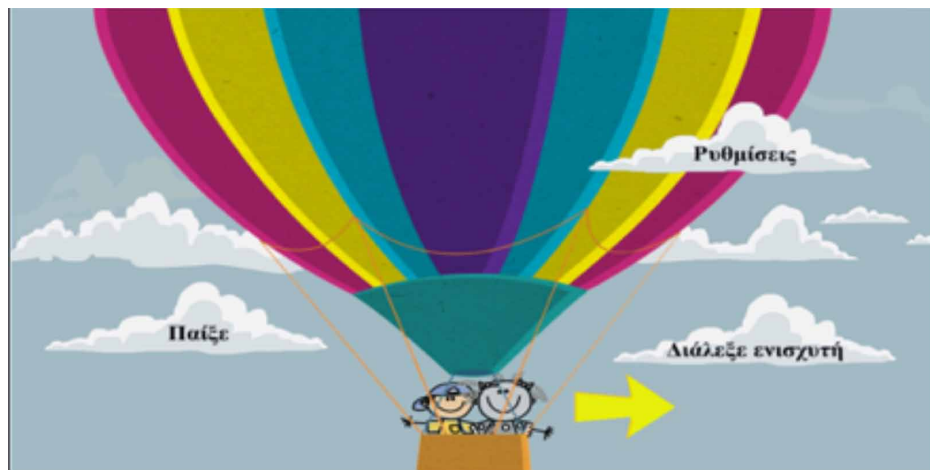


Figure 5. Settings screen



Under the “Additional settings”, the user is provided with a variety of options based on the child’s potential:

- **Choose a level:** Depending on the child’s potential, the user can choose the game’s difficulty level to start with.
- **Sentences per level:** The number of sentences per difficulty level is determined.
- **Presentation of words:** The order in which the words will appear in each level (whether the words will appear in the correct order or shuffled).
- **Timing of help:** Some “aid/help” may be provided if they have difficulty or lose their concentration during the game. Thus, the user can set the timings: (i) when the first help appears in case the player stops playing, (ii) when an appropriate sound will be heard to help them proceed, and (iii) when they will hear the next word of the sentence or (iv) the whole sentence.
- **Animation frequency:** The user can select the number of “amplifiers” to be presented upon success (one or as many as the sentences per level).
- **Reward sound:** The sound that will be heard to reward the player can be selected, or the user can add a new one.

As already mentioned, the game provides an easy to use interface to manage the existing sentences per level or add new ones (see Figure 6).

The left part of the image shows the already registered sentences per difficulty level. Clicking on a sentence displays the details of the sentence on the right. In case we want to add a new sentence, we have to click the “Add new sentence/Προσθήκη νέας πρότασης” button located above the registered sentences. For the convenience of the user, the application has an automated way of entering new sentences. By clicking the “Word registration/Καταχώριση λέξεων” button, the sentence we have entered is automatically divided into the words of which it consists. The user is then asked to pronounce and record their voice when saying the sentence and each word separately by tapping the microphone icons. Finally, the user can choose the level of difficulty of each sentence.

Figure 6. Management of sentences per level



DISCUSSION

For the game's development, the characteristics and properties of learning games that implement the essential combination of fun and learning were taken into account (Gee J., 2005; Prensky, 2001). The main features incorporated during the implementation of the case study are analyzed below.

- **Motivation (game story):** The player should be the game's focus (Federation of American Scientists, 2006) so as not to lose interest in the game, which in parallel should activate the imagination, curiosity, have appropriate graphics and an exciting story. The game should attract the player's attention to focus on the goal and engage them in progress while binding them to it (Prensky, 2001). In this phase, the goals, rules and reward elements of the game are defined.
- **Relevant practice (learning in the environment):** This is where the objectives are adapted to the educational content, and the game is structured based on them to suit the learning environment. In this phase, the learning cycles and the confidential evaluation during the game are defined, i.e. the form and processing of the game based on the educational content. Finally, the rules and the fun factors are added.
- **Gameplay Feedback:** These are the actions where, depending on the player's choices, they give encouragement, help and aim to learn from mistakes. The player should have freedom in the options to feel in control of the game (Buckley & Doyle, 2014). In this way, the interaction and energy of the game are achieved by making learning active and not passive (Federation of American Scientists, 2006).
- **Ability to retrieve knowledge (player experience):** Through hidden assessments, during gameplay, the player is trained, while it becomes easier to retrieve knowledge, resulting in more immediate understanding and consolidation of knowledge.

Moreover, the game should be adjusted based on the characteristics of the target group (children with autism or other learning difficulties). In our case, the game environment followed the design principles presented below:

- Graphics should not have much contrast. Sensitive and soft colors are suggested so that children do not get tired and distracted too much. The essential elements were highlighted with more intense colors.
- Clouds, aerostats and balloons were chosen due to the individualities of the studied population (they loved to see balloons flying and hear the sound when they broke).
- If the player does not respond for a long time during the game, there should be movement in the environment to mobilize and engage them.

Additionally, concerning the content, the difficulty level should be determined based on the learner's cognitive status.

Three high-functioning children with autism used the game for almost a month. The results from its usage were reported by their educators and parents, who were monitoring their progress. Both groups (educators/parents and children themselves) were enthusiastic about its use. The pilot testing of the game supports the successful learning of reading, enhances phonological awareness, and links the hearing of a sentence to its written imprint. An interesting finding was that all children enjoyed playing and were asking to use the game. They did not think of it as an educational process but as a pleasant experience. The use of custom amplifiers was one of the main features that led them to play the game. This feature dramatically helped to reduce distraction and increase playing time. The different aids ("help" feature) and the positive feedback provided when a child faced difficulty finding the correct sentence were crucial elements to maintain the playing. Besides, simple graphics and music and the available options could easily adjust the game to the child's learning abilities. Thus, steady progress was observed. One of the most valuable findings was the children's willingness to play the game. The right choice of amplifier further enhanced this. In most cases, the amplifier was recording the photos and voice of a loved one (e.g. parent or grandfather/grandmother).

The proposed game meets the following objectives of the Writing-Literacy Module of the Curriculum for Students with Autism:

- acquire phonemic awareness, and
- understand the underlying mechanism of reading based on the phoneme-letter relationship.

The target audience for this game is children with autism spectrum disorders or children with special educational needs and learning difficulties of all ages. However, the game can also be used by pre-school children, 6-8 years of age. Usually, children with ASD are supervised by their parents or teachers so that the game can be used by them as well. The only prerequisite is that the children need to be proficient in letter recognition and to know the basics of using the computer to play the game (i.e. move the mouse).

The game's unique characteristics are based on its design to be adapted to each individual's needs. That is considered one of the most critical aspects of ASD due to the nature of autism. To this end, it can be regarded as a generic platform for learning how to read, independently of a child's difficulties. That is one of the innovative features of the game. Besides, the adoption and combination of different pedagogical methodologies (e.g. PECS, TEACCH, etc.) in special education facilitate the learning pro-

cess while maintaining the player's interest. Finally, fully customizable amplifiers address the critical issue of distraction that almost all children with ASD have.

In conclusion, game-based learning for children with ASD should meet specific requirements. In combination with the factors mentioned above, we can summarize the following:

- Teaching information should be divided into smaller sections and presented in a structured and consistent form.
- Multisensory interaction should be provided by displaying written word, image and audio format (audio from recording).
- Repetition should be supported, both for practice and familiarity with words and sentences and when the wrong combination of words occurs.
- Satisfaction and curiosity, for the player not to lose their interest, should be done by exploiting stereotypes and obsessions that can “catch” the player's attention or be used to reward. The goal of the game should not be one but to be divided into small goals, with each obstacle acting as an activation - reward for the sequel. The person in charge (teacher, parent) should select or add the appropriate amplifiers. Thus, enhanced personalization is achieved, as the game can be adapted to the particular interests of each child/player.
- Personalization and adaptation to educational needs based on the individual level of learning should be provided.
- Customization options are essential for processing times (e.g. customized response time or timing of provided help).
- The selection of different and varied rewards and the ability to record a specific reward as a personalized function is a must.
- The game environment should be stable, and the graphics should be soft colors. A few essential elements should be displayed not to cause stress, confuse the child in the choices, and get used to the environment more easily.
- A music carpet can be integrated with the possibility of interrupting it if the concentration is obstructed or the child does not want it.
- For each word, it is necessary to provide the possibility of audio listening (phonix) and matching the words with images (if there is such a possibility).
- The mouse or the keyboard should be limited (e.g., using arrow keys to go back and forth and the space bar to bounce the character).
- The game should provide the option to record the player's progress to evaluate the intervention results.
- The use of social stories could help children with ASD to generalize the gains from the intervention.

All of the above were taken into account when creating the game presented and adapted accordingly. Moreover, two models were selected and combined: the ADDIE (Analyze, Design, Develop, Implement, Evaluate) (Kurt, 2017) and the “Systems Approach Model for Designing Instruction” (Dick, 2005). The aim was to present a generic way of creating a game-based learning environment and to prove its effectiveness in practice. The ADDIE model is an instructional design framework and consists of five phases (Analysis, Design, Development, Implementation and Evaluation). According to this, it is essential in the first phase to analyze the primary factors and the current situation, such as the target audience and the context in which the training will occur. Then the intervention must be planned, i.e. the educational

environment, the material and the educational scenarios must be shaped. After the implementation of the design, the evaluation of the prototype should take place. According to Dick & Carey's "Systems Approach Model for Designing Instruction", the designer must follow a series of steps that will facilitate the transfer of knowledge from the developed game. This model promotes constant interaction and communication between the collaborators involved in the design phase of the game. In the presented case study, the design was defined and organized based on the ADDIE model. The structural method used by the Dick & Carey model to capture details was then adopted, both from the educational side and concerning the design side of a learning game.

The proposed game-based learning application proved to be a valuable solution and asset during the pandemic period, where children with disabilities and learning difficulties were even more in need of support and alternatives for their progress. This is another example of how ICTs can effectively support people with special needs under difficult circumstances.

As far as the future steps are concerned, the game is currently being tested in a larger population with typical children and children with ASD. More levels are being implemented, and the scenario of the game and its graphics are redesigned. Our next step is to develop the game to run in a web-based environment, allowing someone to use it as an application-as-a-service. The proposed design can easily be adapted to other target groups and disciplines (e.g. engineering).

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Chapter 7

Digital Transformation Challenges for the Development of Quality Electronic Medical Records in Greece

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ABSTRACT

This work presents, analyzes, and discusses the digital transformation challenges that need to be addressed for the development of quality electronic medical record (EMR) systems in Greece in the aftermath of the 2019 coronavirus disease pandemic. The authors highlight quality EMR characteristics and provide an overview of factors affecting their adoption within the wider context of the European digital single market towards supporting continuity of care. Key challenges addressed include the linking of EMRs with the medical practice workflow in a standardized manner, building trust and acceptance by making the best use of champions to build capacity, and by financing the digital transformation transition and sustainability in a coordinated manner. Foreseen benefits include better support of medical decisions across all stages of the patient journey, patient empowerment through virtual dossiers with clinically significant information, enhancement of vendor potential to implement innovative tools to support continuity of care, and acceleration of evidence-based research.

DOI: 10.4018/978-1-7998-9198-7.ch007

INTRODUCTION

Over the past two years, the coronavirus pandemic accelerated the adoption of digital solutions (Golinelli et al., 2020; Hantrais et al., 2021) to combat the disease. Telemedicine has been extensively used for consultations, while professional attitudes towards everyday technology use in healthcare have significantly shifted. As a result, many mobile apps have already been implemented for education, the exchange of information, risk assessment, self-management of symptoms, contact monitoring and decision making, offering fast, effective, and easy to use pandemic support digital tools (Kondylakis et al., 2020).

At the same time, the health crisis has pointed out obstacles that need to be overcome to truly move the implementation of digital tools towards highly coordinated, physician-guided, and patient-involved medical care (Mertz, 2021). The value of these systems lies in the data. Next steps for technology-assisted health care include (i) understanding how to better view and use patient data; (ii) build patient connectivity; and (iii) improve patient-clinician communication.

Today, market fragmentation and lack of interoperability across health systems hinder an integrated approach to disease prevention, care and cure. Appropriate regulatory frameworks and high-quality data are necessary to realize and safeguard the rights of individuals and society. Secure access to a comprehensive electronic health record (EHR) anywhere in the European Union (EU) will enable citizens to share their health data for medical treatment, preventive services, and research, irrespective of where the data is located and in line with data protection legislation.

The national health system (NHS) of Greece is responsible for providing healthcare services in the country. The execution of the operational program for implementing the information society strategy for Greece (2000-2010) resulted in the introduction of modern information technology (IT) systems for the vast majority of hospitals in the country (Katehakis et al., 2011). Foreseen benefits included an upgraded quality of services to citizens through business process re-engineering, reducing medical errors, securing medical information, and efficient access to the EHR.

Following the introduction of integrated IT systems at the hospitals, many electronic health (eHealth) services have been introduced, in line with EU priorities, to control costs and improve services in a secure manner (Katehakis, 2018). Today, all the digital services of ministries, agencies, organizations and independent public authorities, which are already provided via the internet, including those for health and welfare, are hosted through the national gov.gr portal, which started its operation in March 2020. Typical categories of available services for the health sector include those for people with disabilities and chronic diseases, health professionals, electronic prescription, electronic pre-approval of drugs, visit and hospitalization, availability of appointments with doctors of the national organization for the provision of health services (EOPYY), the atomic EHR (AHFY, the national electronic medical record), and coronavirus disease 2019 (COVID-19) services, such as for free check-ups, vaccination appointments, vaccination certificate, etc. (<https://www.gov.gr/ipiresies/ugeia-kai-pronoia>). The country participates actively in the EU cross-border services development projects, and a national contact point for eHealth (NCPeH) is already in place. Even though significant progress has been made to link hospitals, regional health systems, and primary care, no uniform access to EHR is available nationwide.

The objective of this work is to discuss challenges related to electronic medical record (EMR) implementation within the context of the Greek NHS. The authors highlight quality EMR characteristics and provide an overview of factors affecting their adoption within the broader context of the European digital single market towards supporting continuity of care. Both the national and the European perspectives are presented together with key factors contributing to EMR adoption. The authors propose specific

directions for implementing quality EMRs in the country in line with international developments and discuss anticipated issues and means for adequately addressing them.

BACKGROUND

EMRs are digital versions of paper records maintained in clinical practice (i.e. physician offices, clinics, and hospitals). Providers use them mainly for keeping notes and information such as medical history, diagnoses, medications, allergies, and immunizations for diagnosis and treatment purposes. Even though EMRs enable providers to track data over time, identify patients for preventive visits and screenings, monitor patients, and improve healthcare quality (Habib, 2010; Kierkegaard, 2011), they were not designed to be shared outside the individual practice (Hersh, 1995; Rector et al., 1991). However, as EHRs evolved, they became a digital tool containing the information collected from all the clinicians involved in a patient's care and could be potentially accessed by all authorized clinicians to provide care to that patient, going beyond standard clinical data collected in clinical settings. EHRs can also share information with other healthcare systems, such as laboratories or specialty EHRs. EHRs can follow patients – to the specialist, the hospital, the nursing home, across or even beyond the country borders (Morrison et al., 2014; Saïod et al., 2017), while at the same time they can assist in promoting legible documentation and improved productivity.

The personal health record (PHR), unlike the EMR and the EHR, refers to a representation of health records managed by the patient (Tang et al., 2006). The growth of mobile computing leads to the need for an integrated method of storing health-related data that healthcare providers and patients can use (Roehrs et al., 2017). As health systems undergo paradigm changes, EHRs and PHRs have to advance to meet the related interoperability challenges (Blobel, 2018) to facilitate care coordination, irrespective of application, vendor or device (Kouroubali et al., 1998; Stroetmann, 2014). Connecting to the EMR requires establishing interfaces to link islands of information based on specific workflows and semantically homogenizing the produced information (Triantafyllidis et al., 2016).

Electronic Health Record Characteristics

EMRs are usually considered an internal organizational system, and the EHR is defined as an inter-organizational system. The EHR is primarily episodic and could be longitudinal. It incorporates administrative, financial, and clinical data. The concept of EHR extends beyond the boundaries of a healthcare provider and includes the concept of timelessness. The main advantage of EHR is the availability of cross-provider medical information. The EHR is an essential tool for improving both the safety and quality of healthcare. The gains from EHR systems depend on meaningful sharing, relying on access to information regardless of place and time, and reusing information for multiple purposes (Prey et al., 2016). That results in less time searching for information and more quality time with patients. Improved organizational efficiency and secondary data uses are typically amongst the most commonly expected benefits (Black et al., 2011). However, physicians must actively use these systems to accrue the benefits (Ajami & Bagheri-Tadi, 2013).

The use of EHRs requires specific user and system attributes and numerous organizational and environmental facilitators. Healthcare providers play a critical role in adopting and utilizing health IT, including EMRs in hospitals. However, many healthcare professionals, from nurses to ambulatory care

physicians, are still reluctant to use the available technologies, leading to limited system use and, eventually, system failure (Bowens et al., 2010; Linder et al., 2006).

Patient-centered and patient owned medical records are known as PHRs. They were introduced as an enabler for the self-management of medical records. PHRs are online systems used by patients and can serve as a lifelong record of health. They support the shift from institution-centered care to citizen-centered care, emphasizing continuity of care, prevention and management of chronic conditions (Katehakis et al., 2017). PHR information is expected to be sent, received, or exchanged from multiple systems, including EHR systems, insurer systems, payer systems, public health systems, clinical trials systems, and/ or collaborative care systems (HL7 International, 2014). The PHR, on the contrary to EMRs and EHRs, is not a legal record. PHR enables integrating main information components in the EMR and EHR systems (Kouroubali, Koumakis, et al., 2019).

EHR is the favored nomenclature for a sophisticated, generic term covering several concepts (Katehakis & Tsiknakis, 2006). It consists of components implemented according to measurable and realistic benefits, including PHR information. It includes wellness information and nontraditional links to external knowledge, like guidelines, protocols, and genetic information, contrasting EMR. It extends beyond the boundaries set by a single healthcare organization. In comparison to PHR is primarily created and managed by healthcare professionals.

EMRs, EHRs, and PHRs can reside on different platforms under various technologies and standards. Although EMRs contain local information and provide fast and accurate delivery, the major advantage of EHRs in medical practice is the availability of cross-provider medical information. Medical information integration leads to a dramatic change in personalized care and poses severe challenges and threats to security and privacy (Heart et al., 2017).

In recent years, several countries move towards developing national infrastructures to support the development of legitimate, state-controlled EMRs and EHR adoption using standardized access protocols (i.e. interoperability). Some prominent initiatives include the following:

- My Health Record in Australia (<https://www.digitalhealth.gov.au/>).
- Elektronische Gesundheitsakte in Austria (ELGA, <https://www.elga.gv.at/>).
- E-health records in Estonia (<https://e-estonia.com/solutions/healthcare/e-health-record/>).
- Kanta digital services in Finland (<https://www.kanta.fi/>).
- L'interopérabilité des systèmes d'information de santé in France (Interop'Santé, <http://www.interopsante.org/>).
- The Electronic Patient Record in Switzerland (EPD, <https://www.e-health-suisse.ch/>).
- The Sequoia Project in the United States (<http://www.sequoiaproject.org/>).
- eHealth Digital Service Infrastructure Operations by the European Commission Connecting Europe Facility (CEF eHDSI, <https://ec.europa.eu/cefdigital/wiki/display/EHOPERATIONS/eHealth+DSI+Operations+Home>).

National implementation of the EHRs offers the ability to electronically exchange health information across healthcare structures of the national health sector. Foreseen benefits are clinical, organizational, and societal. Quality of care, reduced errors, more patient safety and continuity of care are clinical ones. Improvements in the efficiency of service delivery, including financial and operational performance, are seen as organizational benefits. At the same time, societal benefits include research and public health (Menachemi & Collum, 2011). To achieve these benefits, the systems that feed information to the EHR

should be responsive to the complexity of the environment, tailored to the users' needs, and communicate with each other in the context of the automation of operational processes.

Implementation In Greece

During 2000-2006, Greece initiated developing integrated IT solutions for most of the Health Regions. More than 60% of the NHS hospitals of Greece were covered by the programme that included, amongst many others, all essential key EMR components (Katehakis et al., 2011).

Law 3418/2005 (code of medical ethics) provides doctors' obligation to keep medical files for their patients. It also mandates that clinics and hospitals are also obliged to save files and results of all clinic and paraclinical exams. Data collected by private clinics and primary health care must be stored for ten years since the patient's last visit and in any other case for twenty years.

In November 2010, Law 3892/ 2010 (electronic registration and execution of medical prescriptions and referral of medical examinations) put in place the national electronic prescription (ePrescription) system and the obligation to submit prescriptions and dispense medications electronically. The system has provided several benefits for patients, pharmacists, doctors and health authorities (Katehakis & Kouroubali, 2020; Katehakis et al., 2016).

Greek eHealth policy (2014-2020) set priorities for restructuring primary healthcare, pooling financial resources, introducing new managerial and administrative methods, adopting cost-effectiveness and monitoring mechanisms, and developing policies for better resource allocation. The Ministry of Health (MoH) has the overall responsibility for eHealth in Greece. The development of an electronic patient record has been set as a major objective and a priority of the NHS (Milieu Ltd & Time.lex, 2014).

In February 2019, Law 4600/2019 established the national EMR for recipients of health services in Greece (AHFY). Its content is undivided, mandatory, and maintained at a national level for life. AHFY contains the health history of each recipient of health services within the NHS and data, assessments, and information of all kinds related to that person's condition and clinical development during the treatment process. The same law states that by the decision of the Minister of Health, National Patient Registries can be established and operate based on specific criteria. The establishment and operation of these Registries are expected to be carried out following international scientific standards, and in particular with EU law and specific national regulations, relevant guidelines and recommendations of the World Health Organization (WHO, <https://www.who.int/>) and the European Centre for Disease Prevention and Control (ECDC, <https://www.ecdc.europa.eu/>).

In August 2019, Law 4624/2019 implemented the general data protection regulation (GDPR) into Greek legislation, allowing public authorities for the processing of special categories of personal data, if it is necessary, among others for reasons of preventive medicine, for medical diagnosis, for providing health or social care or for the management of systems and health or social care services.

Very recently, Law 4704/2020 facilitated the immaterial operation of the system of electronic prescription of medicines, while Law 4737/2020 and Law 4745/2020 established the district database of epidemiological tests, distinct but connected to the national patient registry for COVID-19. Data of persons tested by the rapid molecular tests are registered in this database.

Greece does not have any national interoperability policies regarding the technical standards to ensure that the structure and format of data are interoperable so that such data may be shared between healthcare professionals or incorporated into more than one database for secondary use. In addition, Greece has no specific legislation that addresses the processing of health data that was initially collected to provide care

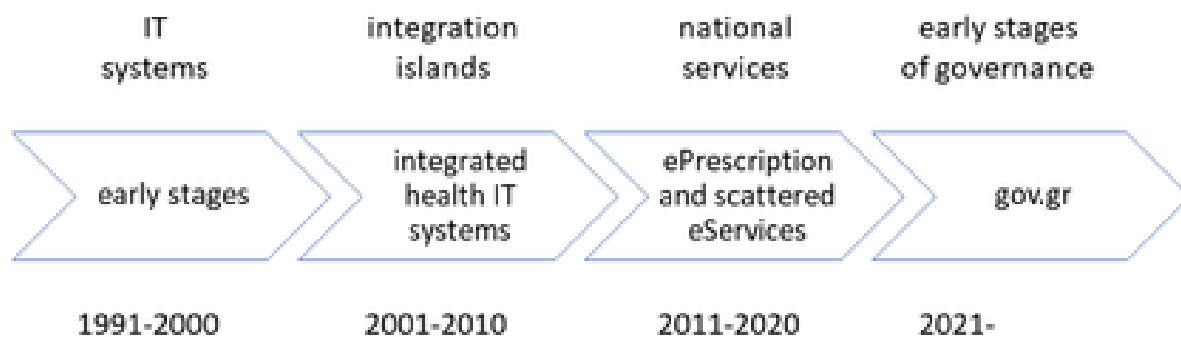
Digital Transformation Challenges

by third-party researchers, i.e. by a different controller than that where the treating healthcare professionals were based, researchers based in not for profit organizations, researchers based in industrial or commercial research organizations and researchers based in other privately funded research organizations (European Commission, 2021a).

The period 2020-2021, the MoH run a project for the design and implementation of the National eHealth Interoperability Framework (NeHIF), with the support of the EU structural reform programme, to address the critical limiting factors for the management and the integration of health-related big data and electronic services such as lack of interoperability, due to the absence of endorsed standards for exchanging data, between NHS IT systems internally (e.g. within hospitals) and externally (e.g. between ePrescription and private diagnostics centers),. The project is expected to recommend the MoH regarding governance requirements for building a sustainable NeHIF.

Figure 1 provides an outline of the digitization process the NHS has passed through since the early 90s.

Figure 1. The digital transformation process of the NHS in Greece



The recently published national strategy for digital transformation in Greece (2020-2025) focuses, amongst others, on health and dignified living (Ministry of Digital Governance of the Hellenic Republic, 2021). Key directions of the strategy include upgrading the digital maturity of the health units to provide quality services and digital health governance by creating an institutionalized framework for the operation of digital health services. It also incorporates into the national strategy the governance of national eHealth standards through NeHIF and the certification of medical applications and introduces new innovative technologies in the NHS.

It is noteworthy that Greece's national recovery and resilience plan (Hellenic Republic, 2021) includes specific components towards improving the resilience, accessibility, and sustainability of healthcare. Specific investments are planned in digital transformation for the health sector, which includes the development of the national EHR, improvement of the digital readiness of hospitals with emphasis on the development of EMRs, and strengthening telemedicine actions. Implementation of the program is imminent.

Greece does not yet participate in the implemented eHDSI services but plans to do so by 2025 (https://ec.europa.eu/health/ehealth/electronic_crossborder_healthservices_en). The introduction of the myHealth app, upon which digital patient records will be stored, has been announced (<https://ictplus.gr/kyriakos-pierrakakis-stoxos-mas-i-epitaxynsi-tou-psifiakou-kratous/>).

The Smart Hospital Challenge

The smart hospital is an operational framework where technological infrastructure and care provision are planned to utilize all the potential of emerging digital technologies towards the benefit of patients and the effective operation of health units. Smart hospitals fully support an integrated vision focusing on moving from digital health services to smart health services to support digital transformation by supporting technologies such as artificial intelligence (AI), virtual reality (VR), connected devices, blockchain, robotics, etc. (Healthcare Information and Management Systems Society, 2021).

This vision also includes creating mutually interconnected and harmoniously co-functioning EMRs of patients, which would connect distinct entities on the market and service providers. Advancing the concept requires EMR systems connected to a national EHR, remote patient monitoring and app connectivity, and analytical capabilities to generate patient and population health insights. The digital hospital of the future is expected to include continuous monitoring of patients, to support personal and portable care, cloud-based, interoperable EHRs, and enhanced digital patient experience with simplified admission, discharge, and other processes (Deloitte, 2017). It is also expected to include virtual learning and development, as well as intelligent staff recruitment and scheduling.

The recent pandemic crises forced several hospitals to act as the hospital of the future, particularly concerning virtual health and the use of technology (Deloitte Insights, 2021), since they had to shift their investments and priorities rapidly in response to the pandemic by enhancing their interoperability capabilities, develop virtual health and digital solutions to provide offerings that enable the shift of patients out of the hospital and by improving consumer experience to meet their expectations. Barriers to data analytics adoption in a hospital environment, such as isolation of data stores, end users' resistance, low data quality, lack of focus on integration, are recurrent in this area (Kouroubali et al., 2021).

Security Considerations

Trust and security are critical for the healthcare domain, which is a highly regulated one. IT security is a major concern due to the high privacy and confidentiality requirements of sensitive healthcare data. Private data needs to be accessed by professionals having a qualified role, with the patient's consent and under strict audit controls. Medical data must only be disclosed or shared after the patient is identified and authenticated with sufficient accuracy.

Many of the security challenges are linked to vulnerabilities existing before the pandemic. Due to the fast introduction of technology advancements, vulnerabilities are constantly being identified, and new threats are emerging. Cyber-attacks on health facilities are designed to prevent their employees from accessing critical care systems. WHO and the Department of Health and Human Services (HHS, <https://www.hhs.gov/>) were the most common targets for the attackers interested in gaining knowledge about the research conducted on COVID-19. As a side effect of the recent increasing trend in telework and telemedicine due to the pandemic, breaches on operating systems in the cloud are expected to rise (Katehakis, Kavlentakis, et al., 2020).

According to (European Union Agency for Law Enforcement Cooperation, 2020), ransomware remains at the center of concern, while advanced forms of malware have been widely used. The report explains that due to COVID-19 social engineering and phishing, exploiting the social vulnerability involves searching for reliable information and data. At the same time, business email compromise causes

even more concern. Cloud migration and digital file conversion for the facilitation of sharing has been central to this malicious activity.

Humans working in the healthcare sector are not IT oriented and primarily consider the significant advantages furnished by digital systems as a waste of time and a drawback on their efficiency in treating patients. This leads to a risk-oriented behavior with very little wisdom in security measures. Security must start and rely on the correct behavior of healthcare workers. And this behavior must be proactive and not reactive and neglected. On the other hand, cybersecurity must not be an agony and an obstacle to healthcare procedures' performance.

The COVID-19 pandemic has surfaced an increased need for efficient, reliable, and secure electronic health and care services (Katehakis et al., 2021; Kondylakis et al., 2021; Kouroubali et al., 2020). As telehealth solutions migrate to the cloud to support flexible and rapid deployment, security concerns must be addressed promptly. The report on cloud security for health services by the EU agency for cybersecurity (European Union Agency for Cybersecurity, 2021) helps healthcare organizations securely adopt cloud services and prepare for cybersecurity challenges. To this direction, specific legal requirements in respect to privacy & data protection, including the GDPR (European Commission, 2016b), the network and information systems (NIS) directive (European Commission, 2016a), and the European cybersecurity act (European Commission, 2019b), cloud security and health such as the medical devices regulation (MDR) (European Commission, 2017c) and the electronic cross-border health services directive (European Commission, 2011), need to be established, aligned and enforced. Typical cloud security challenges that need to be addressed include the lack of trust, lack of security and technology expertise, lack of investments, as well as difficulties related to the integration of cloud with legacy systems (Al-Issa et al., 2019; Chenthara et al., 2019; Georgiou & Lambrinoudakis, 2020). Key data protection challenges relate to data management, deletion, portability, encryption, and privacy by design techniques (Mostert et al., 2018; Voigt & Von dem Bussche, 2017).

THE EUROPEAN DIGITAL SINGLE MARKET

The European digital single market strategy is built on three main objectives: (i) to provide better access to digital goods and services across Europe; (ii) to create the necessary conditions for digital networks and innovative services; and (iii) to maximize the growth potential of the digital economy. In line with this strategy, the European Commission has created policy guidelines towards the digital transformation of health and care to empower citizens and build a healthier society. These guidelines provide direction to current EU activities in the field, presented in Table 1, as identified in (European Commission, 2018).

Table 1. Areas enabling the digital transformation of care

EU Priority Activity Pillar	Details
Secure access to health data	to enable citizens to access their health data nationally securely and across borders in the EU
Personalized medicine	to allow researchers and other professionals to pool resources across the EU, such as data, expertise, computing processing and storage capacities towards personalized medicine
Citizen empowerment	to empower citizens to take care of their health, engage in prevention activities and enable feedback and interaction with healthcare providers with digital tools

Priority is given to establishing better interoperability through open exchange format, EU-wide standardization of EHRs, and the development of EU standards for data quality, reliability and cybersecurity.

The New European Interoperability Framework (EIF)

To guarantee the secure and free flow of data within the EU, the new European Interoperability Framework (EIF) was announced in 2017 (European Commission, 2017b). The new EIF promotes the secure free flow of data within the EU for public services across member states. It was adopted in the context of the digital single market strategy in Europe to support interoperability within the public sector. The twelve underlying EIF principles are fundamental behavioral aspects to drive interoperability actions and include core interoperability principles such as openness, transparency and reusability, principles related to generic user needs and expectations such as user-centricity, inclusion, security and privacy, and foundation principles for cooperation among public administrations such as administrative simplification, preservation of information and others (Katehakis & Kouroubali, 2019). The framework maps the necessary processes towards the development of a European public services ecosystem.

The new EIF requires systems to follow certain principles throughout their lifecycle, from conception, to design, to implementation:

- Digital-by-default, providing services and data preferably via digital channels.
- Cross-border-by-default, accessible for all citizens in the EU.
- Open-by-default, enabling reuse, participation, access and transparency.
- Privacy-by-design and security-by-design to secure infrastructure and building blocks compliant with the legal requirements and obligations regarding data protection and privacy.
- Interoperability-by-design as a standard approach for the design and operation of European public services.

Using a coherent European interoperable environment, the delivery of services that work together can be facilitated within and across organizations or domains. Relevant interoperability principles and a clear implementation roadmap act as facilitators for the development and implementation of EMRs, to enable healthcare providers to share health data outside their organization (Kouroubali & Katehakis, 2019).

To realize the benefits of integrated information systems in healthcare, appropriate interoperability governance must be in place. Interoperability governance establishes the mechanisms of the application of interoperability rules across the care continuum. Strategic and policy decision making needs to incorporate interoperability governance to align strategic objectives with interoperability initiatives (European Commission, 2017a). Thorough knowledge of organizational structures, roles, responsibilities, and decision-making processes is required to establish the appropriate governance framework. Interoperability governance proposes and guides the change management practices that need to be implemented and establishes the foundations for the sustainability of interoperability initiatives at present and future times.

As far as Greece is concerned, a vital issue is relevant to the fact that the Greek, national interoperability framework (eGIF, <http://www.e-gif.gov.gr/>), introduced in 2012, is outdated and not compatible with the new EIF. Data governance is a critical enabling factor. Any new legislation would need to govern and enable distributed and decentralized models to efficiently support all citizens' health and care needs and visitors of the country.

The European Electronic Health Record Exchange Format (EEHRxF)

The interoperability of EHR systems of member states can be supported, beyond ePrescriptions and patient summaries, with the development and adoption of the European EHR exchange format (EEHRxF), which is based on open standards, taking into consideration the potential use of data for research and other purposes (European Commission, 2019a). The framework includes: (i) a set of principles that should govern access to and exchange of EHRs across borders in the EU; (ii) a set of standard technical specifications for the cross-border exchange of data in particular health information domains, which should constitute the baseline for an EEHRxF; and (iii) a process to take forward the further elaboration of an EEHRxF. The European EEHRxF has the potential to facilitate the cross-border interoperability of EHR systems. Incentives for its wider adoption and other measures to tackle the lack of interoperability will help promote the strategic priorities of the single digital market in this area.

Interoperability increases the value of data. In the long term, medical images, lab results and hospital discharge reports are expected to be available across the EU, with the entire health record to follow later on. Data-driven applications will benefit citizens and businesses in many ways, including improving health care, generating new products and services, and reducing the costs of public services. In that respect, the Commission has proposed a Regulation on European data governance as part of its data strategy (European Commission, 2020b). The new rules will allow this data to be harnessed and pave the way for sectoral European data spaces to benefit society, citizens and companies. In the Commission's data strategy of February 2020 (European Commission, 2020a), nine such data spaces have been proposed, facilitating access to public services. The European Commission is already expanding EEHRxF to supply quality data to the European Health Data Space.

Artificial Intelligence

Global efforts to manage COVID-19 have shown that the use of healthcare data is increasing exponentially when it can be interconnected, combined and communicated. According to (EY, 2020) a future eHealth system is expected to support (i) organized and complete data recording; (ii) care anytime anywhere; and (iii) use of advanced analytics to support the transition from digital to smart systems. This cannot be achieved without interoperability, locally and nationally, but globally (Katehakis, Kouroubali, et al., 2020).

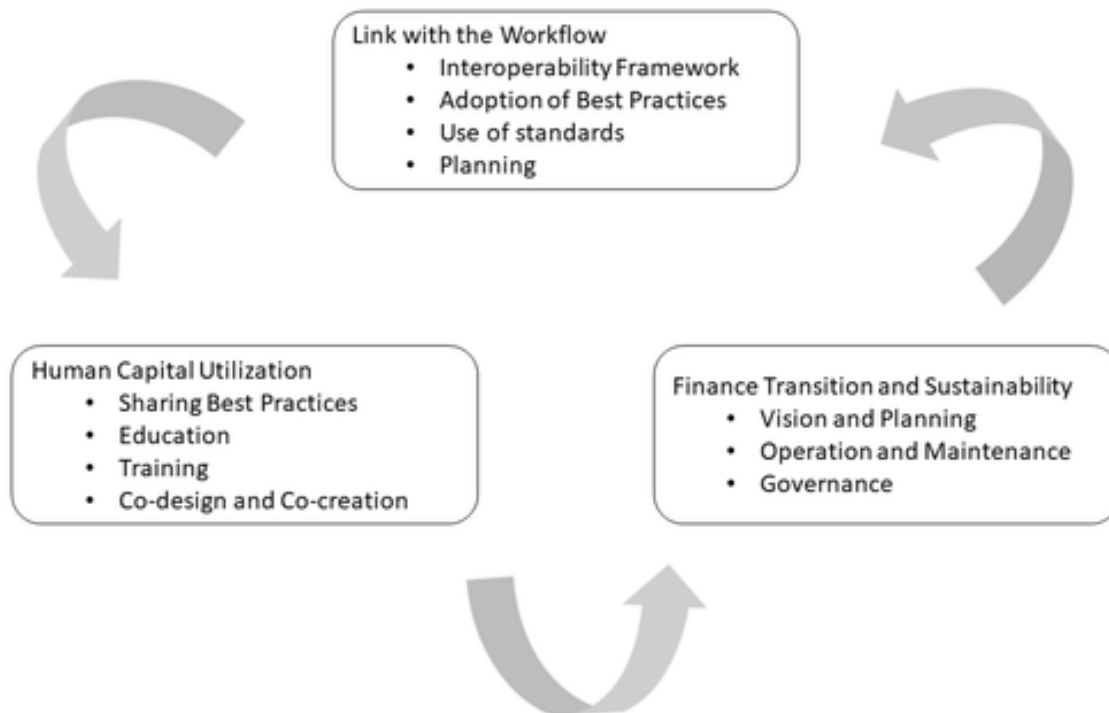
AI technologies can support socially and environmentally beneficial outcomes and provide critical competitive advantages to companies and the European economy. Such action is especially needed in high-impact sectors, including health. However, the same elements and techniques that power the socio-economic benefits of AI can also bring about new risks or negative consequences for individuals or society. The recently introduced AI act (European Commission, 2021b) presents a balanced and proportionate horizontal regulatory approach to AI that is limited to the minimum requirements to address the risks and problems linked to AI without unduly constraining or hindering technological development or otherwise disproportionately increasing the cost of placing AI solutions on the market.

SOLUTIONS AND RECOMMENDATIONS

The three main challenges for Greece in implementing quality EMRs, relate to (i) linking information systems with the clinical and operational workflow through the consistent promotion of open and se-

cure APIs; (ii) engaging champions and key stakeholders; and (iii) securing the financial means for the digital transformation and sustainability (Figure 2). The following sections focus on these challenges and provide recommendations for the effective development of quality EMRs in the NHS and the digital transformation of the healthcare sector in Greece and other similar health systems globally.

Figure 2. Key EMR adoption challenges



Link With the Workflow

Linking information systems with the clinical and operational workflow requires adopting an interoperability framework tailored to national needs, exploiting available best practices and open standards, and implementation based on planning.

Data from multiple distributed sources can be valuable if shared and used within and across organizations following an interoperability framework (European Federation of Pharmaceutical Industries and Associations, 2020). Today health data are stored in silos (i.e. hospital EMRs, national infrastructures, etc.). To address heterogeneity and fragmentation effectively, a common framework must be in place. Efforts are currently made towards that direction for the creation of the NeHIF (Kouroubali & Katehakis, 2019) to support interoperability at a cross-border, national, or regional level but also within certain healthcare organizations (i.e. hospitals) and also to provide for reaching citizens at home, based on certain use cases. Prominent sources for use cases include the following:

- Antilope project (<https://www.antilope-project.eu/resources/>).

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- eHealth Exchange use cases (<https://ehealthexchange.org/use-cases/>).
- IHE use case repository (<https://usecase-repository.ihe-europe.net/>).

The MoH has identified ten use cases (Table 2) as the basis for establishing the NeHIF.

Table 2. Use Cases (UC) defined by the MoH as national priorities in 2019.

UC	Description
1	The ordering, reporting and exchange of laboratory results for intra-hospital, primary care and cross facility use
2	The ordering, reporting, storage and exchange of medical images and results in intra-hospital, primary care and cross facility use;
3	The extension of the Greek e-Prescription system needed to allow pharmaceutical advice and evidence-based prescription in healthcare (hospitals, primary care settings)
4	The creation of a shared care plan for chronic care and disease management focusing on Diabetes type 2, COPD, and hypertension
5	The creation of a universal hospital discharge letter that will incorporate international patient summary specifications to be referenced by the point of care systems directly to the AHFY
6	The creation of a universal e-referral document exchange format to be referenced by the point of care systems directly to the AHFY
7	The introduction of cross facility workflow management, including appointment management;
8	The creation of public health reports allowing secondary use of anonymized information needed to feed independent research as well as patient registries
9	The creation of reimbursement documentation (Admission, Transfer, Discharge –ADT cycle) also allowing the reimbursement of telecare, telemonitoring and telemedicine services
10	The creation of prevention prescription protocols covering the entire cycle from patient notification, screening processes and reimbursement

To support integrated workflows, health IT systems must adopt nationally accepted standards that facilitate syntactic and semantic interoperability to adopt emerging technologies that enable digital transformation in healthcare. It is essential to note that besides having established appropriate national infrastructure, i.e. a national EMR, all relevant legal and regulatory enablers need to be in place. This is a strategic approach that needs to be further supported at all levels starting from technical to semantic, organizational, and legal (Kouroubali, Papastilianou, et al., 2019). The key to shaping digital transformation is taking realistic steps driven by expected benefits for patients and healthcare delivery alike.

Due to COVID-19, it has become increasingly clear that data exchange can raise the quality of care. Yet large parts of the existing digital infrastructure in the healthcare system are not, or is only to a limited extend, suitable for data exchange outside of a specific organization. This affects particular medical software used by doctors working in general practice, healthcare professionals in the outpatient sector, and many hospital information systems (eHealth Network, 2019).

According to (Pan American Health Organization, 2021), countries have already prepared to have established in the next five years interoperating EHRs through national digital health networks, supported by patient portals, allowing total coverage for their populations. Data obtained from different sources reflect the reality of the health situation, letting operators know the trends and distribution of health problems in the population. A country with a health system that presents an essential advancement toward

interoperability with the support of updated, modern, and safe legislation, with all its medical staff being digitally literate, is expected to use predictive models by utilizing quality data effectively. The vision is to have a country with all hospitals connected to real-time EHR platforms where all patients have their own and secure cyber portal, achieving full interoperability in an intra- and inter-sectoral way, supported by sustainable and scalable platforms for digital health.

EU member states need to be open and flexible in the design of joint solutions and to be able to ensure the implementation of the decided solutions nationally. For this reason, the NHS needs to seek cooperation with the private sector and software vendors specializing in the healthcare domain to support development and investment opportunities actively. The main concern of such collaboration is to prepare the market for forthcoming operational changes and the best use of available resources.

Human Capital Utilization

When reaching optimal human resource utilization, there are specific issues to consider relevant to the appropriate promotion of best practices, building appropriate skills through education and training, and designing new services using co-design and co-creation. What is needed is a cultural transformation and a new healthcare providers' cooperation model that does away with existing information silos.

Innovative technologies alone cannot lead to revolutionary changes. EHRs should be seen as an inseparable part of the healthcare process. Although it is the physician and the payer that frequently control the type and quality of care patients receive, implementing the smart hospital vision requires considering continuous adaptation, clinical outcomes, efficiency in the supply chain and care processes and enhancement of own capabilities regarding patient services (Kharbanda et al., 2017). Qualified human resources are a vital ingredient for success. Education, training, and continuous professional development for all, including those citizens and patients who are capable and motivated to become engaged in their care, should be strongly promoted (Stroetmann et al., 2011). Methodologies should be adopted to document lessons learned, experiences, and good practices and encourage sharing of relevant knowledge.

An important factor influencing user adoption is user confidence. Professionals should be encouraged with a transparent motivation system and a detailed presentation of realistically envisioned benefits (Kouroubali et al., 1997). Effective communication can facilitate engagement and acceptance for professionals and patients through strategies such as co-design measures. Individual initiatives should not be rejected but should be exploited to become part of the national strategy if they meet specific quality criteria. The production of communication guidelines and learning objectives that can reach different audiences is essential for the assimilation of innovation (Lorenzi et al., 2009; Tsiknakis & Kouroubali, 2009; Tsiknakis et al., 2005).

Overall, a culture of sharing, trust and collaboration with other healthcare professionals and patients still needs further building. Resistance to the changes inflicted by digitization is common in many countries (Thiel et al., 2019). Physicians, in particular, often act as veto players. Therefore, a clear framework that fosters acceptance drives developments towards better patient treatment generates benefits for the patients themselves and those engaging in secondary use. Therefore, continuous training and education in the logic of the constant improvement of available standards and processes are considered to be essential. Clear strategic objectives need to include emphasizing and adopting best practices, providing support to users, improving the quality of available solutions and establishing co-creation processes with all stakeholders involved.

Patients are the ones who are expected to benefit most from the use of EHRs. For this to happen, EMRs must be in a position to interoperate with each other and encompass intelligence. All systems need to be built using current clinical guidelines that identify, summarize and evaluate the highest quality evidence. Social networking tools already enable patients to find each other, support each other, learn from each other and help each other make decisions. From the perspective of patients, it is evident that solutions for sharing medical information electronically are needed. Widespread adoption of EMRs will require to provide with clear benefits to clinical activities. At the same time, they need to make the professionals' lives easier, not more complex.

Finance Transition and Sustainability

Sustainability requires vision and planning, operation and maintenance under certain service level agreements and governance. Quality and secure EMR deployment do not come without cost. Therefore, both initial costs and the extra expenses to support the operation and maintenance of such systems should be considered. Without the proper stimulation, hospitals will not improve their EMR-related competence. Funding should be provided and assured, while responsibilities for sustainability should be clearly defined (Katehakis & Kouroubali, 2020).

As mentioned in (Thiel et al., 2019), most funding schemes for digital healthcare solutions and services are made for an analogue age. Caregivers are paid based on the patients' visit and the care they provide, without considering the value of preventing harm, reducing costs, and making better utilization of doctor's time through the provision of remote care and mobile tools and apps.

Before the pandemic, health was not a priority within national e-government initiatives. There was a lack of a holistic understanding of the potential of digital transformation of the health sector, which is expected to require enhanced collaboration with the private sector towards building capacity for better policy dialogue. Significant investments for the initial acquisition and setup of EMRs have already been made in Greece, without substantial payoff. Still, EMR adoption is low, and no uniform way of evaluating and establishing comparable service level agreements with vendors providing technical support is in place. Without a considerable, coordinated effort, which will likely include realigning financial incentives, EMR adoption in hospitals will lag. Nevertheless, these investments are unlikely to pay back unless end-users, healthcare providers and patients alike endorse them.

Countries that succeed in digitalizing their healthcare systems feature an effective strategy, strong political leadership and a coordinating institution with a clear national mandate. Any new legislation and guidance would need to be developed to govern and enable distributed and decentralized data models (European Federation of Pharmaceutical Industries and Associations, 2020) that support the use, management, and sharing of data and information while at the same time they address the issues of access, privacy, ethics, interoperability, and ownership. This will require multidisciplinary and intergovernmental governance structures and formal agreements to exchange data and information and new flexible laws to introduce innovations in digital health. Data governance is fundamental in this effort. Key steps to close the digital gap include changing the mindset and liberating the data.

The development of quality EMRs is not an issue to be resolved by technology on its own. It requires institutional interventions and legislation to properly manage a governance model that will facilitate co-responsible ministries (such as those for health, digital governance, development, social security, economics, etc.) for a coordinated approach towards ehealth interoperability and quality EMRs.

Proposed Actions

Key actions that need to be taken on the way towards quality EHRs are the following:

- Define data quality and interoperability standards. Establish a national interoperability framework and let EMRs interoperate with each other and with EHRs and PHRs. Meet expectations. Support interoperability by design. To do this, the implementation should be meaningful, based on appropriate technical characteristics and common implementation standards.
- Raise awareness. Expose best practices. Inform everyone that EMR systems are available and promote the use of open APIs. Use incentives for motivating EMR adoption and use. Take learnings from the multiple digital health data pilots in member states or disease areas to create a positive environment that builds a sustainable ecosystem of health data utilization. Build a coherent dissemination and communication strategy.
- Invest in human resources and the development of healthcare practitioners' digital skills and literacy. Provide appropriate education and training to facilitate the best use of digital solutions to deliver better outcomes. Provide resources to upskill both data consumers and data producers with the necessary competencies to understand their data and manage it appropriately.
- Establish robust central services in the core, national infrastructure services by financing standardization and quality assurance. Establish a way to monitor and control progress. A balance between long and short-term objectives should be maintained. Focus on standardized APIs that will allow the healthcare industry and individuals to access structured electronic health information securely. Provide guidelines and resources for quality and secure enablement.
- Establish an interoperability governance body for the healthcare domain as a critical enabler to a holistic approach towards linking EMRs, in line with eHealth and national digital policy governance. Interoperability should be guaranteed sustainably and not as a one-off target or project. As such, operators, clinicians, and/ or vendors whose systems are connected should be involved in the use cases definition and interoperability specifications development process from early stages. The magnitude of the investment needed should not be underestimated if the EHR implementation is to be successful.

The global practice has shown that the proliferation of public eHealth services is reinforced when the public maintains the role of a central regulator rather than when it attempts to operate them competitively to the private sector with the risk of degrading the value of the services provided in the minds of the users. Services of this type are public goods, and as such, they should have the most negligible dependency on contractors and the maximum development momentum at the end-user level. Additional issues to take into consideration for the successful and large-scale implementations of the EHR in an NHS focus on leadership, governance and vision, clear definition of the business case, objectives, benefits and outcomes, a realistic implementation plan, change management, health system reform, evaluation and assessment of similar initiatives, stakeholder involvement, vendor selection, infrastructure and information-structure, education and training, resources, and legislation (Esterle & Kouroubali, 2010). Subsequent efforts should be paid towards establishing an integrated EHR backbone, emphasizing issues relevant to protecting sensitive information and cultivating trust among all relevant stakeholders.

FUTURE RESEARCH DIRECTIONS

Healthcare is a complex, knowledge-driven industry that continuously creates massive amounts of clinical, financial and research data. Digital health initiatives focus on three main objectives: (i) to expand healthcare coverage; (ii) to optimize resources; and (iii) to enhance services. The amount of data generated by public bodies, businesses and citizens is constantly growing. Not all data need sharing. Still, since data are sensitive, this has to be done to be trusted and protected when shared. For businesses and citizens to stay in control of data, they need appropriate tools. Careful and attentive analytics can transform data into knowledge that can improve patient outcomes and operational efficiency.

The focus of current research directions in healthcare aims to support healthcare systems' transformation in their efforts towards fair access to innovative, sustainable and high-quality healthcare for all. Digital solutions can support healthcare delivery across all stages of the patient pathway. Research areas include life coaching via digital tools, early diagnosis tools, EMRs and workflows to keep track of treatments, day-to-day symptoms and essential documents, monitoring tools for citizens with chronic conditions, remote rehabilitation and post-operative care.

It has been demonstrated repeatedly that the use of guidelines by healthcare providers is an effective way of achieving objectives, such as improving effectiveness and quality of care, standardizing medical care, decreasing variations in clinical practice, and achieving the best balance between cost and effectiveness (Kredo et al., 2016). Clinical practice guidelines are usually produced at national or international levels by medical associations or governmental bodies through evolving processes. Local healthcare providers may have their own set of guidelines or adapt them from existing top-level approaches, while healthcare payers such as insurers practicing utilization management also publish guidelines (Moses & Feld, 2008).

Horizon Europe (https://ec.europa.eu/info/research-and-innovation/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe_en) aims to find new ways to keep people healthy, prevent diseases, develop better diagnostics and more effective therapies, use personalized medicine approaches to improve healthcare and wellbeing, and take up innovative health technologies, such as digital ones. Regarding competition challenges, measures need to be taken to facilitate reusing specific data held by the public sector (e.g., reusing health data could advance research to find cures for rare or chronic diseases). Work has to be done towards giving citizens control on using the data they generate by making it easier and safer for companies and individuals to voluntarily make their data available for the broader common good under precise conditions.

The digital compass (<https://digital-strategy.ec.europa.eu/en/policies/digital-compass>) sets objectives to achieve the EU's vision for the digital future. It uses the four points of the compass to identify the main goals to reach over the next decade: a digitally skilled population and highly skilled digital professionals, secure and substantial digital infrastructures, digital transformation of businesses, and digitization of public sectors. Key policy areas to ensure these goals are met include cloud computing, AI, digital identities, data, and connectivity.

CONCLUSION

COVID-19 was a driver and accelerator of digital healthcare innovation during the pandemic. Despite recent efforts, large amounts of health data of every citizen continue to be confined in data silos. Reusing data is often not an option due to the limited interoperability among digital health solutions, rendering

the vision for better healthcare largely unattainable. Often, data are of variable quality and unstructured, as free text, posing more significant challenges for automatic processing (Romero et al., 2020). In addition, there is a massive gap between public and private sectors, and interoperability tends to work only in high impact cases such as national registries (Kouroubali & Katehakis, 2019). EMRs are considered to be a core building block of electronic data collection, processing and sharing.

Digital transformation is a change management process to close the gap between demand and supply. Governance of interoperability in the healthcare domain is needed within the greater context of public services interoperability. Health data and advanced data analytics can help accelerate scientific research, personalize medicine, and provide early diagnosis of diseases. Advancing digital transformation focuses first on individual, well-prioritized, meaningful services rather than large-scale, all-encompassing programs. Interoperability is crucial for having appropriate open access to correctly disaggregated data and integrating local and national systems.

The improvement of the health of the population requires quality and secure EMRs. A significant challenge for interoperability is to transfer patient information from one care setting to a different one, translate it, and simultaneously conserve the clinical meaning of the information.

The NHS in Greece is transitioning towards health IT systems powered by cloud computing and data analytics. Building on existing human effort and experience and already available infrastructure, the significant funding required can be better controlled. By having the entire EHR available, it will be far more possible to tailor medical care to each individual's clinical needs and empower healthcare professionals and citizens to make informed decisions.

ACKNOWLEDGMENT

This research was supported by the Center for eHealth Applications and Services of the Institute of Computer Science, Foundation for Research and Technology – Hellas.

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Chapter 8

The Impact of 3D Printing Technology on the COVID–19 Pandemic

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ABSTRACT

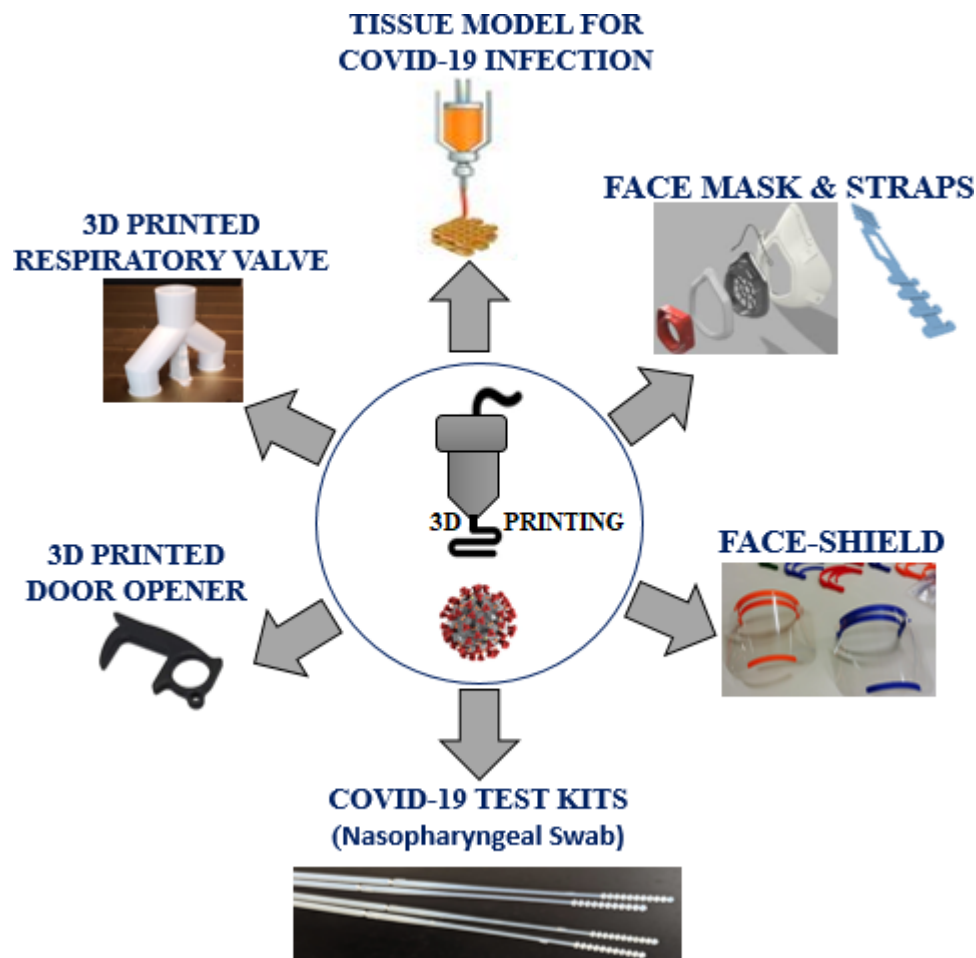
3D printing technology has influenced the healthcare and medical sector during the COVID-19 pandemic. 3D printer machines fabricated numerous medical kits and accessories. These include face shields, specimen collectors, personalized face masks, ventilators, protective eyewear, personal protection equipment (PPE), and isolation wards/chambers. All these were fabricated in a short period as requirements were increasing expressively. The chapter describes several of these applications of 3D printing, which assisted in looking after numerous lives throughout the COVID-19 pandemic. The cooperation of the 3D-printing knowledge with the worldwide healthcare community will develop innovative and essential prospects in the upcoming days. Also, numerous important proposals are described that were applied to fight against the COVID-19 outbreak, monitored by a discussion about the upcoming trend of how additive manufacturing can help people worldwide to control any upcoming pandemic situation.

DOI: 10.4018/978-1-7998-9198-7.ch008

INTRODUCTION

In December 2019, the COVID-19 or SARS-CoV-2 disease was first noticed in Wuhan City, China (Huang et al., 2020). In the meantime, the virus has rapidly spread worldwide, and the WHO (World Health Organization) has announced this virus disease as a pandemic in March 2020 (WHO, 2020, Situation Report 23). The origin of this virus in bats, pangolin, and human transmission mainly happen through straight, incidental, or close interaction with diseased persons or infected patients through infested secretions, for example, saliva, respiratory secretions, or respiratory droplets, which are ousted when a sick patient on speaks, sneezes or coughs. Also, this virus can be spread via aerosol, droplets (Barua et al., 2021), and physical contact (direct or indirect) from contaminated surfaces, wherein the virus may stay up to 72 hours (Wesemann et al., 2020; van Doremalen et al., 2020). The disease COVID-19 infects people both symptomatically and asymptotically (WHO, May 27, 2020). At times the oxygen level of an infected person drops so much that they are admitted to the hospital or maybe ICU (Intensive Care Unit) (Tabashi et al., 2020; Cavallo et al., 2020). Due to COVID-19, the healthcare systems and other organizations are facing lots of pressure and colossal crisis. For protection from this virus, face masks, face shields, head caps, gloves, sanitizers, contact-less door openers, and PPE (Personal Protection Equipment) are needed. As the number of active cases increases rapidly, an emergency was seen in supply chain disturbance and crisis in the recommended products for protection. To meet the crisis, different organizations like research institutes, universities, companies, etc., came up with a solution and started supplying the items to the hospitals to fulfill the crisis (Advincula et al., 2020). Numerous devices have been created, like face shields, face masks, contactless door openers, test swabs (Tsikala et al., 2020; Larrañeta et al., 2020; Das et al., 2020), etc. In this situation, 3D printing has appeared as one extraordinary manufacturing procedure for its flexibility and accessibility to rapidly produce compound and uniform objects (Guo et al., 2013; Franchetti et al., 2017). An additional intention is that individuals involved with the 3D printing process are innovative, resourceful with interdisciplinary connections and uses. For that reason, 3D printing technology permits the operator to produce desire objects directly from a .stl file format that can be originated merely and shared in different maker hubs or social media also (Vordos et al., 2020). 3D printed products may contain various characteristics and textures because of uses variances of materials, and different software and setting, even for the same design (Clifton et al., 2020; Kabir et al., 2021). PPE (Personal Protection Equipment) and healthcare kits always maintain the standards. So, there is a necessity for understanding every machine, practice, and standard to certify that 3D printed products can be helpful in the resolving plan with the minimum risk for healthcare individuals and patients. Figure 1 shows the various applications of 3D printing technology in the COVID-19 pandemic. This chapter targets to look over the practice of 3D printing technology during this pandemic of COVID-19. It emphasizes several healthcare devices, PPE (Personal Protection Equipment), and different uses, providing their foundation and deliberating their practice and regulatory issues.

Figure 1. Uses of 3D printing in the pandemic of COVID-19

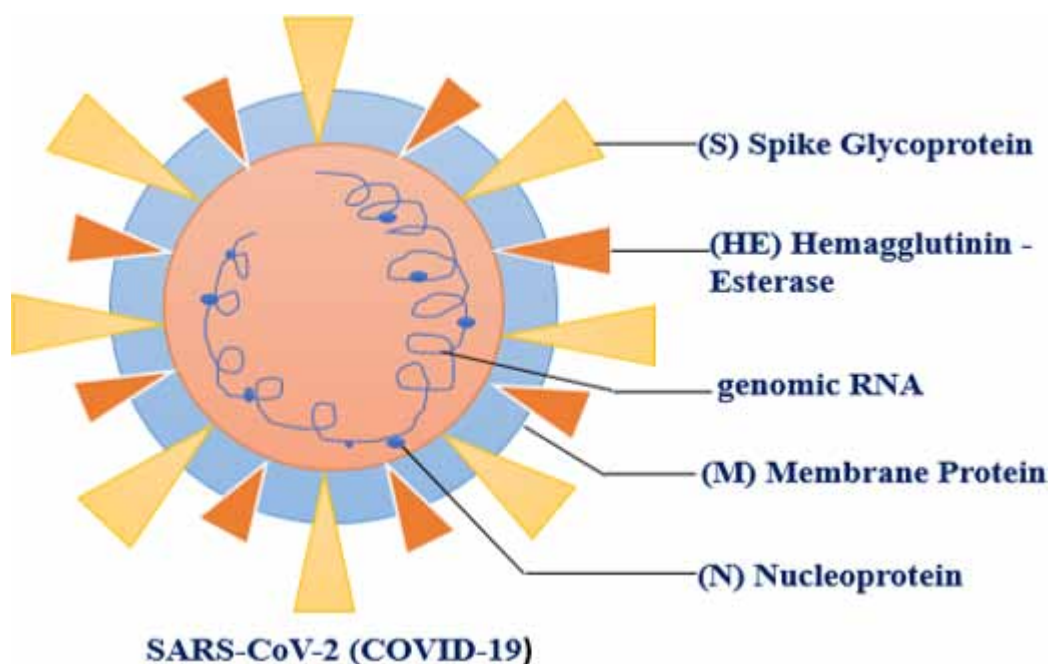


SARS-COV-2 (COVID-19)

COVID-19 or 2019-nCoV is an encircled single-stranded +VE-RNA virus, which has crown-shaped surface glycoprotein projections and belongs to the coronavirus family (Song et al., 2020; Li et al., 2020). It has a phosphorylated nucleoid capsid protein and nucleocapsid composed of genomic RNA (Li et al., 2020). It originates from a standard group of families with viruses like SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome), which appeared in earlier periods (Song et al., 2020) (Barua et al., 2021). This virus has S-protein (Spike). Coronavirus is highly transmissible and has a 3-15 days incubation period. The virus contaminates the human respiratory epithelial cells via binding by ACE2 (Angiotensin-Converting Enzyme 2) receptors. Figure 2 shows the genome structure of novel coronavirus (COVID-19). The main clinical symptoms of the COVID-19 disease are dry cough, fever, malaise, fatigue, and breathing difficulty. Severe infection like ARDS or acute respiratory distress syndrome, pneumonia, and death happens in the aged and patients with comorbid situations. Studies have shown that coronavirus typically comes into the body via respiration and causes pneumonia by infecting the lungs (Singhal et al., 2020). In the investigations performed on the lungs of the COVID-19 positive

patients, consolidation pneumonia and ground-glass opacities were noticed in the lungs of certain patients who undertook chest Computed tomographic (CT) image scans (Berheim et al., 2020). Many studies on COVID-19 diagnosed patients presented that the coronavirus also influenced the cardiovascular system (Nishiga et al., 2020; De Felice et al., 2020). The detection of virus-related RNA primarily identifies the COVID-19 disease in nasopharyngeal swab or Broncho-alveolar lavage (BAL) through the polymerase chain reaction RT-PCR (Reverse Transcriptase-Polymerase Chain Reaction) (Tsikala et al., 2020).

Figure 2. Genome structure of novel coronavirus (COVID-19)

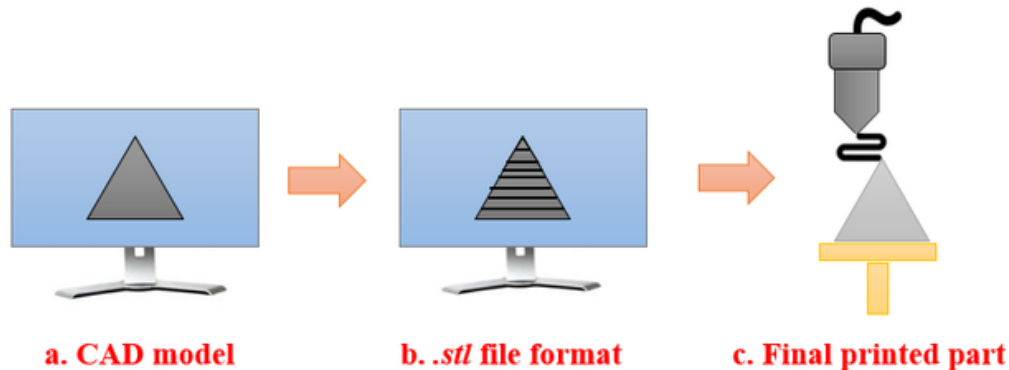


THE ADDITIVE MANUFACTURING TECHNOLOGY

The additive manufacturing technology, known as the layer by layer manufacturing process, is built on the principle of layered fabrication of several materials like metals, powders, plastic, ceramics, and living cells (Barua et al., 2019). This process makes different and complex three-dimensional geometries by a CAD (Computer-Aided Design) model or CT image scanning (Computed Tomography) (Yan et al., 2018; Ngo et al., 2018). This technique can make the customized structure and tissue scaffold (in the case of the bio-printing process) and rapidly produce and fabricate defective regions directly (Figure 3). Like this, additive manufacturing technology deals with new prospects in healthcare to solve different problems and construct tissue scaffolds (Mardis et al., 2018; Barua et al., 2019). 3D printing technique has recently expanded great significance in the healthcare area, especially implant, biomedical tools, cell printing, etc. (Schubert et al., 2013; Barua et al., 2019). The fabrication procedure contains numerous phases like CAD software, model design, material selection, fabrication, testing, etc. The preferred model is designed by CAD software. Then the model is converted into .stl format. The most crucial factor of

the designed creation is the material applied to make the object. The appropriate material selection is vital for this manufacturing process (Barua et al., 2020). The information is complete to be sent to the machine; usually, G-Code is used.

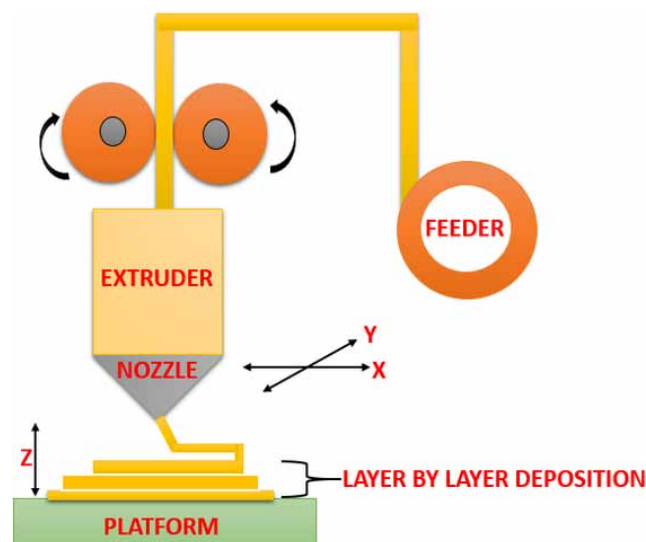
Figure 3. A basic 3D printing process



FDM (Fused Deposition Modelling)

In this process, thermoplastic polymer filament is used as a base material to create the desired object. Initially, the thermoplastic polymer filament is heated until it reaches its liquid phase to flow within the nozzle. At that time, this liquid material will extrude from the nozzle and deposit on the surface to create the initial layer of the desired model, which has to be printed (Figure 4). This process will continue until the desired model is prepared (Mwema et al., 2020) (Yang et al., 2020). This technique is low-cost and easy to custom and connect. Various types of thermoplastic polymer filament are available, for example, ABS, PLA, Nylon, TPU, etc. (Wickramasinghe et al., 2020).

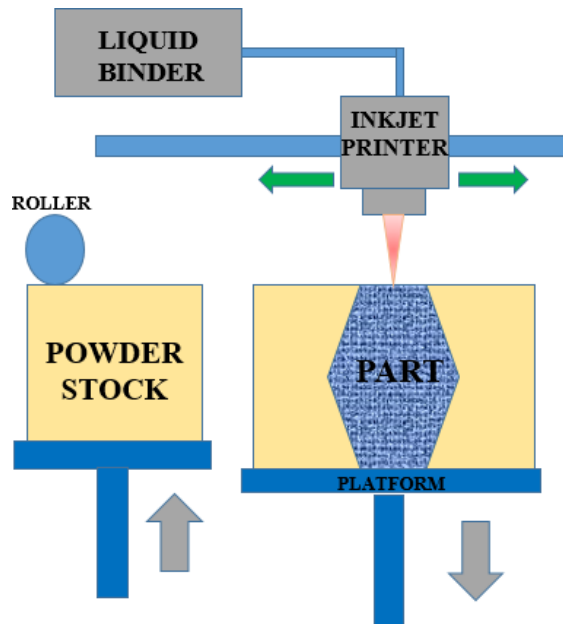
Figure 4. Fused deposition modelling process



Binder Jetting 3D Printing Process

Binder jetting is a 3D printing procedure that applies a liquefied binding agent that dropped on top of a surface plate to create the initial layers of material (powder) and build an object (Gao et al., 2019). This procedure can be applied to create a variation of materials containing metals and non-metals like ceramics, polymers, and sands (Figure 5). This procedure permits color printing and custom metals and non-metals like ceramics and polymers materials (Methani et al., 2020). Binder jetting process is mostly quicker than others processes and can be faster by growing the number of print head holes. Additionally, the process is reasonable, simple, and proficient in fabricating huge products (Meenashisundaram et al., 2020).

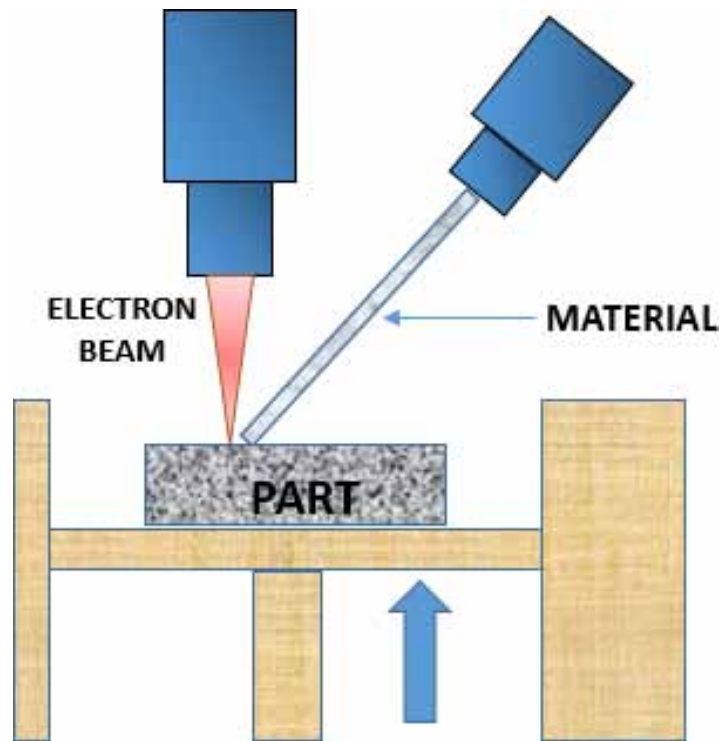
Figure 5. Binder jetting process



DED (Directed Energy Deposition)

DED (Directed Energy Deposition) is an additive manufacturing method that practices a focused high energy light, such as an electron beam, laser, or a plasma arc, to liquefy the material deposited through a nozzle. Directed Energy Deposition is also known as the metal 3D printing process (Figure 6). This process is mainly applied in the manufacture of superalloy objects (Ryu et al., 2020). The Directed Energy Deposition process is also used for printing metals, alloys, and non-metals like ceramics and polymers (Saboori et al., 2018).

Figure 6. Directed energy deposition process



Material Jetting Process

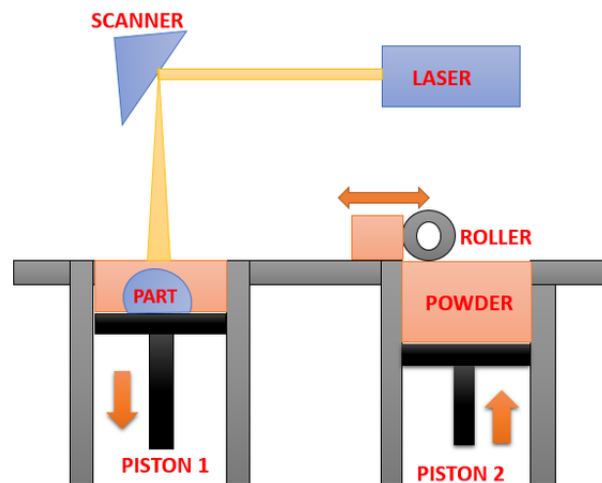
In this process, the material is designated and dropped layer by layer. This procedure provides light-sensitive material drops from the printer head, constructing an object layer by layer by the UV (Ultraviolet) light (Parab et al., 2019). The material jetting process makes objects of great dimensional accuracy with a precise surface finish. A wide variety of materials like transparent material, rubber, or ABS-like photo-polymers are used and make the process is the multi-material printing process. (Jockusch et al., 2020).

Powder Bed Additive Manufacturing (PBF)

These additive manufacturing processes are SHS (Selective Heat Sintering) process, EBM (Electron Beam Melting) process, and SLS (Selective Laser Sintering) process. The powder material is melted by focusing a LASER light or an electron beam (Figure 7). Many materials are used in this manufacturing

process, like pure metal powder, composite material powder, ceramics, hybrids, and polymers (Fereiduni et al., 2019).

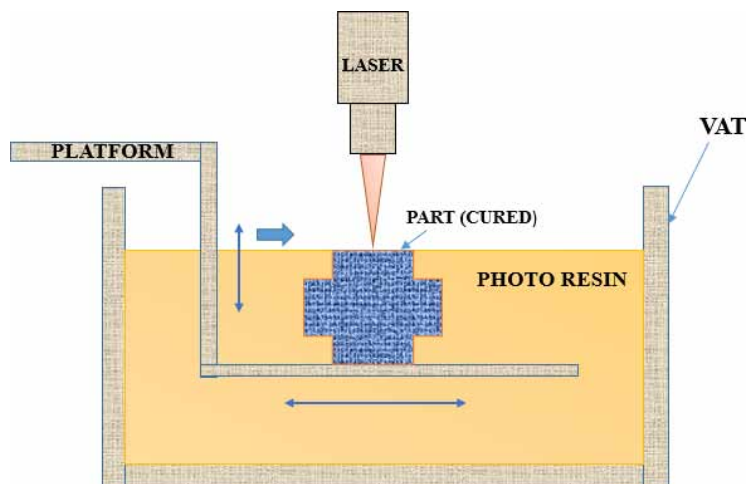
Figure 7. Powder bed additive manufacturing process



Vat Polymerization Additive Manufacturing Process

This process is usually established on the principle of applying an energy light like LASER or UV (Ultraviolet) light to the curing of photosensitive polymers (Figure 8). The typical examples of this process are SLA (Stereolithography) and DLP (Digital Light Processing) (Stefaniak et al., 2019). SLA (Stereolithography) is the first additive manufacturing procedure to be commercialized and patented. All kinds of vat polymerization processes apply photopolymers resins as a fabricating material. When the material is exposed to the focused light source, the material molecules become molten and quickly bind each other and cure into a solid phase (Barua et al., 2019). In this method, the liquid material is held in

Figure 8. Vat polymerization process

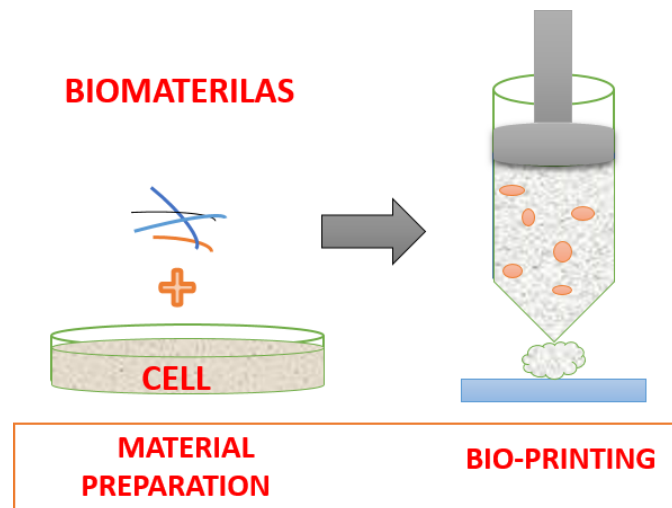


a vat or basin with the construct platform partly submerged adjacent to the liquid surface. Applying the data provided by a CAD file, the device guides the light source to exactly cure the liquid material into a solid layer (Marsico et al., 2020). At that time, the build platform is re-submerged into the remaining resin, and the process is repeated for the subsequent layers until the design has fully printed.

Bio-Printing

The bio-printing process has appeared as an emerging tool for constructing the tissue scaffold and artificial organ in biomedical and tissue engineering (Datta et al., 2021). Bio-printing allows exact engagement of cells, hydrogel-like biomaterials (Figure 9), and biomolecules in particularly preplanned positions in

Figure 9. Bio-printing process



confined 3D configurations (Biazar et al., 2018). Bio-printing is the arrangement of a three-dimensional printing process with biomaterials to print the parts that mimic natural bones, living tissues, and blood vessels in the living body (Murata et al., 2020) (Datta et al., 2019; Barua et al., 2020). It is mainly applied in connection with modern drug delivery and in recent times as tissue scaffolds to support healing the injured ligaments or tendons etc. (Charbe et al., 2017).

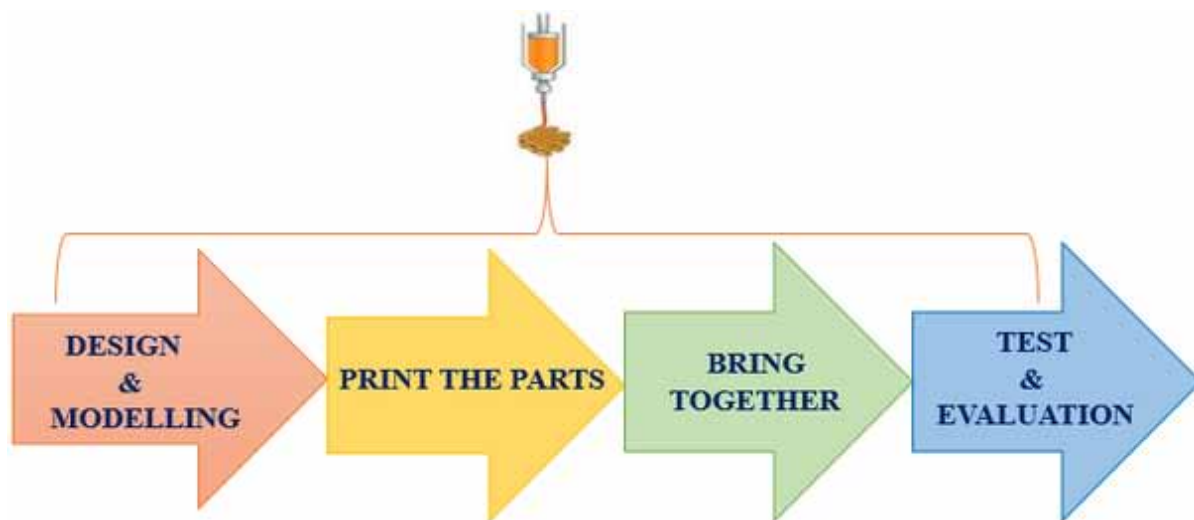
ADDITIVE MANUFACTURING AND THE COVID-19 PANDEMIC

Additive manufacturing allows the latest results for an extensive range of requirements stretching from individual protection kits to health devices and quarantine wards. This flexible technique is matched to report resource–demand inequities produced by socio-economic inclinations and disturbances in supply chains (Choong et al., 2020). The worldwide haziness created by the pandemic of COVID-19 has rushed the world into an emergency that is still evolving. Logistical problems due to disturbances in

transportation and manufacturing, together with pushbacks in contrast to globalization and free trade, have controlled supply chains, ensuing in severe deficiencies of vital things. Healthcare structures are on a battle footing to upsurge their goods, beds, and skilled employees. Crisis-response struggles are in motion to improve the lack of much-needed medicinal provisions (Tarfaoui et al., 2020). It is essential for manufacturing plants, the demand of supplies, and strategies for various necessary amenities, specifically for healthcare. In this situation, a solid progressive manufacturing setup allowed by the spreading of 3D printing workshops has an excessive perspective (Oladapo et al., 2021). Altogether, due to this pandemic, the demand for medical devices was increased (Belhouideg et al., 2020) and generated the latest market of products for the common public. It activated many supply chain interference, quickly creating a lack of several critical objects, for example, PPE, face mask, face shield, etc. (Shokrani et al., 2020; Cox et al., 2020).

Regarding this problem, firms, agencies, and companies started to collaborate to supply the public and hospitals facing a shortage of items (Fiorillo et al., 2020; Livingston et al., 2020; Mueller et al., 2020). By the way, additive manufacturing has appeared as a prospective flexible key providing several types of required items, representing the possibility of additive manufacturing for a confined and flexible fabrication of planned items, decreasing supply chain reliance (Thomas et al., 2020; Choong et al., 2020; Silva et al., 2013). Figure 10 displays the basic plans for the improvement of 3D-printed medical devices. Also, another important cause that made additive manufacturing a significant implement during the COVID-19 pandemic is the massive number of consumers worldwide (Vordos et al., 2020; Cox

Figure 10. Basic plans for improvement of 3D-printed medical devices



et al., 2020). Moreover, the cost of feedstock, generally the polymers' filament, is still lowering for this type of 3D printing (Choong et al., 2020; Franchetti et al., 2017). Therefore, the capability to produce objects for providing the pandemic unavailability is not limited to production: manufacturers, individuals who have access to quick manufacturing apparatuses. For example, 3D printers have been confirmed to expressively contribute throughout the COVID-19 pandemic (Novak et al., 2020). Nowadays, the

The Impact of 3D Printing Technology on the COVID-19 Pandemic

printable files of any model are available on the Internet, like different maker hubs, several open-design sources, etc. (Vordos et al., 2020).

Another advantage of additive manufacturing technology is that the problematic parts that need a long time of planning via conventional procedures can be rapidly invested in manufacturing by the additive manufacturing process. It has a slight lead time to bring minor batches of objects, creating a practically instant response to the emergency (Mueller et al., 2020; Franchetti et al., 2017; Manero et al., 2020). The performance capability for additive manufacturing also endorsed the rapid fabrication of the main plans and machine models. Additionally, an additive manufacturing ability for low-end devices does not involve multifaceted arrangements or infrastructure. Table 1 shows the different 3D printing process that helps in making the essential COVID-19 equipment. A technical note on device manufacturing was given as an example (Vordos et al., 2020) (François et al., 2020), linked to the pandemic of COVID-19 for Greater Paris University Hospitals and many state institutes. To fight against the pandemic of COVID-19, massive testing is the only way to prevent it. Therefore, the swab sample was collected from the upper respiratory tract and examined by RT-PCR (Reverse Transcription Polymerase Chain Reaction) (WHO, MAY 27, 2020). A nasopharyngeal swab gives the highest sensitivity (Callahan et al., 2020). The FDA

Table 1. A full description of the crucial initiatives for fabricating essential equipment by different additive manufacturing procedures during the COVID-19 pandemic

Product Name	Manufacturing Process	Material	Open Source
Face Shield	FDM/SLS	PETG/PLA	No
Face Shield	SLA	Nexa3D developed material	No
Face Shield	SLS/SLA/DLS	DSM Somos resin	Yes
Face Shield	FDM	ABS	Yes
Face Mask	SLA/SLS	PLA/ABS	No
Face Mask	FDM	TPU/PETG	Yes
Face Mask	SLA	Formlabs Draft Resin	No
Ventilator parts	High-Speed Sintering	Windform P1	Yes
Ventilator parts	SLS	Medical Grade Nylon	No
Ventilator parts	FDM	ABS	No
Ventilator parts	SLS	PLA	Yes
Nasopharyngeal swabs	Envision One cDLM printer	Soft C-29C resin	Yes
Nasopharyngeal swabs	SLA	Surgical Guide resin	Yes
Nasopharyngeal swabs	Carbon3D M2 Printer	Carbon3D resin	No
Nasopharyngeal swabs	NXE 400	Nexa3D material	No

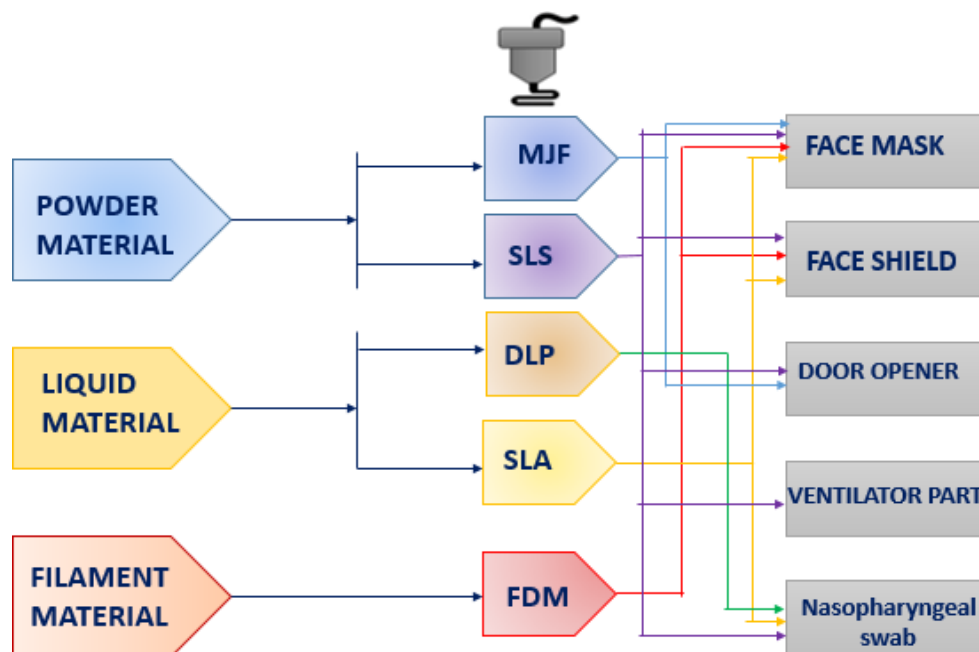
approved this test (Food and Drug Administration) (Sinha et al., 2020). The test kit contains a polymer base stick whose head is covered with synthetic material. At the time of the swab collection, the health worker uses the stick to collect the swab from the upper part of the respiratory tract. Then the sample is collected and stored in a vial in viral transport media, and then the sample is sent for examining. The swab must be sterilizable and supply for a consistent and safe examination (Arnold et al., 2020; Tino et

al., 2020). The isolation of infected and suspected patients of COVID-19 disease is a must to prohibit the spread of the disease (Barua et al., 2021; van Doremalen et al., 2020).

As per the various studies, infected patients may transmit the coronavirus via droplets and aerosols (Wesemann et al., 2020; Larrañeta et al., 2020). Thus, the local infection can be decreased by some strategies. A negative airflow isolation chamber was introduced for the infected patients (Cubillos et al., 2020). The device contains a square frame chamber fixed and wrapped with a transparent polymer bag where negative air constantly flows and avoids it from going into the chamber, contaminating the external area. 3D printed products are used, which permits nebulization, oxygen delivery, and suction (Rösch ET AL., 2020). The novel coronavirus may stay on different surfaces for up to 3 days or 72 hours (Tino et al., 2020; van Doremalen et al., 2020). Therefore, avoiding direct interaction with surfaces is a powerful tactic to decrease infection for the duration of this COVID-19 pandemic, mainly in community and health centers (Tino et al., 2020). Some items, for example, door handles, buttons, switchboards, etc., are possibly virus transmitters because of the maximum time of contact with different persons (François et al., 2020). To permit the opening and closing of the door with forearms or elbows, non-contact door opener devices are attached to door handles (Mueller et al., 2020; François et al., 2020). Various types of non-contact door opener devices like circular, rectangular, spherical, and cylindrical are fabricated by different types of the additive manufacturing process such as FDM, SLS, etc. (Materialize Acts, 2020). Figure 11 displays the different types of additive manufacturing methods involved in making the essentials required for COVID-19.

Additionally, non-contact hand-free devices are used to open the doors, push buttons, open water taps, and additional regular works are customized for various uses. One of the numerous uses for additive manufacturing technology is the learning area. This technology can be applied by fabricating simple methods to help healthcare personnel improve skills and abilities (Hervás-Gómez et al., 2020; Buehler et al., 2013; D'Urso et al., 1998).

Figure 11. Different types of additive manufacturing methods involved in making COVID-19 essentials



By the way, AuMed (Creat3D, 2020) created a manikin to support the teaching of inexperienced healthcare employees in the diagnosis of COVID-19 by swab testing process (nasopharyngeal) (Hervás-Gómez et al., 2020).

The usage of additive manufacturing in training is increasing, following the improvement of Industry 4.0. The 3D printing process is now well-combined into the fight against the COVID-19 by making suitable tools, as low-cost desktop 3D printing machines with low-cost desktop models permit cost-effective three-dimensional models.

FUTURE PERCEPTION OF 3D PRINTING

The existence of the COVID-19 pandemic warned the world how impulsive product demand could encounter the resources to an amount where even 1st world nations face severe problems in confirming the elementary hygienic requirements of societies. Moreover, the excessive need for products includes groceries, sanitizers, masks, PPEs, the mental stress of pandemic on the ordinary people, and affected significant anxiety purchasing and hoarding of different merchandise. Furthermore, despite the improvements in the worldwide healthcare networks, the pandemic of COVID-19 carried a strong message regarding the exposure of the global community to such a global emergency, with the consequent financial crisis. As the re-occurrence of these severe circumstances might be predictable in the future, availability to internal manufacturing techniques containing 3D printing can offer persons with substitute explanations, serving to control the influence of an unexpected rise in demand.

Though present 3D printing types of machinery face numerous serious inadequacies that avoid routine usage, the current methods need engineering assistance and capability to plan and exemplify the CAD (computer-aided design) files. Most of the printed products, irrespective of the 3D printing technique, need post-processing, for example, support elimination, washing, and post-curing; all entail preceding information.

3D printing requires ongoing maintenance containing standardization, cleaning, and additional consumables, etc. Moreover, large-scale manufacturing of items with the existing 3D printing rapidity and setting is controlled by price and manufacturing interval, which is the utmost challenging problem throughout the COVID-19 pandemic. Consequently, large-scale expenses are required before 3D printing meaningfully can be applied as a bulk manufacturing process.

CONCLUSION

The incidence of the novel coronavirus (SARS-CoV-2) pandemic has hampered healthcare areas, clinics, hospitals, and the community with a recorded requirement for personal protective equipment and particular remedial devices. Worldwide supply chains have also been unsettled by this uncertain pandemic, producing the vital transportation of urgent healthcare goods an extra challenge. 3D printing is also being practiced to offer working out and conjure reliefs for healthcare personnel to handle the limited group expert staff. The facility to fabricate the complex humanoid structures or organs in exact replicas allows 3D printing of actual size health manikins to supplement training materials and enable healthcare workers to practice COVID-19 swab testing processes with typical swabs. Several measures of the manikin are made with transparent materials to expose the internal configurations of the mouth,

throat, and nasal cavity. Instructors can explain the processes plainly while highlighting special protection to minimize uneasiness in persons.

ACKNOWLEDGMENT

The authors acknowledge the Centre for Healthcare Science and Technology, Heaton Hall, IEST-Shibpur, India, and thank Mrs Nibedita Bardhan for language proofreading.

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Chapter 9

RFID Applications for Patient Safety in the Healthcare Sector

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ABSTRACT

Internet of things (IoT) is revolutionizing industries through enabling object identification, traceability, real-time communication, and monitoring. In healthcare (HC), IoT can reduce the unneeded physical contact through the possibilities of remote monitoring and tracking of patients, which can be used in pandemic control scenarios. One area of paramount importance in HC is patient safety. Published statistics suggest a mounting number of patient mistreatments due to the erroneous identification of the patient or the drug administered. Radio frequency identification (RFID) is envisioned as a disruptive innovation in HC and represents several opportunities for increased safety. The authors explore the potentials and challenges of RFID adoption in HC with a focus on patient safety. The findings suggest that there has been a surge in IoT applications in HC research in the last two years concerning pandemic control. However, the high costs of adoption and implementation, security and privacy concerns, and human safety risks are among the main barriers to adopting IoT in HC.

INTRODUCTION

The Internet of Things (IoT) technologies are opening tremendous opportunities and domains of new applications which promise better quality for our lives (Cleveland & Haddara, 2021). IoT refers to an interconnected web of smart devices, sensors, and humans. Data can be collected and communicated through the Internet to be analyzed for patterns or trends via (big) data analytics applications (Rahman et al., 2020). Legacy machines and devices can also become *smart* by equipping them with sensors, actuators, and means to connect to the Internet to enable inter-communication among devices, remote control, and two-way communications with cloud servers (Vollen & Haddara, 2019). Many research

DOI: 10.4018/978-1-7998-9198-7.ch009

articles have argued that IoT technologies have a potentially massive impact on the healthcare domain (Rahman et al., 2020). Xu et al. (2014) argue that IoT provides new opportunities to improve healthcare. When healthcare is powered by IoT's universal identification, sensing and communication capacities, the objects can be tracked and monitored constantly. These objects can be related to logistics, diagnosis, therapy, recovery, medication, management, finance and even daily activities (Xu et al., 2014). In addition, Wireless Sensor Networks (WSN) sensors can make IoT-based healthcare services mobile and personalized (Xu et al., 2014). The importance of IoT applications has been highlighted even further during the COVID-19 pandemic. The pandemic has exhausted virtually all healthcare (HC) personnel and facilities worldwide and exponentially increased the workload (Sangeeta Mehta et al., 2021). Thus, several researchers have identified potential IoT technologies that may aid in the remote pandemic control, testing, and monitoring of patients (Nasajpour et al., 2020).

Patient safety is one of the main goals of healthcare institutions around the globe. Especially with the increasing population and patients worldwide, patient safety becomes a critical public health concern. However, there is a large number of medical errors that happen every year. There are various types of medical errors classified into the following nine main types (Tariq, 2020).

- 1- Prescription errors.
- 2- Failure to prescribe, administer, or dispense medication.
- 3- Patient receiving medication too late or too early.
- 4- A patient is receiving a drug not authorized for them.
- 5- Improper use of medication.
- 6- Wrong dose prescription or drug preparation.
- 7- Administrative error.
- 8- Failure in considering a patient's medical conditions or potential drug interactions.
- 9- Failure in following proper dispensing/prescribing rules for a medication.

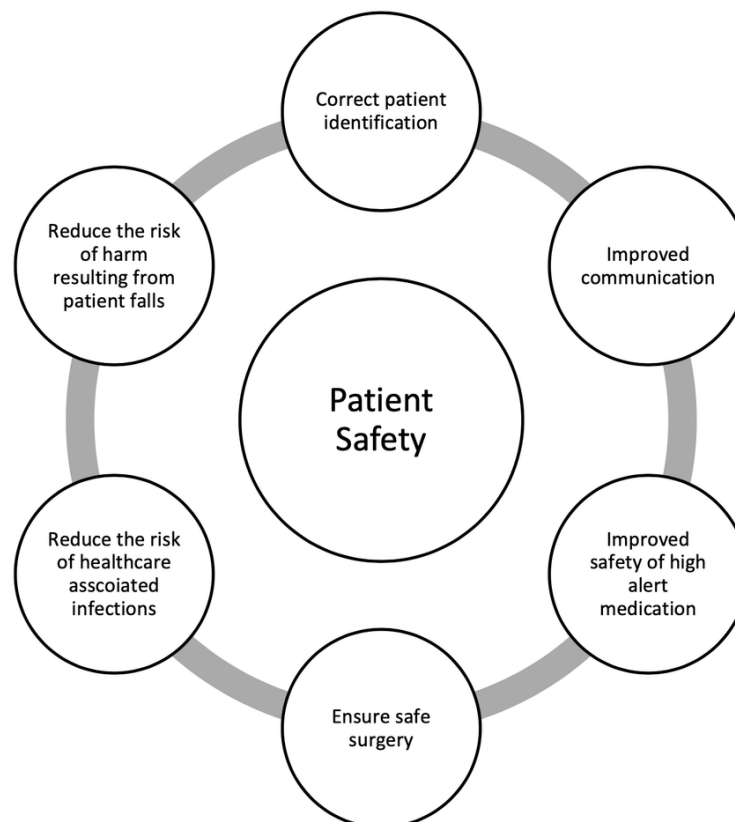
The American Food and Drug Administration (FDA) reports that it receives circa 100,000 medical error reports, which can happen in drug stores, hospitals, and patient homes (Team, 2021). It is estimated that around 7,000-9,000 Americans die due to a medication error every year (Jaam et al., 2021). Globally, about 42.7 million adverse events happen each year out of 421 million hospitalizations (WHO, 2018). The World Health Organization (WHO, 2018) states that there are 1 out of 300 chances for a patient to be harmed when in healthcare due to medical errors. The majority of medical errors are attributed to specimen misidentification, adverse drug events and incorrect blood transfusions (Cornes et al., 2019), which are all mainly caused by misidentification of patients and their related medication (Aguilar et al., 2006; Mehrjerdi, 2015). However, the FDA has estimated that half of the medical errors caused by misidentification are preventable by introducing integrated Information Technology (IT) and Information Systems (IS) infrastructure in order to achieve patient safety, as depicted in Figure 1.

Radio Frequency Identification (RFID) is believed to be the next-generation technology for tracking and data collection. It has successfully been applied in several industries such as manufacturing, retail and logistics. Over the past years, RFID has emerged as a powerful technology for data collection and automated tracking of the identity, location and movement of people, products, assets, and any other object of interest (Yao et al., 2012). However, RFID technology is not new. One of the predecessors of passive RFIDs is "The Thing", a.k.a. "The Great Seal Bug", which was introduced in 1945 and invented by Léon Theremin (Glinsky, 2000). *The Thing* was gifted as "a gesture of friendship" in the form of a

wooden carved great Seal of the United States given to the United States ambassador from the Soviet Union in 1945, which turned out to be a spying and listening device used by the Soviet intelligence KGB (Glinsky, 2000).

On the other hand, the active RFID devices were introduced in 1973 by Mario W. Cardullo (Roberti, 2005). Thus, it took a substantial amount of time for organizations to realize the importance of the technology and to commercialize the RFID technology to deliver value-adding applications related to intelligent management and tracking of objects in the areas of manufacturing, agriculture, supply chain, transportation and healthcare (Tzeng et al., 2008).

Figure 1. International Patient Safety Goals version 2017. Adapted from Joint Commission on Accreditation of Healthcare (2017).



RFID systems use radio waves to capture and transfer data without any human intervention (Yao et al., 2012). A standard RFID system consists of three components: (1) an RFID tag that is attached to an object for identification, (2) an RFID reader that requests the data from the tag, and (3) the middleware that processes and transmits or store the information from the readers (which are connected to the tagged object). As mentioned earlier, RFID tags can be either passive or active. Passive RFID tags have no internal power source, rely on fixed readers and are mainly used for identification and access control. In contrast, active RFID tags are battery-powered, broadcast their signal, and provide a much longer read

distance, making them more suitable for real-time tracking (Panagiotis & Ria, 2006; Sajid & Haddara, 2016). The RFID system can also be integrated with an information system to provide intelligent services based on the information provided through the middleware (Ajami & Rajabzadeh, 2013; L. Hu, Ong, Zhu, Liu, & Song, 2015). Even though RFID promises several benefits for the healthcare industry, the adoption of RFID technology in the health sector has not been as striking as anticipated and still lags compared to other sectors. That is mainly due to concerns related to costs, security, privacy, electromagnetic interference, and lack of industry standards (Yao et al., 2012; Zailani et al., 2015). Even though RFID costs have indeed fallen dramatically over the past years, it has yet to pass the tipping point of economic rationality for hospitals (Aguilar et al., 2006; Sun et al., 2008).

The objective of this chapter is twofold. First, this study aims to explore existing state-of-the-art patient safety-related applications of RFID and explore the challenges affecting the adoption of RFID for improving the quality and patient safety in healthcare. Hence, the following research questions are proposed to guide this research: How can RFID contribute to improving patient safety in healthcare? And: what are the challenges related to the adoption of RFID technology in such application domain?

METHODOLOGY

This research is based on secondary research, where findings from selected research within the scope of this study were analyzed and discussed. To address the research questions in focus and cover relevant publications, the authors conducted a literature review on central topics, including RFID technology, RFID adoption, and RFID applications within the context of healthcare. In general, literature reviews represent a well-established method for accumulating existing knowledge within a domain of interest. In this chapter, we have applied a systematic review approach (Bryman, 2012). This approach is characterized by adopting explicit procedures and conditions, potentially minimizing bias (Bryman, 2012).

The research articles selected have been collected through literature searches using Business Source Premier and Google Scholar between the years 2006 - July 2021. At first, the authors decided to include only relevant papers with at least five citations, which lead to a low number of papers. In addition, most of these papers were before the year 2014. Hence, the authors decided to remove this constraint to enable a wider spectrum and more recent publications in this review. For the literature search, the keywords “RFID” and “healthcare” were used in different forms, in combination with the keywords “adoption”, “patient safety”, “drug compliance”, “patient tracking”, “patient monitoring”, “patient identification”, and “patient management”. In addition, the authors mixed the above keywords with the “COVID-19” and “Corona” keywords to include papers covering RFID applications in the COVID-19 pandemic context.

After the literature has been identified, the authors then skimmed through the abstracts to check the relevance of each paper to this study. After identifying the selected potential articles, the authors then read the papers independently to pinpoint the reoccurring main themes discussed in the existing body of knowledge. In total, 108 papers were deemed relevant and were included in this review. The following table provides an overview of the themes discussed in the extant literature, based on the scope of this study. Some papers fall under more than one theme or topic based on their scope and focus. In addition, publications within the COVID-19 context are presented separately per theme in the table below and shown in Fig. 4.

RFID Applications for Patient Safety in the Healthcare Sector

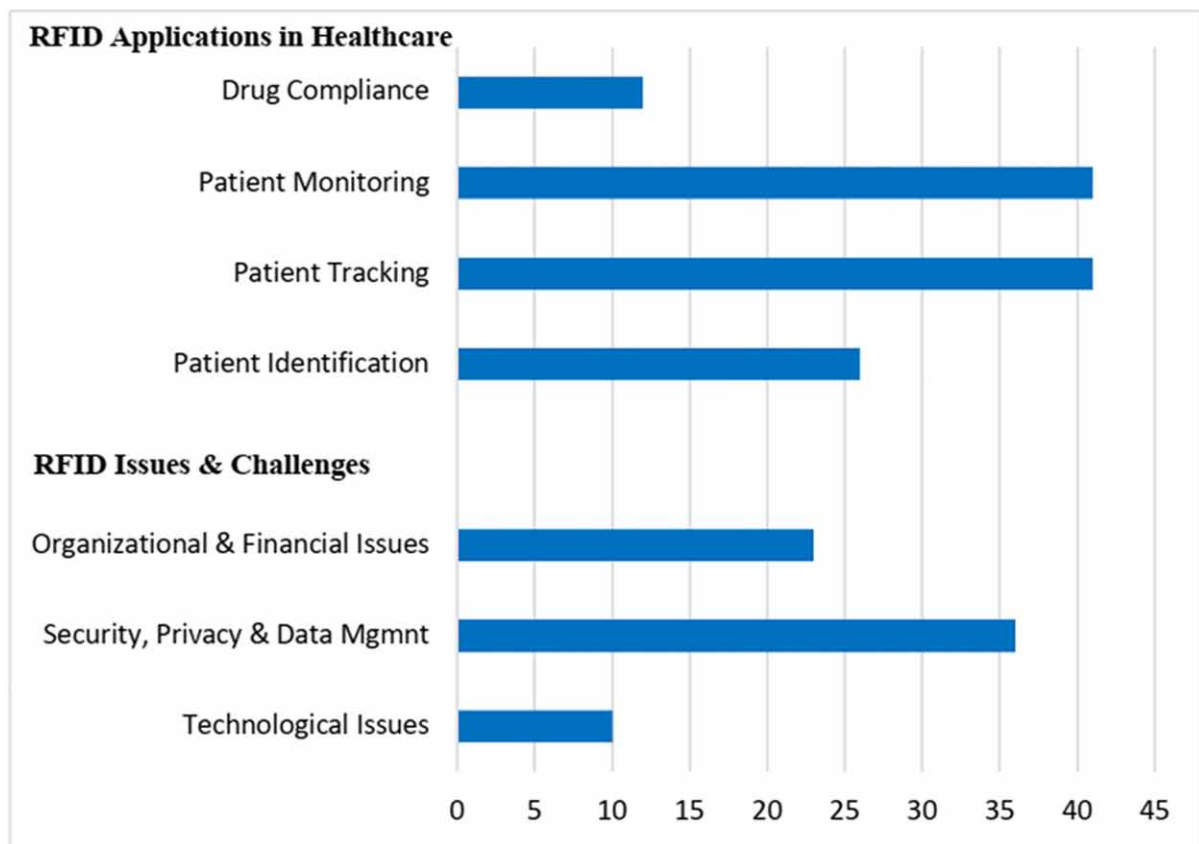
Table 1. Overview of selected papers

Main theme	Topic	Papers
RFID Applications in Healthcare	Patient Identification	(Aguilar et al., 2006; Bradley, et al., 2018; Chung & Peng, 2018; Cornes et al., 2019; Chen et al., 2019; Coustasse et al., 2015; Feng Zhu et al., 2020; Ferguson, et al., 2019; Hosaka, 2019; Macbean, & Jackson, 2019; Asamoah, et al. 2018; Hu et al., 2015; Khalid et al., 2017; Liao et al., 2016; Pérez, et al., 2016a, 2016b; Paaske et al., 2017; Panagiotis & Ria, 2006; Podaima et al., 2018; Tayyaba et al., 2021; Turcu, 2017; Tzeng et al., 2008). Within the COVID-19 Context (Garg et al., 2020; Murugan, Khan et al., 2021; Shaun Mehta et al., 2020; Silveira et al., 2021).
	Patient Tracking	(Aboelmaged & Hashem, 2018; Aguilar et al., 2006; Al-Masri & Hamdi, 2015; Alsinglawi et al., 2016; Alyami et al., 2016; Amendola et al., 2014; Binhotan & Altameem, 2020; Chung & Peng, 2018; Pérez et al., 2018; Ariffin et al., 2015; Atkins & Alharbe, 2014; Azevedo & Ferreira, 2010; Catarinucci et al., 2015; Kuo, 2018; Liao et al., 2016; López et al., 2018; Pérez et al., 2016a, 2016b; Omar et al., 2016; Paaske et al., 2017; Panagiotis & Ria, 2006; Podaima et al., 2018; Pérez et al., 2012; Raad & Sheltami, 2016; Turcu, 2017; Tzeng et al., 2008; Wauben et al., 2015; Xie et al., 2021; Yao et al., 2012; Yazici, 2014) Within the COVID-19 Context (Fernández-Caramés et al., 2020; Karthi & Jayakumar, 2020; Rajasekar, 2021; Shaun Mehta et al., 2020; Weizman et al., 2020).
1.1.	Patient Monitoring	(Aboelmaged & Hashem, 2018; Aguilar et al., 2006; Al-Masri & Hamdi, 2015; Amendola et al., 2014; Atkins & Alharbe, 2014; Binhotan & Altameem, 2020; Catarinucci et al., 2015; Cleveland & Haddara, 2021; El Abkari et al., 2021; Kaur et al., 2020; Kaur, Atif, & Chauhan, 2020; Khan, 2017; Liao et al., 2016; Longva & Haddara, 2019; Merilampi, et al., 2018; Naresh, Reddi, & Murthy., 2020; Pérez et al., 2018; Omar et al., 2016; Podaima et al., 2018; Raad & Sheltami, 2016; Rahman et al., 2020; Tzeng et al., 2008; Yao et al., 2012; Yazici, 2014) Within the COVID-19 Context (Abuelkhail et al., 2021; Bailey, 2021; Bianco & Marrocco, 2021; Fernández-Caramés et al., 2020; Rajeshwari, 2020; Saralaya et al., 2020; Silveira et al., 2021; Singh & Sahu, 2021; Weizman et al., 2020)
	Drug Compliance	(Asamoah, et al. 2018; Coustasse et al., 2015; El Abkari et al., 2021; Hu et al., 2015; Katsiri et al., 2016; Pérez et al., 2016a, 2016b; Paaske et al., 2017; Panagiotis & Ria, 2006; Pérez et al., 2012; Sun et al., 2008; Takacs & Hanak, 2008)
RFID Issues & Challenges	Technological Issues	(Aboelmaged & Hashem, 2018; Aguilar et al., 2006; Atkins & Alharbe, 2014; Hu et al., 2008; Hu et al., 2015; Paaske et al., 2017; Rosenbaum, 2014; Yao et al., 2012; López et al., 2018)
	Security, Privacy & Data Management	(Amanze et al., 2020; Ambarkar & Shekokar, 2020; Atkins & Alharbe, 2014; Azevedo & Ferreira, 2010; Benssalah & Drouiche, 2018; Coustasse et al., 2015; Cleveland & Haddara, 2021; Desouky et al., 2020; Fakhr, 2016; Feng Zhu et al., 2020; Hu, Ong, Zhu, Liu, & Song, 2014; Hu et al., 2015; Kim, 2014; Naresh et al., 2020; Noori et al., 2020; Paaske et al., 2017; Rahman, Bhuiyan, & Ahamed, 2017; Rahman et al., 2017; Rahman et al., 2014; Rosenbaum, 2014; Winston et al., 2016; Yao et al., 2012; Zailani et al., 2015; Wu et al., 2018; Xie et al., 2021; Zhu, 2020) Within the COVID-19 Context (Abuelkhail et al., 2021; Alam, 2020; August et al., 2020; Fernández-Caramés et al., 2020; Garg et al., 2020; Safkhani et al., 2020).
1.1.	Organizational, Financial, & Other Issues	(Abugabah et al., 2020; Ajami & Rajabzadeh, 2013; Amendola et al., 2014; Anif et al., 2015; Ariffin et al., 2015; Coustasse et al., 2015; Dey et al., 2016; Fakhr, 2016; Iranmanesh et al., 2017; Lee & Shim, 2007; Ma & Wang, 2016; Manzoor, 2018; Pérez et al., 2016a, 2016b; Mehrjerdi, 2015; Rosenbaum, 2014; Yao et al., 2010; Yao et al., 2012; Yazici, 2014; Zailani et al., 2015; Jose et al., 2019) Within the COVID-19 Context (Angurala et al., 2020; Ho et al., 2020; Ho et al., 2021; Safkhani et al., 2020)

FINDINGS

In total, 108 papers were identified and included in this review. The research papers commonly addressed more than one topic or theme. Both authors identified the themes presented in Figure 2 as the main focus of the papers. Below is a figure that shows the number of papers per topic.

Figure 2. Overview of publications per topic



In addition, the papers were spread across the years, starting as early as 2006 until the time of this review in July 2021. The figure below demonstrates an apparent surge in the number of papers starting from the year 2014, with peaks in the years 2016 (14 papers), a drop in 2017 (4 papers), and a rise again in 2018 with 14 papers, followed by a decline in 2019 with six papers, and a surge in 2020 with 31 papers, and finally 13 papers were published in 2021, until the time of this review. It is important to note that 18 of the papers published in 2020 and 2021 focused on the use of RFID within the COVID-19 pandemic context.

RFID Applications for Patient Safety in the Healthcare Sector

Figure 3. Number of papers per year

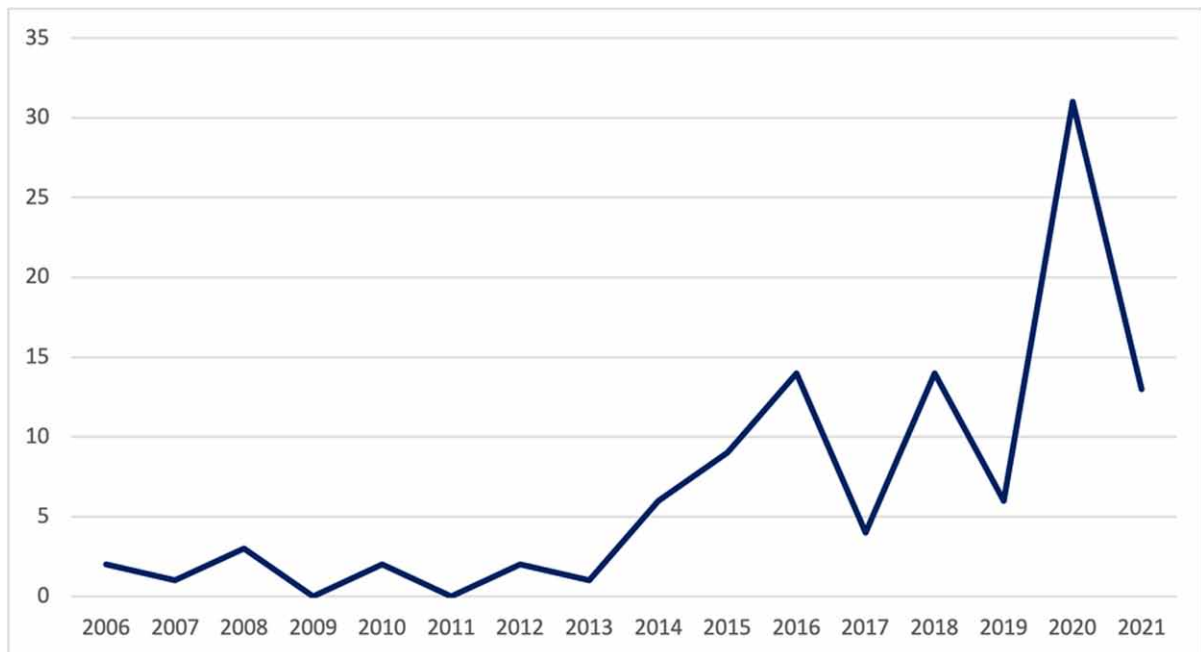
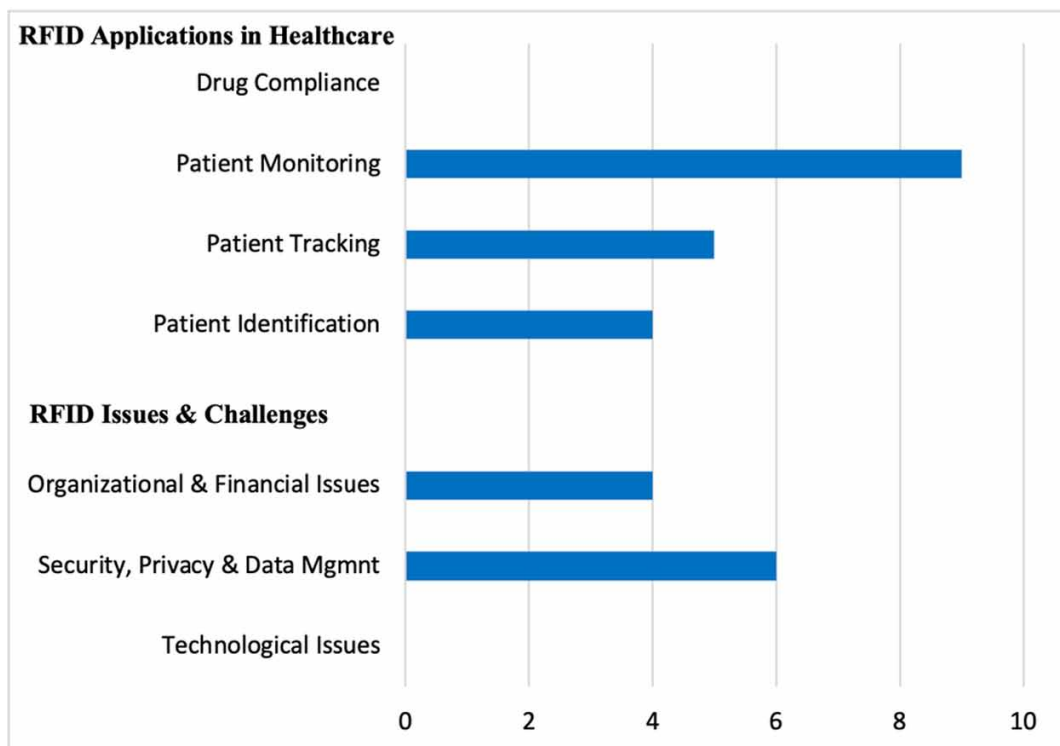


Figure 4. Overview of RFID Application in Healthcare



RFID in Healthcare: Applications for Improved Patient Safety

As stated earlier, medical and human errors in hospitals cause about 42.7 million adverse events each year (WHO, 2018), which demonstrates a critical need for improved patient safety. RFID has massive potential for improving healthcare quality for patients by reducing human errors during interactions between patients and healthcare personnel (Hu et al., 2015). However, the adoption of RFID technology in hospitals has been modest, mainly due to high costs and difficulties justifying the investment (Aguilar et al., 2006; Yazici, 2014). Literature has suggested numerous applications of RFID in healthcare. These applications include patient tracking, identification and monitoring, medication tracking, identification and administration, equipment and asset tracking, and a collection of sensor-derived data (Ajami & Rajabzadeh, 2013; Tzeng et al., 2008; Yao et al., 2012). Within patient safety, which is the focus of this paper, four main applications are identified: *patient identification*, *patient tracking*, *patient monitoring*, and *patient drug compliance*. In addition, the literature findings on the most common challenges and barriers of RFID adoption in healthcare are also presented below.

Patient Identification

Daily, hospitals face the problem of misidentifying patients. Misidentification of patients is one of the main reasons for medical errors in hospitals and is considered a risk to patient safety (Podaima et al., 2018; Ferguson et al., 2019). Positive patient identification (PPI) applications using RFID technology may include a smart wristband with a passive RFID tag that can be scanned to identify patients and reveal information such as date of birth, name, insurance information, allergies, blood type and medication requirements (Panagiotis & Ria, 2006; Tzeng et al., 2008). Several studies suggest that hospitals should work to prevent these errors from occurring by implementing a satisfactory patient identification system that can improve the safety procedures of hospitals (Aguilar et al., 2006; Khalid et al., 2017; Liao et al., 2016; Paaske et al., 2017). RFID plays a crucial role in the rapid identification of patients and can determine several attributes such as name, age, blood type, emergency contact, and previous medical history of the patient (Tayyaba et al., 2021). Likewise, (Al-Masri & Hamdi (2015) and Podaima et al. (2018) suggest that smart RFID technologies can potentially minimize errors resulting from misidentifications of patients. Other researchers propose an RFID-based identification of patients to query and retrieve correct related medical data from the various existing healthcare information systems, potentially minimizing patient-handling errors (Omar et al., 2016; Turcu, 2017). Identification through RFID may also be used for blood sample identification (Cornes et al., 2019) and correspondingly to identify surgical patients to ensure that the correct surgical procedure is performed on the right patient (Panagiotis & Ria, 2006). Some other studies investigated the authentication protocols used in patient identification in general (Feng Zhu et al., 2020) and attempted to develop more subtle protocols that could secure the patient identification process while preserving their anonymity during the COVID-19 era (Garg et al., 2020; Shaun Mehta et al., 2020). Murugan et al. (2021) proposed a system combining RFID to identify COVID-19 patients and robots for treatment and blood sample handling. Others argue that RFID tattoos can also aid in the process of COVID-19 patient identification (Silveira et al., 2021).

Patient tracking

Managing supply chains, monitoring medical inventories, supplies, and assets are currently among the most commonly used RFID applications in healthcare (Coustasse et al., 2015; Hornyak et al., 2016; Turcu, 2017). However, these are not the only applications of RFID for tracking purposes in hospitals. RFID is now moving beyond the perception of only being used as an asset tracker to being viewed as a technology for improving patient care and safety by tracking vulnerable patients (Omar et al., 2016; Yao et al., 2012). This may include tracking the movements of long-time elderly (Alsinglawi et al., 2016; Liao et al., 2016) or disoriented patients (Aguilar et al., 2006) and newborns to avoid baby-snatching (Azevedo & Ferreira, 2010; Tzeng et al., 2008). RFID tracking of patients has also been used to rapidly locate and identify patients in the emergency care to quickly start providing the needed medical assistance (Chung & Peng, 2018; Pérez et al., 2012). According to Wauben et al. (2015), most of the time spent in hospitals is a wait time. Thus, RFID patient tracking capabilities have the potential to reduce waiting times through the automatic display of the phase in which a patient is currently at, which can also provide transparency for patients and staff in the surgical trajectory, and improve patient flow and reduce wait times (Wauben et al., 2015). RFID tracking can also be used to identify patients ready to leave the hospital to minimize unneeded extended stays to enhance resource allocation (Podaima et al., 2018). It can also track elderly patients with chronic diseases in their homes (Raad & Sheltami, 2016). Another potential tracking application is the movement tracking of visitors, staff, and patients to locate and identify people that have been in contact with people carrying infectious diseases. During the Severe Acute Respiratory Syndrome (SARS) epidemic, a few Asian hospitals applied RFID for such purposes. Stored data from the RFID systems allowed the hospitals to identify and locate people in contact with the SARS infected patient before the diagnosis was made (Panagiotis & Ria, 2006; Tzeng et al., 2008). Another case study presented how RFID was adopted and used in psychiatric wards to track patients (Ariffin et al., 2015). The case study suggests that RFID traceability aided in increasing the value of health care practices and improving the workflow in the psychiatric wards rather than the personnel spending time checking on the whereabouts of the patients (Ariffin et al., 2015). Other studies demonstrate the advantages of RFID applications for patient traceability in the intensive care unit (ICU) (Pérez et al., 2018). A study reviewed the extant literature on the use of RFID tracking and localization technologies in healthcare. They identified potential benefits in how RFID can effectively monitor patient monitoring and barriers concerning the security and privacy of patients (Xie et al., 2021). Some other studies focused on specific contexts, like the “Hajj” period, which is the Muslim pilgrim time of the year in which a large number of people move together in almost the same periods. Thus, an RFID framework was proposed by Binhotan & Altameem (2020) to efficiently track (and monitor) individuals taking part in the hajj rituals.

COVID-19 also generated a lot of research interest on how to track patients and individuals effectively. Shaun Mehta et al. (2020) developed a contact-tracking framework that utilizes RFID in combination with GPS positioning technologies. Others used RFID for tracking and tracing COVID-19 patients in real-time (Fernández-Caramés et al., 2020). Others investigated the use of wearable RFID devices during the COVID-19 pandemic, like RFID bracelets Weizman et al., 2020, and the combination of RFID and blockchain technologies to secure real-time tracking communications (Fernández-Caramés et al., 2020). The COVID-19 proposed tracking applications are also intended to control the virus spread through tracking individuals during quarantine and self-isolation periods.

Patient Monitoring

RFID (in combination with other IoT-based sensors) may also be used for patient monitoring and collection of sensor-derived data. Several studies argued that RFID and other bio-sensory devices can be used in monitoring patients with chronic diseases effectively. For example, using Glucose monitoring devices combined with RFID tags can be used to monitor diabetes patients effectively and enhance their life quality (Cleveland & Haddara, 2021; Longva & Haddara, 2019). Another study by (2020) argues that RFID when combined with mobile phones and other bio-sensors, can efficiently monitor the psychological state of psychiatric patients and reduce physical contact. Aguilar et al. (2006) suggest using an implantable RFID that serves as a portable medical record. During the SARS outbreak, the Show Chan Hospital in Taiwan established the “Intelligent digital health network” project, using active RFID tags for patient monitoring to keep track of the body temperature of potentially infectious patients with a fever. The remote data link RFID feature was also later applied to a senior citizen home to remotely transmit movements and physiological data of handicapped or bedridden patients. This allowed the medical staff to monitor patients and take appropriate action if needed (Tzeng et al., 2008).

Several studies state that integrating the RFID with a healthcare information system (HIS) may also improve decision-making and diagnosis, as it allows medical staff to access accurate patient information immediately, and thus make the right decisions promptly (Atkins & Alharbe, 2014; Kaur et al., 2020, Yao et al., 2012). Also, RFID in integration with other IoT technologies, like sensors, mobile networks, digital signatures, or wireless sensor networks, can help in emergencies and incidents such as patient falls or heartbeat irregularities (Catarinucci et al., 2015; El Abkari et al., 2021; Khan, 2017). In a case study in Saudi Arabia, Raad & Sheltami (2016) proposed and tested a prototype that uses RFID wristbands and sensors for tracking and wireless ECG sensors to monitor patients’ vital signs and transmit the data remotely to home-staying elderly patients who suffer from chronic diseases. Likewise, Atkins & Alharbe (2014) proposed a multi-layered framework that integrates RFID equipment with other IoT technologies to enable real-time patient monitoring. Another study surveyed the current technological applications of RFID in body-centric systems for patient monitoring and gathered information about the patient’s living environment via IoT sensors (Amendola et al., 2014). While the study suggests that RFID applications in healthcare are mainly still in the experimental period, however, recent advances in biomaterial engineering pave the way for tattoo-like thin surface electronic devices that are fully bio-compatible and self-dissolvable within a specific period. They thus could be used as temporary wireless wearable sensors for patient monitoring (Amendola et al., 2014). Similarly, other researchers suggest that the use of RFID-enabled smart bandages may potentially monitor the post-surgical patient’s status by assessing temperature and monitoring damaged tissues and the healing process (Podaima et al., 2018).

Wearables, like RFID bracelets, were also recommended to be used for COVID-19 patient monitoring in real-time (Rajeshwari, 2020; Weizman et al., 2020) (Rajeshwari, 2020; Weizman et al., 2020). In addition, RFID tattoos were proposed for real-time temperature monitoring of individuals (Bailey, 2021; Silveira et al., 2021). Others suggested employing RFID tags exploiting an auto-tuning microchip for humidity sensing to test the efficiency of face masks and indicate when the face mask should be replaced (Bianco & Marrocco, 2021). Securing the real-time tracking data exchange has also been an exciting domain. Several studies utilized encryption protocols (Abuelkhail et al., 2021) and the combination of blockchain technologies (Fernández-Caramés et al., 2020) to secure location data.

Patient Drug Compliance

RFID systems can potentially be used and adopted to improve drug compliance. Sun et al. (2008) demonstrated a Wisely Aware RFID Dosage (WARD) system for hospitals that, by using RFID wristbands on patients in combination with barcodes on drug packages, can reduce the risk of medication error and build a safe and effective patient care environment in hospitals. Pérez et al. (2012) present a similar but slightly more sophisticated system, combining active and passive RFID tags to pinpoint a patient in a specific area and identify the correct dose of prescribed medications. Patient drug compliance solutions can also be used at the patient's home after leaving the hospital by attaching an RFID tag to the medicine container that records each time it is opened. Such a solution was demonstrated by Takacs & Hanak (2008), in which they introduced a home robot prototype with human face detection, and an RFID tagged tablet dispenser that works to improve drug compliance and monitor medicine intake. Correspondingly, another study (Anif et al., 2015) proposed a prototype that applies RFID tags to medications and an RFID reader along with a web-based system to track the use of medication. The system also alerts healthcare personnel if the medications have expired.

Moreover, RFID-enabled smart bandages can aid in controlled drug delivery for after-surgery patients based on their wound monitoring data (Podaima et al., 2018). Another research conducted at a Greek hospital presented RFID technologies for blood sample management via a blood bank management system (Katsiri et al., 2016). The study's findings suggest that RFID combined with barcodes can aid in better blood samples' management and reduce the risk of misidentification and blood product waste (Katsiri et al., 2016). Similarly, Coustasse et al. (2015) argue that RFID technologies can aid blood transfusion departments in better managing blood samples and facilitating identification and transfusion of blood operations to the correct patient. In general, RFID is deemed effective in drug and equipment monitoring and tracking within healthcare facilities (Binhotan & Altameem, 2020).

CHALLENGES OF RFID ADOPTION IN HEALTHCARE

Even though there are many benefits of applying RFID to improve patient safety, literature has also identified several challenges affecting RFID adoption in the healthcare industry. These challenges can be organized into three main categories: (1) technological issues, (2) security, privacy and data management issues, and (3) organizational and financial issues.

Technological Issues

There are a few technological limitations of RFID, which cause RFID adoption, especially in healthcare. RFID adoption in hospitals for asset and patient management is usually hindered by the potential technical complexity of the technological environment (Aboelmaged & Hashem, 2018). Also, RFID wireless transmissions may cause electromagnetic interference (EMI) with biomedical devices. This is a challenge for RFID applications in healthcare, as EMI generated by RFID tags can critically affect the performance of electronic biomedical devices and electronic medical equipment, which pose a threat to patient safety in medical environments (Rosenbaum, 2014). According to Hu et al. (2008), RFID tags could cause EMI to medical equipment such as external pacemakers or syringe pumps, which may lead the equipment to

switch off in the proximity of an RFID tag. That would directly put patients' health in danger. Another technological challenge of RFID is related to the accuracy and reliability of RFID systems.

Compared to barcodes (used by most hospitals today), which are generally reliable, RFID tags might not work as expected in some situations or with certain products (Aguilar et al., 2006). The accuracy of an RFID reading depends on various factors like tag placement, read distance, the object tagged and angle of rotation, in addition to the presence of items containing liquid, metal objects and local magnetic interference, which do not always result in a 100% accurate RFID read rate (Rosenbaum, 2014). For the implementation of RFID systems in the healthcare industry, there is also a lack of industry standards and guidelines (Atkins & Alharbe, 2014) and a gap in research on the effect of the radio signals on humans (López et al., 2018; Haddara & Helgesen, 2018), which make such implementation challenging in hospital environments (Aguilar et al., 2006; Yao et al., 2010). According to Aguilar et al. (2006), the lack of industry standards is due to the potential security violations and privacy implications of RFID technology today.

Security, Privacy, and Data Management Issues

Data privacy, management and security, are imperative considerations in the healthcare sector. In the case of RFID technology, guaranteeing security and privacy is one of the most challenging issues for information delivery (Aguilar et al., 2006; Coustasse et al., 2015; L. Hu et al., 2015; Pérez et al., 2016a). Challenges related to privacy mainly originate from counterfeiting unencrypted sensitive data within RFID tags, intercepting data during transmissions, or unauthorized access to sensitive data (Rahman et al., 2017). From a legal perspective, unencrypted patient data stored in RFID tags may also be perceived as a violation of government regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the USA (Rosenbaum, 2014; Yao et al., 2012), or the data protection regulation (GDPR) in Europe (O'Connor et al., 2017), which may result in hefty fines. Because RFID tags rely on wireless interfaces, RFID systems may also be subject to timing attacks, fault integration and power analysis attacks, besides the physical attacks through the direct access to the tags (Rosenbaum, 2014; Wu et al., 2018). When it comes to data transmission, eavesdropping is also a principal concern (Rosenbaum, 2014). According to several studies (e.g. Coustasse et al., 2015; Rahman et al., 2017; Zailani et al., 2015), privacy and security threats are the factors that slow down the adoption of RFID in healthcare. In addition, the security concerns may escalate exponentially when RFID technologies are integrated with human-centric IoT sensors, which could directly affect the human's well-being (Kim, 2014). While data security, privacy and data access are paramount concerns in RFID use in healthcare, however, few technical types of research have addressed these issues (Atkins & Alharbe, 2014; Rahman et al., 2017; V. S. Naresh, S. Reddi, & N. V. Murthy, 2020; Cleveland & Haddara, 2021). Hence, few studies have proposed frameworks to address these challenges within healthcare contexts (Benssalah et al., 2018; Wu et al., 2018; Rahman et al., 2017; Rahman et al., 2014). The proposed frameworks enable preserving the patient's privacy and data secrecy while accessing the various healthcare services. In addition, other research recommended the use of digital signatures to enhance patient privacy (Benssalah et al., 2018; El Abkari et al., 2021). Another study on privacy and security concerns in healthcare suggests that cognitive factors, the persistence of data captured through RFID, and the awareness of security policy can influence medical staff's adoption and use of RFID in hospitals (Winston et al., 2016). In addition, authentication protocols and cryptosystems were deemed effective in securing RFID data exchange (Amanze et al., 2020; Desouky et al., 2020; Noori et al., 2020; Xie et al., 2021; F. Zhu, 2020; Feng Zhu et al., 2020).

Several recent types of research have also studied the security and privacy protocols and mechanisms of data exchange and anonymity preserving (e.g. (August et al., 2020; Garg et al., 2020)) during the COVID-19 pandemic context. For example, Safkhani et al. (2020) proposed an RFID security protocol to ensure supply chain integrity. Others suggested technologies to enhance the RFID security during the pandemic, like combining blockchain with RFID (Alam, 2020; Fernández-Caramés et al., 2020), or 128-bit encryption schemes (Abuelkhail et al., 2021), to secure communications and sensitive data exchange.

Organizational, Financial, and Other Issues

A significant initial investment is required to realize the benefits of deploying an RFID system (Coustasse et al., 2015). Even though the cost of RFID tags have showed a significant decline during the past decade, the cost of RFID tags is still considered substantial (Mehrerjerdi, 2015). Today, a passive RFID tag costs between 7 to 15 cents. Each active RFID tag can cost 25 dollars to more than 100 dollars depending on its sophistication, which is considered a significant investment for hospitals in cases where all assets, staff and patients are tagged. In addition to the RFID tags and readers, the RFID infrastructure also requires middleware, databases, servers and cloud-based applications and infrastructure. In addition, training, business process redesign, organizational change and RFID infrastructure maintenance are also additional costs that need to be accounted for (Yao et al., 2012). A study conducted in the US concludes that the adoption cost is regarded as the top barrier for RFID adoption (Dey et al., 2016).

Another pilot study (Coustasse et al., 2015) in an American hospital estimates a long-term return on investment (ROI) through a 5-year ROI of 2%, with an approximate payback period of four years. This study is one of the very few papers to present an ROI estimation. There is minimal research investigating the financial feasibility of RFID implementation projects, which signifies a significant barrier to RFID adoption regarding top managers' investment decisions (Azevedo & Ferreira, 2010). On the other hand, other researchers argue that RFID-based tracking systems are proven to be cost-effective when used for psychiatric patients tracking (Ariffin et al., 2015). Likewise, additional case studies (Pérez et al., 2016b) argue that RFID technology is invaluable in assisting with the everyday clinical practices in hospitals. Thus, the high technology costs may then be justified by the high costs of the service and the high risk to the patient (Pérez et al., 2016a, 2016b). As in almost any technology implementation and adoption project, top management support is a crucial success factor in the initial phase of RFID implementation in hospitals (Zailani et al., 2015). That supports the findings of Lee & Shim (2007), who also add that top management often lack awareness about the potential benefits and cost savings related to RFID, which pose a challenge to RFID adoption. Also, besides the technological culture needed within organizations (Jose et al., 2019), the medical teams' readiness for technology is considered one of the main barriers to RFID adoption in the healthcare industry (Yazici, 2014). Nevertheless, the involvement of the medical team during the several phases of the RFID implementation projects could potentially minimize the resistance to change threats and increase the adoption rates (Pérez et al., 2016b). Moreover, a study conducted in Iran concludes that environmental barriers and governmental data use policies may hinder RFID adoption in the healthcare sectors in developing countries (Fakhr, 2016). It is also argued that cultural and ethical issues may be regarded as technology adoption barriers (Abugabah et al., 2020; Amir, 2016). In addition, training healthcare personnel and safety issues may slow the pace of RFID adoption in HC (Abugabah et al., 2020).

Within the COVID-19 context, several studies researched the use of RFID technologies in combination with other platforms and devices to control the spread of the virus. For example, Angurala et al. (2020)

investigated the use of RFID for identifying patients in combination with drones for remote blood sample collection. Another study developed an RFID security protocol for ensuring supply chain integrity in HC facilities (Safkhani et al., 2020). Few studies focused on healthcare workers' safety rather than the patients. For example, Ho et al. (2020) surveyed the use of real-time locating systems for contact tracing of healthcare staff during the COVID-19 pandemic in Singapore, and Ho et al. (2021) used surveillance technologies to enhance the exposure management and tracking for healthcare staff during the pandemic.

DISCUSSION

Findings from the reviewed literature show that RFID technology (in combination with information systems, sensors, and mobile technologies) can improve patient safety by reducing medical and human errors caused by patient misidentification, poor decision making, insufficient patient monitoring, poor patient tracking, inability to respond rapidly, and non-compliance with medications. In addition, several studies presented the potential of RFID applications in COVID-19 pandemic control and tracking and tracing of the public. However, some issues related to RFID pose a challenge to hospitals and other medical institutions who consider adopting RFID systems to improve patient safety. These challenges are related to technological, data management, security and privacy, and organizational and financial issues. Medical errors have become a leading cause of death on a global basis. It is found that medical errors are causing 250,000 deaths per year in the U.S. alone (Cha, 2016). Misidentification, and specimen or medication misidentification, is the leading cause of death due to medical errors (Mehrjerdi, 2015). Thus, hospitals and other institutions can apply RFID for patient identification, tracking, monitoring, and drug compliance systems (Tzeng et al., 2008). According to a case study by Aguilar et al. (2006), positive patient identification systems allow the personnel to quickly obtain up-to-date information about the patients (including medication requirements) and prevent medical personnel from taking shortcuts when identifying patients and medications. This suggests that RFID-enabled patient and medication identification systems do indeed reduce misidentification and non-compliance with medications, which thus improve patient safety.

As previously stated, patient-related applications of RFID, such as patient identification, tracking and monitoring, promise many benefits related to efficiency and patient safety. However, there are also some challenges when it comes to the privacy and security of patient information stored in RFID tags, e.g. a malicious person might access a patient's electronic medical record, or the patient could be disposed to physical tracking, because RFID tags automatically respond to queries from RFID readers without alerting the tagged person (Hu et al., 2014; Hu et al., 2015). Because RFIDs tag actual people, patient-related RFID applications are much more complicated than asset-related applications (Yao et al., 2012). These security and privacy challenges are amplified by the lack of industry standards and security protocols for RFID in healthcare (Rosenbaum, 2014). According to Aguilar et al. (2006), these controversial privacy implications of RFID technology and the potential for security violations with existing RFID products are the main reasons for the lack of industry standards for healthcare. Hence, as long as safe RFID protocols and industry standards are lacking, there will exist a trade-off between improved patient safety and risks related to privacy and security issues.

On the other hand, the measures enforced by GDPR oblige organizations to inform the e-health user subjects (patients) on how their data will be used, processed and stored (O'Connor et al., 2017). That is referred to as *privacy by design*. While the GDPR entails consent of the target system users, however,

it is argued that it is still challenging to ensure that the patients are fully aware of what they consent to and how their data will be used in an IoT environment (O'Connor et al., 2017). Hence, the benefits and convenience of RFID systems should be weighed against the risk of privacy and safety before adopting RFID for patient-related applications. This trade-off can be exemplified by the case of Asian hospitals that implemented tracking of visitors, personnel and patients during the SARS outbreak in 2003, where RFID technology was used to hinder the disease from spreading at the hospitals (Tzeng et al., 2008). This demonstrates that patient-related applications of RFID can improve patient safety and even save lives. However, at the current state of RFID systems, protocols and standards, this could be at the expense of privacy and safety considerations. Through RFID enabled patient identification and monitoring, hospitals can also improve decision-making and diagnosis (Aguilar et al., 2006; Tzeng et al., 2008). However, these benefits can only be realized if hospitals implementing RFID systems have a satisfactory level of sophistication, including interoperability and integration capabilities among their IT systems and data analytics infrastructure to take the benefits to their full potential. This represents a challenge to RFID adoption, as hospitals that do not have such systems in place might be hesitant to apply RFID due to the associated high costs (Aguilar et al., 2006).

Ajami & Rajabzadeh (2013) argue that healthcare organizations will face several challenges if RFID systems are used alone, but will reduce medication, diagnosis and medical errors if integrated with electronic health records, hospital information systems, and supported by decision support systems. This indicates that the potential value of the system is derived from the data analysis in the underlying applications (Rosenbaum, 2014). Hence, hospitals implementing RFID technology should provide efficient mechanisms to transform collected data into valuable information, as this is where business value is generated.

When it comes to the adoption of RFID technology, healthcare still lags behind other industries. One of the factors affecting adoption is the cost of RFID infrastructure. In addition to costly RFID tags, implementing an RFID environment can be expensive and complex, especially if the hospital lacks the infrastructure required to support such a system or if integration with existing hospital information systems becomes problematic (Ma & Wang, 2016). For RFID projects, ROI is usually achieved after a long time, making it challenging to address the potential return on RFID investments (Azevedo & Ferreira, 2010). To overcome the barriers of high RFID costs, Yao et al. (2012) suggest that low-cost, effective systems should be designed, combining passive RFID and active RFID tags with barcodes to save costs and at the same time achieve the same goals similar to the more sophisticated RFID systems. However, the focus on cost reduction in future advances of RFID tag design will most likely be at the expense of the RFID tag's limited computational capabilities, making it challenging to design and implement sufficient security functions (Hu et al., 2015). Hence, RFID may still be too expensive and risky for cost-conscious hospitals. Another factor affecting the adoption of RFID for patient safety-related purposes are the organizational challenges. Many hospitals are hesitant to invest in RFID because it is still not widely adopted, and there is a lack of healthcare organizations with demonstrated success in RFID implementation (Lee & Shim, 2007; Yao et al., 2012). According to Lee & Shim (2007), the lack of awareness about RFID is a significant barrier to RFID adoption in healthcare. Even though hospitals may see how vital RFID will be in the future, top management, whose support is a critical factor for RFID implementation, might not fully understand or see the benefits or importance of RFID technology for healthcare applications (Lee & Shim, 2007; Zailani et al., 2015). Lee and Shim (2007) found that many top managers did not even expect to see an overall reduction in costs from adopting RFID. They further argue that with better knowledge of IT, the degree of uncertainty about the adoption will

decrease, which will result in a less risky adoption. This suggests that healthcare organizations that are more knowledgeable about information technology are more likely to adopt RFID (Zailani et al., 2015). Hence, to speed up RFID adoption in healthcare, technology awareness needs to be improved among less tech-savvy managers and healthcare personnel.

The COVID-19 outbreak seems to generate an increasing interest in IoT in healthcare in general, and RFID applications specifically minimize physical contact between patients and healthcare staff. We believe that our experience with the current pandemic might accelerate IoT and RFID technologies in the healthcare sectors worldwide.

CONCLUSION

The RFID adoption in healthcare opens up a lot of potential opportunities to improve patient safety. That includes using RFID for patient identification, patient tracking, patient monitoring and improving drug compliance. Implementing RFID technologies for such purposes can reduce the chances of medical and human errors in hospitals and other healthcare institutions. The adoption rate of RFID in healthcare is meager, contradicting first predictions in the early 2000s, and the future of RFID in the healthcare industry remains uncertain. This is mainly due to several challenges and barriers, like high adoption costs, lack of industry standards, lack of proper privacy and security protocols, and the relatively meager awareness of its importance to the healthcare industry. To increase the adoption of RFID in healthcare, there is a need for adequate security and privacy measures and regulations, more seamless integrations with existing information systems, institutional support and increased awareness among top management, and the development of RFID systems that are more customized for hospitals. Further, because of the COVID-19 outbreak, some studies also focused on tracking and monitoring healthcare staff and professionals, which took the safety concerns beyond the patients' context which has been almost the exclusive focus of research in the last decade.

Future research should investigate the issues affecting RFID's adoption in healthcare, particularly related to patient's privacy and security. These were found to be paramount factors affecting the adoption of RFID for patient safety-related purposes. Specifically, studies investigating the impact of the compliance with the GDPR's privacy on IoT in healthcare, and evaluating if this directive resolves the reported privacy concerns in literature, and the feasibility of the GDPR compliance by the healthcare industry. Also, the current pandemic highlighted the importance of using RFID technologies for tracking and tracing healthcare professionals. More research is needed on this topic, as currently, very few studies focus on service providers. In addition, there is an apparent research gap on the technological issues that may affect RFID adoption and implementation in healthcare. Finally, there are also legislative and social challenges with adopting new technologies in general and RFID and IoT. Once legal and social challenges and issues are resolved by consolidated legislation and improved RFID technology security standards, healthcare organizations are expected to speed up their pace to adopt RFID for patient-related applications.

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Chapter 10

Blockchain Technology and Healthcare Applications: A Comprehensive Study

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ABSTRACT

Blockchain technology (BCT) is an evolving digital technology that changes digital operations' dimensions by conducting distributed ledger transactions without the involvement of third parties. The chapter aims to examine the use of BCT in healthcare and develop a hierarchical theoretical framework. The framework is based on the stakeholder principle and exposes BC's effect on smart healthcare. Its decentralised existence is an ideal catalyst for the much-needed transition toward well-organised healthcare as it solves the most pressing issues.

INTRODUCTION

Developing new innovative healthcare-related digital technology promotes healthcare facilities and improves the clinical infrastructure of innovative clinical systems (Joshi et al., 2018). Smart clinical systems (SCSs) are medical systems that combine with the new digital technology or cloud data and electronic medical records, electronic health archives, data transmission, and exchange technologies for health services. SCSs face increased demand, but there are still problems relating to data security, safety, and system security (Karame et al., 2012; Han et al., 2013; Kostakis, 2014; Duan et al., 2016).

DOI: 10.4018/978-1-7998-9198-7.ch010

Blockchain technology (BCT) and SCSs have fascinated clinical healthcare systems and other industries (Kostakis, 2014; Duan et al., 2016). Blockchain technology (BCT) is the biggest buzzword, and its significant relevance came in the form of Bitcoin (2009), which became the most famous, safe and secure application (Efanov and Roschin, 2018). A bitcoin (primary cryptocurrencies) is a very safe, secure, publicly most extensive transaction system through network or Internet (Buterin et al., 2014; Akins et al., 2015; Underwood, 2016), as it prevents errors and double spending—a primary feature of BCT decentralization, anonymity, tamper-proof, and auditability (Sharples et al., 2016; Zheng et al., 2018; Agbo et al., 2019). Its name indicates that it is in chain form, which consists of a chain of the block containing information that is stored on the nodes of computers (on an encrypted digital ledger, spread across a network of synchronized replicated databases) where data is safe and secure and shared in the same manner (Kosba et al., 2016). BCT and SCSs will eliminate conventional pitfalls in knowledge exchange, data protection, and privacy maintenance, simplify user-centered smart healthcare systems and create a multiparty medical alliance chain involving government, businesses, and individuals to facilitate smart healthcare's industrial upgrading (Zheng et al., 2018; Agbo et al., 2019). The chapter's objective is to systematically study various consensus algorithms and the current work in healthcare regarding BCT, their basic ideas and problems.

BACKGROUND

Blockchain technology is a network of peer-to-peer nodes that stores transactional records (also known as blocks) of the public in many databases and is also known as the “chain.” This form of storage is commonly referred to as a “Digital Ledger” (DL). Several studies have reported that BCT is the basis of cryptocurrencies. Electronic cryptocurrencies are used to control and regulate the data, store, and transfer. They follow strict protocols and are very trusted, safe, and secure technology (Sharples et al., 2016; Zheng et al., 2018; Agbo et al., 2019; Kosba et al., 2016; Drescher, 2017; Rutland, 2018; Holbl et al., 2018). The terms block and chain were used separately in Satoshi Nakamoto's original article but were ultimately popularized as a single word, blockchain, by 2016. Any transaction in this ledger is signed with the owner's digital signature, verifying the transaction and protecting it from tampering. As a result, the data in the digital ledger is exceptionally secure. Put another way, the digital ledger is similar to a Google spreadsheet that is exchanged by multiple computers in a network and stores transactional records based on actual transactions. The intriguing aspect is that everyone can view the data, but they cannot alter it. At the same time, blockchain technology eliminates time-consuming mechanisms and allows quicker transaction processing, saving time and money (Kosba et al., 2016; Drescher, 2017). A blockchain is a continuously growing list of documents known as blocks connected using cryptography. It is a platitude that has no real context that a layperson can recognize. A cryptographic hash of the previous block, a timestamp, and transaction data is included in each block (as a Merkle tree). A blockchain is sensitive to data alteration by design. Once the information has been registered, the input cannot be changed retroactively without affecting all subsequent blocks (Lamport et al., 1982; Kosba et al., 2016; Drescher, 2017; Rutland, 2018; Holbl et al., 2018). According to Global Data's Thematic research study, the market for cryptocurrencies decreased by 20% in 2018 compared to previous years. That was because companies tend to use conventional methods for their early-stage ventures rather than blockchain technology. However, countries have strong expectations due to the reports or the facts about

the blockchain technology has real value, and its reach can expand being more user-friendly over time (Lamport et al., 1982; Kosba et al., 2016).

Most people believe that Blockchain and Bitcoin are interchangeable terms, but this is not the case. Blockchain technology is a system capable of serving various applications in various industries, including banking, supply chain, manufacturing, etc. Still, Bitcoin is a stable currency thanks to blockchain technology (Kosba et al., 2016; Drescher, 2017).

Several studies explained that a blockchain is usually operated as a distributed ledger by a peer-to-peer network that follows a protocol for inter-node communication and validating new blocks. While BCT records cannot be changed, they are protected by design and represent a distributed computing system with high Byzantine fault tolerance. The blockchain has been described as “an open, distributed ledger that can securely and permanently record transactions between two parties” (Merkle, 1987).

First, blockchain technology was invented in 2008 by a group of people known as Satoshi Nakamoto. Although the terms block and chain were used separately in Satoshi Nakamoto’s initial article of 2016, they have become synonymous with blockchain. Satoshi Nakamoto’s true identity is also unknown (Crosby et al., 2016; Nakamoto, 2018), but he made significant improvements to the design by using a Hashcash-like method to timestamp blocks without requiring them to be signed by a trusted party and adding a difficulty parameter to regulate the rate at which blocks have been added to the chain. Nakamoto introduced the design as a critical component of the cryptocurrency bitcoin, where it acts as the public ledger for all network transactions (Ren, 2014; Nakamoto, 2018).

After the blockchain was invented, Bitcoin became the first digital currency to address the double-spending problem without using a trustworthy authority or central server. The bitcoin architecture has influenced public-readable applications, and blockchains are commonly used by cryptocurrencies (Kuo et al., 2017; Rutland, 2018; Holbl et al., 2018). The blockchain can be thought of as a form of payment system. Private blockchains have been proposed for business use, but the promotion of such privatized blockchains without a proper security model has been dubbed “snake oil” by Computerworld. On the other hand, others have argued that, if carefully built, permissioned blockchains could be more decentralized and, therefore, safer in practice than permissionless blockchains (Swan, 2019; McGhin et al., 2019).

The bitcoin blockchain file size, which contains all network transactions, surpassed 20 GB in August 2014. From January 2015 to January 2016, the bitcoin blockchain grew from 50 GB to 100 GB in size, and from January 2016 to January 2017, it grew from 50 GB to 100 GB in size. By early 2020, the ledger had expanded to over 200 GB (Kotla et al., 2009).

According to Accenture, implementing the technology diffusion theory indicates that blockchains achieved a 13.5 percent adoption rate within financial services in 2016, putting them in the early adopters’ phase. In 2016, industry trade groups joined to form the Global Blockchain Forum, a Chamber of Digital Commerce initiative (Borge et al., 2017; Nakamoto, 2018).

Other studies have explained that Gartner found that only one percent of chief information officers (CIOs) use blockchain, and 8% of CIOs were active in experimenting with blockchain (May 2018) (Drescher, 2017; Rutland, 2018; Holbl et al., 2018). Again in 2019, as a base report, 5% of CIOs thought that blockchain technology was a game-changer (for their business benefit) (Ghosh and Richardson, 2014). However, BCT is based on an open platform that is a distributed ledger and cannot be entirely managed or owned by a single entity. As a result, any digital transaction is recorded on several computers. Information can be kept permanently without the fear of loss, making it one of the easiest ways to hold transactions (as needed) (Ghosh and Richardson, 2014).

Consequently, various versions have been developed for different industries and categorized as blockchain applications (Chuen, 2015; Gervais et al., 2016). Public blockchain technology is open to the general public, being used in real-world scenarios by Bitcoin, Ethereum, and Litecoin, to name a few. The key benefit is that no one entity can fully control the network (Burgess and Colangelo, 2015).

Data is secure, which contributes to the immutability of documents. All nodes linked to this public blockchain have equal jurisdiction, resulting in a fully distributed public blockchain (Gervais et al., 2016). The private blockchain is a private blockchain that invites participants to use, and only people who constitute part of the blockchain ecosystem can see all the transactions (Burgess and Colangelo, 2015; Chuen, 2015; Gervais et al., 2016).

These blockchains are much more centralized and regulated than public blockchains. Since they are more centralized, they can be governed and supervised by someone who can ensure that the governors properly guide participants. Usually, these are used in private companies to store confidential information about the company (Nomura Research Institute, 2016).

Consortium or Hybrid Blockchain includes two types of users. The first is the user who has complete control over the blockchain and determines the level of protection for a specific user. In contrast, others just access the blockchain. All nodes can access the blockchain, but the information level depends on which node is accessing the data (Johnson and Menezes, 2001). The categories mentioned earlier in blockchain are bitcoin, multichain, and BCT in the banking sector. Bitcoin is the most popular money transaction app after the verification and validation from both ends without any fraud. It is a cryptocurrency digital app that can make payments to anyone online without involving a third party. For example, send a certain amount of money to a friend by sending bitcoins from one account to another using the recipient's Account ID (Kim et al., 2019). The transaction is then added to the blockchain, and the recipient receives the bitcoin. Bitcoin is such an easy app. Anyone can handle this, and data are secure as all information is encrypted, making it the most reliable form of currency possible (Li et al., 2020). Another type of BCT, multichain, is applicable in security, improving and enhancing users' security. It is a susceptible app (makes banking easy, secure, and reliable). It can prevent unauthorized access of data, which will only be available to the organization's authorized person. There are multiple nodes, but only a few nodes will access the data (Xu et al., 2016). The Network Administrator governs all the access. Next, for banking purposes, blockchain in the banking sector is a hybrid type in which people's data must be public, allowing all information to be shared. Still, access to blockchain banking must be limited to a single bank, as well as all of its branches (Xu et al., 2016). In addition, blocks are a decentralized, distributed, and often public digital ledger that consists of digital records that can be used to transfer data from one device to another (as shown in figure-1). As a result, any affected block cannot be changed retroactively without affecting all subsequent blocks (Johnson and Menezes, 2001; Kostakis, 2014; Duan et al., 2016; Cai et al., 2016). BCT allows the participants to verify and audit transactions independently and relatively inexpensively (Kostakis, 2014; Duan et al., 2016; Cai et al., 2016). A blockchain database is managed autonomously using a peer-to-peer network and a distributed timestamping server. They are authenticated by mass collaboration powered by collective self-interests (Karame et al., 2012). Such a design facilitates robust workflow where participants' uncertainty regarding data security is marginal. The use of a blockchain removes the characteristic of infinite reproducibility from a digital asset. It confirms that each unit of value was transferred only once, solving the long-standing problem of double-spending. A blockchain has been described as a value-exchange protocol (Kostakis, 2014; Duan et al., 2016; Cai et al., 2016; Li et al., 2020). A blockchain can maintain title rights because it provides a record that compels offer and acceptance when correctly set up to detail the exchange agree-

ment. As a result, the transaction data is replicated continuously across the network. Since the network will not validate any mistake, it will be denied (Bentov et al., 2014; Vukolic et al., 2016). Evidence has explained that immutability in BCT is ensured by a participant network of computers rather than any centralized authority. Assets may be tangible, including houses or money, or intangible, such as patents or scientific documents (Mazieres, 2015). As shown in figure-1, BCT is a set of sequentially ordered records organized in a block structure. Each data block includes a hash known as digital fingerprint/unique identifier, timestamped batches of recent transactions, and the previous block's hash. Each block is linked in sequential order in this design, and the connected blocks are referred to as a blockchain. It's almost impossible to alter one of the blocks in the middle of the chain because all blocks are essential to be modified simultaneously. The data on the blockchain network is permanent thanks to this mechanism (Metropolitana et al., 2016). Another feature that makes blockchain technology a smart contract is a computer protocol that automatically executes when certain conditions are met. It is distinct from blockchain technology. The smart contract was introduced as a core feature of BCT 2.0, allowing BCT to be used for purposes other than cryptocurrencies, such as Bitcoin (Blockchain 1.0). Blockchain 3.0 has only recently become popular, but the definition has yet to be fully developed. According to others, Blockchain 3.0 would revolutionize blockchain technology's throughput, one of the most significant challenges (Cachin et al., 2016). One of the main advantages of BCT is that all participating nodes in the network will have a copy of the entire blockchain. Since transactions on the BCT are only valid if all participating members agree to them, all transactions are primary to be accepted. Furthermore, all transactions are tracked, making it difficult to conceal the fraudulent activity. When a user (user A) uses blockchain to conduct a transaction with another user (user B), a new block is generated to record the transaction. Every transaction is checked by broadcasting it through network nodes. If the new transaction is verified, a new block is added to the chain and the spread through network nodes allows other nodes to update their blockchains. Finally, another recipient receives the transaction (user B). Figure 2 depicts the entire procedure (Schwartz et al., 2014; Kwon et al., 2014).

BLOCKCHAIN IN HEALTHCARE

Today, blockchain technology has established itself in most countries' healthcare systems. It has proven to be very useful in integrating healthcare facilities and multiple intermediaries in the medical care system (Underwood, 2016; Vukolic, 2016). As shown in figure-3, BCT has a proven digital network system that can store patients' longitudinal digital information or histories. That information may be used by consumers, insurance companies, and other medical experts (Kim et al., 2018).

Several studies have explained that interoperability between organizations and service providers is one of the main benefits. BCT is involved in the maintenance of data privacy, decentralization, and transaction with cost reduction. Also, it assists in delivering precision medicine, improving patient care facilities that provide excellent outcomes, and providing the linking facility of medical records at the international level. That may be helpful in an emergency because hospitals can quickly access patient data rather than obtain medical records from individual patients (Kim et al., 2018).

By integrating these features, blockchains can provide real-time patient monitoring and data updates by tracking various nodes through the Internet of Things (IoT). It can be used by medical care providers and a variety of intermediaries when combined with a database. As a result, it enables easy access

to patient information through service providers, lowering costs and improving coordination between healthcare organizations (Rivest et al.,2001; Schwartz et al.,2014; Kwon et al.,2014; Kim et al.,2018).

Healthcare digital information exchange (HCDIE) and the Integrating the Health care Enterprise (IHE) play an excellent role in every health care setting and provide better facilities to patients and insurance companies, financial and operational services (revenue cycles), and supply chains of back-office data input. An excellent advantage is cost containment while data accuracy and security are added (Yuan and Wang,2016; Zheng et al.,2018). Therefore, in the long term, the benefits of incorporating the medical network would result in low-cost solutions and virtual health systems. Health care information, health claims, interoperability, patient access, and supply chains are only a few of the data-driven healthcare fields where blockchain technology can be used (Schwartz et al.,2014; Kim et al.,2018).

Medical Records and BCT

BCT plays a vital role in healthcare or medical care settings because it can safely collect patients' health records and securely store the longitudinal data in blocks. BCT's advantage is providing invaluable insights for healthcare providers or experts and different population segments.

Evidence has proven that BCT networks improve healthcare coordination among other healthcare experts easily swiped by patients (their medical records). This advantage becomes practical during patients' medical emergencies. The patient's details are broadcast instantaneously to the hospital's admissions department, which use the blockchain to access health care accounts (Yuan and Wang,2016; Cyran,2018; Kim et al., 2018).

Currently, digital or electrical wearable devices use the Internet of Things to provide unified medical care services, no matter where the patient is located. Furthermore, integrating digital health data from mobile apps with genomics will produce helpful knowledge about sub-populations that are vulnerable to certain diseases or react to specific treatments (Cyran, 2018; Kim et al.,2018)

Internal and External Regulation

Internal medical regulation focuses on different drugs, medical instruments or equipment, and supply chains by medical institutions, while external regulation centres with three main activities: first, medical supply chain regulation; second, medical whole process regulation; and third, medical waste treatment process regulation (Yoon 2019).

Both medical regulations are concerned with ensuring the consistency and sensitivity of all medical service-related products and the movement of medical products, related healthcare operations, information systems, and materials and goods across the supply chain. The source of materials or goods is also a subject of drug supply chain management which deals with its expiration or manufacturing date, drug development process, and product delivery (Clauson et al., 2018; Cyran, 2018; Kim et al., 2018). For example, a centralized supply chain management system in medical or other industries exposes corruption, fraud, and tampering (Bocek et al., 2017). Therefore, the medical industry needs a solution to improve every product or service's security, integrity, and digital data records. That necessitates BCT, which can permanently monitor, significantly reducing the time required and the possibility of human error. BCT also makes transactions secure and transparent (Cyran, 2018; Kim et al., 2018).

As a result, the security of medical supplies and equipment can be enhanced by implementing blockchain through storing unique device identifiers for each medical device and using smart contracts

to monitor and publish firmware updates. Invariance can be used in blockchain-based medical device monitoring to avoid device failure, theft, and malicious tampering (Bocek et al., 2017; Clauson et al., 2018; Cyran, 2018; Kim et al., 2018).

Management of Medical Experts

One of the advantages of BCT is that it keeps all records contributing to the avoidance of medical disputes, providing valuable services to patients. For example, health services are blockchain-based projects that enable clients to communicate with the world's best physicians anonymously and safely. However, BCT considers three main criteria for managing medical experts through the smart process - identification, personnel screening, and customer selection (Brodersen et al., 2016). It can be used for information sharing, patient monitoring, identity assurance, and authentication, which allows for large-scale interoperability among healthcare providers, patients, and other agents (Bocek et al., 2017; Clauson et al., 2018). Patient data is only stored and accessed anonymously by an appointed physician at a given time. Information on the validity of physician certificates and licenses is updated in an immutable decentralized database (Brodersen et al., 2016; Clauson et al., 2018).

Treatment Improvement

Healthcare BCT focuses on the two types of treatment - Telemedicine and targeted therapy. In several nations, the number of patients has risen exponentially, making it impossible to receive for physicians and nursing staff to treat them (Griggs et al., 2018). BCT-based Telemedicine is seen to achieve equitable and cost-effective medical care that is tamper-proof, anonymous, and transparent. It can also be used to promote the security analysis and management of medical sensors. For example, a smart contract has been introduced in the medical chain that allows doctors to review their cases remotely and offer advice or second opinions. Furthermore, the data might be securely transmitted using blockchain asymmetric cryptographic encryption (Bocek et al., 2017; Clauson et al., 2018). In addition, drug research and development institutions can identify the data after user authorization, allowing for drug-targeted research and development (Jamil et al., 2019).

Medical Claims and Insurance

Medical claims and insurance will also benefit from blockchain technology because it can be handled quickly and efficiently, saving time and money. Since patients' bank and health savings accounts will be connected via the blockchain, interoperability standards and application programming interfaces might provide real-time claim settlement and make it more accessible to treatment. Therefore, the application of BCT can reduce the complications and cost of medical insurance and protect patients' interests. It can also reduce the uncollected funds of hospitals and the management cost of insurance companies (Guo et al., 2018).

Supply Chain

Blockchains may also be used to link patients, service providers, and organizations by supplying chains that track and execute orders in real-time. Consumers should learn about the efficacy, origins, and side

effects of the ingredients of the drugs. That could result in increased efficiency and quality control across the supply chain. A blockchain-enabled supply chain can monitor products back to the producer, handle payments between sellers and buyers, lower costs, and eliminate human error (Dutta et al.,2020).

Access to Patient's Data Information/Records

Patients have access to their medical records, which is another advantage of an open ledger. That is contingent on the interoperability of healthcare data, which can be accomplished after regulatory and legal standards are met. Furthermore, a healthcare blockchain can be connected to the most recent medical studies to assist patients in receiving the most up-to-date treatments. Patients will be more educated and explore suitable care options with their physicians based on science rather than conventional wisdom (Mohanta et al., 2018). By creating safe and trustworthy health record data, connecting transactional data, providing access to patients and documenting their consent, blockchain technology is helpful for health care data interoperability (Ichikawa, 2017).

Inter-connectivity

Traditionally, healthcare records have been disjointed and kept in service provider silos. That is because Electronic Health Records (EHRs) were created on an episode-by-episode basis, without considering the linkages needed for lifetime records or various service providers, and therefore lacking associations, common architectures, and standards. There is also no system for sharing patient data with stakeholders or patients (Ivan et al., 2016; Wu et al.,2019). As a result, each time a medical service is offered, a patient's common clinical data cannot be changed in a central pool. Interoperability is highly beneficial to both patients and medical care providers. Data interoperability enables networks to promote population health programs, and the blockchain can be used to gather vast volumes of patient data to aid such large-scale efforts (Ivan et al., 2016; Wu et al.,2019).

CONCLUSION

Blockchain technology has many applications in healthcare, as it leads to integrated healthcare data, aiding countries in developing national healthcare systems. We believe that the blockchain can help healthcare the way the Internet did for the media.

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Chapter 11

New Aspects and an Artificial Intelligence Approach for the Detection of Cervical Abnormalities: The COVID-19 Pandemic Era

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DOI: 10.4018/978-1-7998-9198-7.ch011

ABSTRACT

The COVID-19 pandemic has challenged health systems worldwide by decreasing their reserves and effectiveness. In this changing landscape, the urge for reallocation of financial and human resources represents a top priority. In screening, effectiveness and efficiency are most relevant. In the quest against cervical cancer, numerous molecular ancillary techniques detecting HPV DNA or mRNA or other related biomarkers complement morphological assessment by the Papanicolaou test. However, no technique is perfect as sensitivity increases at the cost of specificity. Various approaches try to resolve this issue by incorporating several examination results, such as artificial intelligence are proposed. In this study, 1,258 cases with a complete result dataset for cytology, HPV DNA, HPV mRNA, and p16 were used to evaluate the performance of a self-organizing map (SOM), an unsupervised artificial neural network. The results of the SOM application were encouraging since it is capable of producing maps discriminating the necessary tests and has improved performance.

INTRODUCTION

Cervical cancer (CC) is the third most common cancer and the fourth leading cause of cancer death in females worldwide (Jemal, Bray, Center et al., 2011). More than 85% of these cases and deaths are in developing countries, predominantly due to the absence of cervical screening infrastructures to detect and treat precancerous lesions and early-stage cervical cancer. Despite the advances in screening, cervical cancer remains a serious public health problem even in developed countries, in part due to the high percentage of detection failures (Leyden, Manos, Geiger et al., 2005).

CC is known to be caused almost exclusively by human papillomavirus (HPV) infection, the most typical sexually transmitted infection worldwide. About 100 types of HPV viruses that can infect humans have been identified. Among them, 15 possess a high-risk oncogenic potential and might cause CC. Improved understanding of HPV infection and the natural history of cervical neoplasia have resulted in the implementation of the HPV DNA test along with the Papanicolaou test (Pap-test) or as a standalone test (US Preventive Services Task Force, 2018).

Nowadays, several ancillary techniques for CC screening are available. The most established are HPV DNA typing and mRNA identification of the viral E6/E7 oncogenes linked to oncogenic activation. Notably, mRNA typing with nucleic acid-based amplification (NASBA) (Smits, van Gemen, Schukink et al., 1995) and mRNA-Flow-FISH techniques in screening programs produced excellent results with enhanced PPV; thus reducing unnecessary recalls and referrals to colposcopy (Coquillard, Palao, & Patterson, 2011; Kottaridi, Tsiodras, Spathis et al., 2011; Narimatsu & Patterson, 2005; Sorbye, Fismen, Gutteberg et al., 2010; Trope, Sjoborg, Eskild et al., 2009). At that time, it was evident that the immunocytochemical detection of p16 could increase the diagnostic accuracy of the Pap-test (Tsoumpou, Arbyn, Kyrgiou et al., 2009; Valasoulis, Tsoumpou, Founta et al., 2011); a growing body of literature shows promising results for this biomarker, either as a standalone or combined with Ki-67 assessment.

Several published studies have so far attempted to clarify the role of each technique as a candidate unique test to substitute the Pap test (Benevolo, Vocaturo, Caraceni et al., 2011; Carozzi, 2007; Coquillard, Palao, & Patterson, 2011; Cuschieri & Wentzensen, 2008; Cuzick, Arbyn, Sankaranarayanan et al., 2008; Denton, Bergeron, Klement et al., 2010; Kottaridi, Tsiodras, Spathis, Chranioti, Pappas, Kassanos, Panayiotides, & Karakitsos, 2011; Mathew & George, 2009; Mayrand, Duarte-Franco, Rodrigues et al., 2007; Narimatsu & Patterson, 2005; Naucler, Ryd, Tornberg et al., 2009; Smits, van Gemen, Schukink,

van der Velden, Tjong, Jebbink, & ter Schegget, 1995; Sorbye, Fismen, Gutteberg, & Mortensen, 2010; Trope, Sjoborg, Eskild, Cuschieri, Eriksen, Thoresen, Steinbakk, Laurak, Jonassen, Westerhagen, Jacobsen, & Lie, 2009; Tsoumpou, Arbyn, Kyrgiou, Wentzensen, Koliopoulos, Martin-Hirsch, Malamou-Mitsi, & Paraskevaidis, 2009; Valasoulis, Tsoumpou, Founta, Kyrgiou, Dalkalitsis, Nasioutziki, Kassanos, Paraskevaidis, & Karakitsos, 2011). As a concluding remark, the performance of the methods mentioned above differs significantly, affected by the disease incidence and the prevalence of HPV infection in the population study group; therefore, the application of a single method, despite apparently improving key performance indicators, might not reliably determine an individual women's risk of harboring cervical intraepithelial neoplasia (CIN). However, most published studies (Cuzick, Arbyn, Sankaranarayanan, Tsu, Ronco, Mayrand, Dillner, & Meijer, 2008; Karakitsos, Pouliakis, Meristoudis et al., 2011; Mathew & George, 2009; Mayrand, Duarte-Franco, Rodrigues, Walter, Hanley, Ferenczy, Ratnam, Coutlee, & Franco, 2007; Naucier, Ryd, Tornberg, Strand, Wadell, Elfgren, Radberg, Strander, Forslund, Hansson, Hagmar, Johansson, Rylander, & Dillner, 2009; Schiffman, Kinney, Cheung et al., 2018; Spathis, Kottaridi, Chranioti et al., 2012) conclude that the sensitivity of cytology combined with the HPV DNA test is higher than the sensitivity of each method.

Computer science and artificial intelligence enabled the development of computer-assisted systems to support clinical diagnosis or therapeutic and treatment decisions. Various classification techniques such as neural networks (Bountris, Haritou, Pouliakis et al., 2014; Cochand-Priollet, Koutroumbas, Megalopoulou et al., 2006; Cruz & Wishart, 2006; Hassan, Ruusuuvuori, Latonen et al., 2015; Karakitsos, Chrelias, Pouliakis et al., 2012; Karakitsos, Cochand-Priollet, Guillausseau et al., 1996; Karakitsos, Kyroudes, Pouliakis et al., 2002; Karakitsos, Stergiou, Pouliakis et al., 1997; Karakitsos, Stergiou, Pouliakis et al., 1996; Kourou, Exarchos, Exarchos et al., 2015; Marchevsky, Tsou, & Laird-Offringa, 2004; Markopoulos, Karakitsos, Botsoli-Stergiou et al., 1997; Pantazopoulos, Karakitsos, Iokim-Liossi et al., 1998; Perroti, Pouliakis, Margari et al., 2018; Pitoglou, 2018; Pouliakis, Karakitsou, Margari et al., 2016; Pouliakis, Margari, Karakitsou et al., 2018; Simões, Izumi, Casagrande et al., 2014; Vilhena, Vicente, Martins et al., 2017), discriminant analysis (Karakitsos, Megalopoulou, Pouliakis et al., 2004; Marchevsky, Tsou, & Laird-Offringa, 2004; McHugh, Shinn, & Kay, 2000; Megalopoulou, Koutroumbas, Pouliakis et al., 2006), classification and regression trees (CARTs) (Breiman, Friedman, Stone et al., 1984; Karakitsos, Pouliakis, Meristoudis, Margari, Kassanos, Kyrgiou, Panayiotides, & Paraskevaidis, 2011; Sá, 2007; Tzivras, Megalopoulou, Pouliakis et al., 2008) or genetic algorithms (Saiti, Naini, Shoorehdeli et al., 2009) have been used in medicine, as well as, to facilitate CC prevention processes.

The Covid-19 pandemic has drastically altered social life and imposed severe pressure on health systems. With fears of an impending global financial crisis coupled with devastating climate change, the sense of normalcy has been altered. In this changing landscape, the urge for reallocation of financial and human resources is paramount. The relatively novel vaginal or urine self-sampling modalities, most promising in secondary CC prevention, represent feasible approaches requiring limited infrastructures (Daponte, Michail, Daponte et al., 2021). However, the wildly prolific global anti-Covid vaccination movement, with a vocal manifesto in social media, might be detrimental in the long term in primary CC prevention, causing declining rates of HPV-vaccine uptake (Daniels, Saxena, Roberts et al., 2021). The implementation of new approaches in secondary CC prevention could address some of these issues (Gajjar, Ahmadzai, Valasoulis et al., 2014; Karakitsos, Chrelias, Pouliakis, Koliopoulos, Spathis, Kyrgiou, Meristoudis, Chranioti, Kottaridi, Valasoulis, Panayiotides, & Paraskevaidis, 2012; Koliopoulos, Valasoulis, & Zilakou, 2009; Kyrgiou, Pouliakis, Panayiotides et al., 2016; Kyrgiou, Stasinou, Arbyn et al., 2012; Kyrgiou, Valasoulis, Founta et al., 2010; Lima, Gajjar, Valasoulis et al., 2014; Mnimatidis,

Pouliakis, Valasoulis et al., 2020; Nasioutziki, Daniilidis, Dinas et al., 2011; Paraskevaidis, Athanasiou, Paraskevaidi et al., 2020; Pouliakis, Karakitsou, Chrelias et al., 2015; Purandare, Trevisan, Patel et al., 2013; Stasinou, Valasoulis, Kyrgiou et al., 2012; Tsakiroglou, Bakalis, Valasoulis et al., 2011; Tsoumpou, Valasoulis, Founta et al., 2011; Valari, Koliopoulos, Karakitsos et al., 2011; Valasoulis, Koliopoulos, Founta et al., 2011; Valasoulis, Pouliakis, Michail et al., 2021; Valasoulis, Pouliakis, Michail et al., 2020; Valasoulis, Stasinou, Nasioutziki et al., 2013; Valasoulis, Tsoumpou, Founta, Kyrgiou, Dalkalitsis, Nasioutziki, Kassanos, Paraskevaidis, & Karakitsos, 2011). However not yet an unsupervised neural network.

In this chapter, we investigate the feasibility of a rarely used AI technique, namely the Self Organizing Map (SOM) approach, to successfully combine results from numerous other techniques (i.e. cytology, HPV DNA test, HPV mRNA tests and p16) aiming to predict the cervical pathology status correctly. The evaluation of the SOM performance is based on the result of the histological examination, which is the gold standard (i.e. a result that is considered infallible). In other words, the SOM is expected to identify the histological status of the cervix correctly. The proposed AI method was selected because it can create clusters in the data set and create maps that indicate the separation of the clusters in space when visually examined. Additionally, SOM is an unsupervised AI tool; unsupervised methods have not been extensively explored in medical applications. Only our group has implemented SOM to investigate issues related to cervical pathology (Salamalekis, Pouliakis, Margari et al., 2019).

MATERIALS AND METHODS

I. Involved Institutes and Ethics

This was a multicentric study involving several divisions from three medical sites: the 3rd Department of Obstetrics and Gynecology, the Department of Cytopathology and the 2nd Department of Pathology of the Medical School of the National and Kapodistrian University of Athens (all based in “ATTIKON” University Hospital, Athens), the 2nd Obstetrics and Gynecology Department, Medical School, Aristotle University of Thessaloniki, Greece and the Department of Obstetrics and Gynecology, University Hospital of Ioannina, Greece. The University Hospital ethics boards approved the study, and participating women signed an Informed Consent (ICON) form to use their epidemiologic, diagnostic and ancillary test data.

II. Cytology/ Papanicolaou Test

All cytological and ancillary examinations were based on ThinPrep Liquid Based Cytology (LBC) material obtained before the colposcopic examination. The smears were routinely prepared for cytological examination, and the remaining material in the ThinPrep vial was used for additional evaluation of biomarkers related to the HPV lifecycle. The cytological findings for each woman were formulated according to the revised Bethesda classification system (TBS 2001 system) (Henry, 2003; Smith, 2002).

III. Molecular Tests

Concerning the HPV lifecycle biomarkers, we used: a) HPV DNA typing using the CLART® HUMAN PAPILLOMAVIRUS 2 (HOLOGIC) kit for the simultaneous detection of 35 different HPV genotypes by PCR amplification of a fragment within the highly conserved L1 region of the virus (Gomez-Roman,

Echevarria, Salas et al., 2009); b) NASBA assays (Tyagi, Bratu, & Kramer, 1998) (NucliSENS EasyQ® HPV v1.0) that was used for the identification of E6/E7 mRNA of the HPV types: 16, 18, 31, 33 and 45; c) the PermiFlow® (Invirion Diagnostics, LLC, Oak Brook, IL) kit for the identification of E6/E7 mRNA expression of high-risk HPV using FLOW cytometry (Narimatsu & Patterson, 2005) and d) the immunocytochemical expression of p16 using the CINtec® (now ROCHE) Cytology Kit (Klaes, Benner, Friedrich et al., 2002).

Each HPV biomarker has a distinct clinical role. HPV DNA test identifies the presence of HPV virus, the applied assay identifies the presence of 35 different HPV subtypes, possessing either low oncogenic potential (i.e. Low Risk, lrHPV's in the sequel) or highly oncogenic (i.e. High Risk, hrHPV's in the sequel, for example, 16, 18, 31, 33 and 45 among others); especially subtypes 16 and 18 are considered the two most oncogenic genotypes and account for the vast majority of cervical cancers worldwide. However, the presence of hrHPV's does not necessarily cause CC since, in most cases, the infection is short-lived and cleared by the human defence mechanisms. However, persistent infection and a compromised immune system permit the viral DNA to be integrated into the host DNA (women's DNA), achieving virus replication. At this point, the infection becomes potentially dangerous. The two other molecular methods identify such status: the NASBA assay, which determines the integration of five of the most hazardous high-risk subtypes (16, 18, 31, 33 and 45) and the FLOW cytometry (PermiFlow) method, which identifies the integration of 15 high-risk subtypes. The second method cannot differentiate these 15 high-risk subtypes; in contrast, the NASBA methodology recognizes each subtype but is limited to only five of them. Finally, p16 is a protein with an essential role in cell cycle regulation and acts as a tumor suppressor in preventing numerous cancers, including cervical cancer. As an established biomarker to improve the histological diagnosis of CIN3 cases, p16 is a valuable pathology tool (see Gold standard section) and can be applied in cytological material as well, as in this study (Darragh, Colgan, Cox et al., 2012)

IV. Histological Confirmation

The histological material was obtained during colposcopy and/or during treatment by conization. The obtained histological samples were fixed and prepared according to standard histopathology protocols. The histological diagnosis was the gold standard and was used as the target category of each woman. Punch biopsies were performed by experienced colposcopists (with more than ten years in colposcopy practice). The three-tiered Cervical Intraepithelial Neoplasia (CIN) grading system was used for reporting the histological diagnosis. Clinically negative (CN) cases were included in the study. These were defined as CN if the cytology, colposcopy and HPV testing () tested negative. Despite the lack of histological biopsies due to ethical hurdles, these women were included and analyzed in a target category of less than CIN2 (< CIN2).

V. Gold Standard

Our target was to classify each woman into one of the following categories: a) <CIN2, this included the histologically negative and CIN1 (including HPV and HPV suspect) cases as well as the CN cases, and b) ³CIN2, this category included the histological categories: CIN2, CIN3, SCC and ADENO-CA.

DATA FORMULATION

For each case, a vector of numerous variables was created (Table 1). That had the result of the cytological examination expressed according to TBS 2001. The HPV DNA test examination results were defined as 35 individual values (either positive or negative), one for each HPV DNA genotype. Additionally, concerning the found subtype, five other variables were investigated: the total number of HPV subtypes and the number of high risk and the number of low-risk types identified in two separate variables. For the NASBA HPV mRNA typing, we used the result for each HPV type (16, 18, 31, 33 and 45), and the result of the NASBA mRNA typing was expressed as positive or negative. The result of the PermiFlow test was involved using two methods, either as a percentage and either as positive or negative (the cut-off value to assign a flow cytometry result was 1.5%). In addition, the result of the immunocytochemical expression of p16 was included.

Table 1. Variables entered to the SOM model, including the result of the cytological examination and various parameters related to the molecular tests

Variable name	Description	Value Range
BETHESDA_VALUE	The result of the cytological examination was expressed according to the Bethesda 2009 system and mapped to numeric values	WNL@1, ASCUS@2, LGSIL@3, ASC-H@4, HGSIL@5, SCC@6, ADENO-CA@6, note that SCC and ADENO-CA are mapped to the same number
HPV DNA Arrays A6, A11, A16, A18, A26, A31, A33, A35, A39, A40, A42, A43, A44, A45, A51, A52, A53, A54, A56, A58, A59, A61, A62, A66, A68, A70, A71, A72, A73, A81, A82, A83, A84, A85, A89	The existence of individual subtypes according to the HPV DNA (HPV typing) examination	0 if the specific subtype is not found 1 if the specific subtype is found <blank> if there is no result
HR	Positive if one or more High-Risk subtypes were found during HPV typing	POSITIVE, NEGATIVE or MISSING
LR	Positive if one or more Low-Risk subtypes were found during HPV typing	POSITIVE, NEGATIVE or MISSING
No_HR	The number of high-risk subtypes that were found during typing	An integer or MISSING
No_LR	The number of low-risk subtypes that were found during HPV typing	An integer or MISSING
No_Subtypes	The total number of HPV subtypes that were found during HPV typing	An integer or MISSING
NASBA	The result of HPV mRNA identification result as positive or negative (it is the outcome of the NASBA method)	0 if negative, 1 if positive, <blank> if there is no result
N16, N18, N31, N33, N45	The specific result of the E6/E7 mRNA test in the particular HPV subtype	0 if negative, 1 if positive, <blank> if there is no result
FLOW	The result of the identification of E6/E7 mRNA expression of high-risk HPV using FLOW FISH cytometry technique	0 if negative (<1.5%) 1 if positive (>1.5%) <blank> if there is no result
FLOW_PERCENTAGE	The result of E6/E7 mRNA expression of high-risk HPV using FLOW FISH cytometry technique expressed as a percentage	A number or <blank> if there is no result
p16	The result of the p16 immunocytochemical examination	0 if negative 1 if positive, <blank> if there is no result

ARTIFICIAL INTELLIGENCE TECHNIQUES (THE SOM APPROACH)

The self-organizing map (SOM), often mentioned as a self-organizing feature map (SOFM), is an unsupervised type of ANN (Kohonen, 1982) widely applied to clustering problems and data exploration. SOM produces low-dimensional (usually two dimensional) representations of the training samples' input space (i.e. the input features). This two-dimensional representation is called a map, and thus SOM performs some dimensionality reduction (i.e. the feature space is mapped to a 2D space). SOMs are different from other ANNs due to the maps because they apply competitive learning and are unsupervised (i.e. the output is not used during training). In contrast, in this study, other training methodologies, i.e. the supervised techniques, such as the backpropagation of the error algorithm, use the actual category, i.e. the histological categorization, to train the ANN.

SOM visualization is handy as it creates low dimensional views of high dimensional data. Thus, essential features are relatively easy to identify. SOM was proposed in the 1980s by Teuvo Kohonen, and therefore sometimes is also called Kohonen map or Kohonen network (Kohonen, 1988, 2001). SOMs are extremely elegant ANNs, as they represent abstraction models of biological neural systems.

SOM is an automatic data-analysis method closely related to classical vector quantization (Kohonen, 1988). SOMs represent the supplied input data (in this study, the measurements, Table 1) in an automated manner using nodes in a grid (called map and is two dimensional in this study) in a way that nodes are neighboring to other nodes representing similar data. In short, nodes that represent similar inputs are adjacent in the grid, and additionally, less similar models are situated away in the map. This topographic organization on maps makes it possible to have a visual insight into the relationships of the input data, especially when it is a high dimensional case (in this study, there are more than 50 different inputs, Table 1). During the training phase, the map nodes are adjusted to similar group inputs in neighboring nodes. In a second step, the nodes are labelled according to the inputs' classes (in this study, according to the golden standard of histology: ³CIN2 or <CIN2). This process is called calibration and is not considered part of the training phase. The assignment of the nodes to classes is usually performed via a majority logic method, e.g. in our case, a node is assigned to class ³CIN2 (marked with a + sign in our case) when the majority of the input measurements are assigned to this node do belong to class ³CIN2. The final step is the SOM operation to classify data. For this purpose, an unknown input is fed to the map and subsequently classified according to the most similar node. The similarity is measured using a metric such as the Euclidian distance (Kohonen, 2013).

The SOM ANN in this study was created within the MATLAB software environment and programming language (The MathWorks, Inc. Natick, Massachusetts, USA), and for the implementation of the SOM, the SOM toolbox for Matlab 5 (Vesanto, Himberg, Alhoniemi et al., 2000) was used.

Performance Evaluation

To assess the performance, various statistical measures were extracted: specificity, sensitivity, positive and negative predictive value (PPV and NPV respectively), false positive and false negative rates (FPR and NPR) and overall accuracy (OA).

RESULTS

The sets of examination results from 1258 women were included in this study. The correlation of the cytological results with histology is presented in Table 2.

Table 2. Correlation of the cytological with the histological diagnosis of the complete data set used in the study

		HISTOLOGICAL RESULT									
		ADENO-CA	SCC	CIN-3	CIN-2	CIN-1	HPV	HPV-SUSPECT	NEGATIVE	CN*	TOTAL
BETHESDA CLASSIFICATION	ADENO-CA	6	1	0	0	0	0	0	0	0	7
	SCC	1	6	0	0	0	0	0	0	0	7
	HGSIL	0	8	45	42	15	2	0	7	0	119
	ASC-H	0	1	1	2	0	2	0	3	0	9
	LGSIL	1	0	7	17	64	46	12	24	0	171
	ASCUS	1	0	3	9	29	26	6	18	0	92
	WNL	0	0	1	3	16	8	4	36	785	853
TOTAL		9	16	57	73	124	84	22	88	785	1258

* CN: Clinically Negative

For the SOM ANN, a topographical map of dimensions 80 by 80 using a hexagonal lattice structure was selected to have an adequate number of nodes. Since SOM is an unsupervised method after training of the SOM, the map nodes should be assigned to individual histological categories (i.e. $^1\text{CIN2}$ and $^3\text{CIN2}$, the first marked with a minus sign and the second with the + sign). To assign the nodes to the categories, a “voting” technique was applied, i.e. each input vector was fed to the SOM. It was determined which node each vector was assigned, and finally, the node was labelled according to the histological class of most of the vectors. If no vector was mapped to a node, then the node had no mapping to a category.

The map showing the category assignment of each node is presented in Figure 1. This topographical map shows that the $^3\text{CIN2}$ cases are concentrated to the lower part and towards the right and that there are many nodes not assigned to one of the two histological groups.

As mentioned, SOMs can produce useful maps providing visual representations of the data for each input feature. Figure 2 illustrates the cytological result colored according to severity (see Table 1 for mapping). Interestingly, low values (blue colors) mapped to negative cytological cases have an excellent relation to the histologically negative nodes (the nodes with the – sign) and cases with pathology in cytology correspond to the histologically positive ($^3\text{CIN2}$) results (those with the + sign).

Similarly, Figure 3 depicts the topographic maps for the characteristics of the HPV DNA typing results. The existence of hrHPV genotypes (in yellow color) is related to a positive histological outcome. However, numerous histologically negative cases harbor an HPV subtype. In contrast, lrHPV expression seems unrelated to the histological outcome since both lrHPV positive and negative cases are connected to a positive histology result (i.e. $^3\text{CIN2}$). Finally, the number of hrHPV subtypes follows a similar pattern with HR positivity.

A more detailed mapping for each HPV subtype is presented in Figure 4. From the SOM visualizations, it is evident that the majority of the subtypes (considering the complete panel of the 34 subtypes)

Figure 1. SOM with each node assigned into ³CIN2 category (+ sign), <CIN2 category (- sign) or no category (blank)

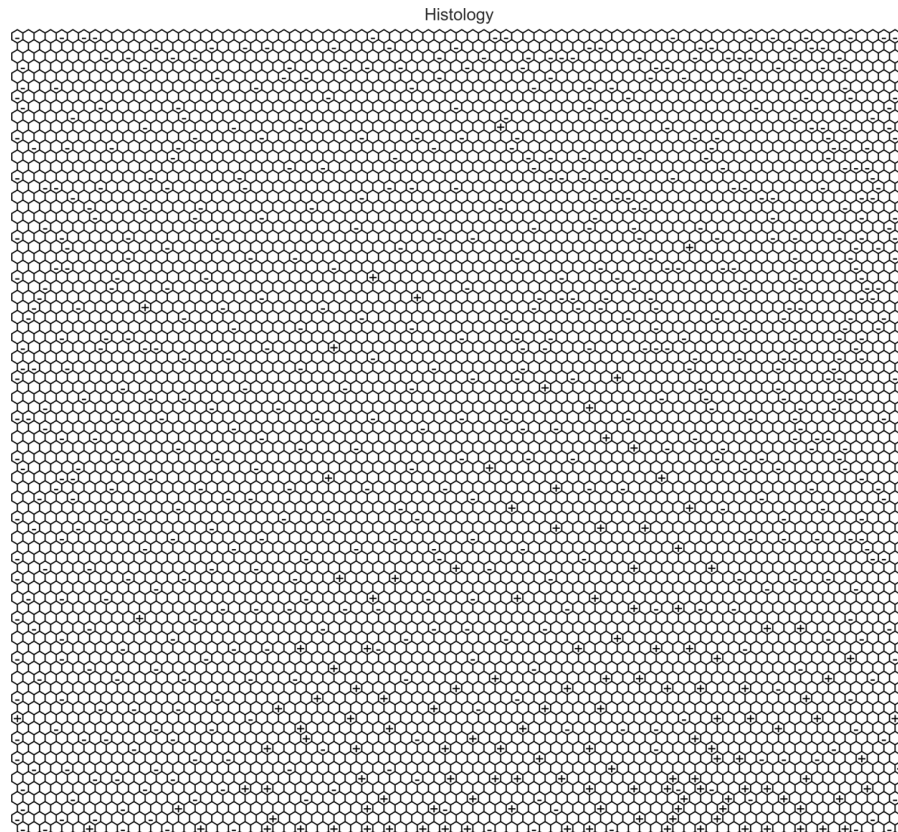


Figure 2. SOM with labelled nodes and coloring according to the cytological result (expressed according to the Bethesda Classification System)

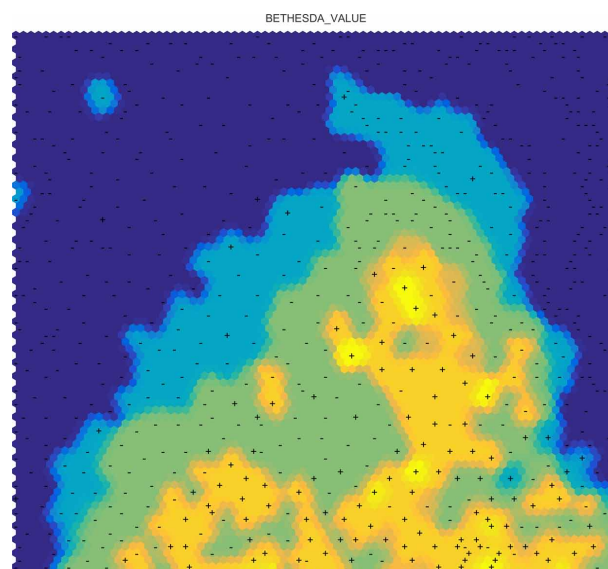


Figure 3. SOM with labelled nodes and coloring according to (from left to right, top to bottom): the existence of HR HPV DNA, the existence of LR HPV DNA, number of HPV subtypes identified, number of HR HPV subtypes and number of LR HPV subtypes

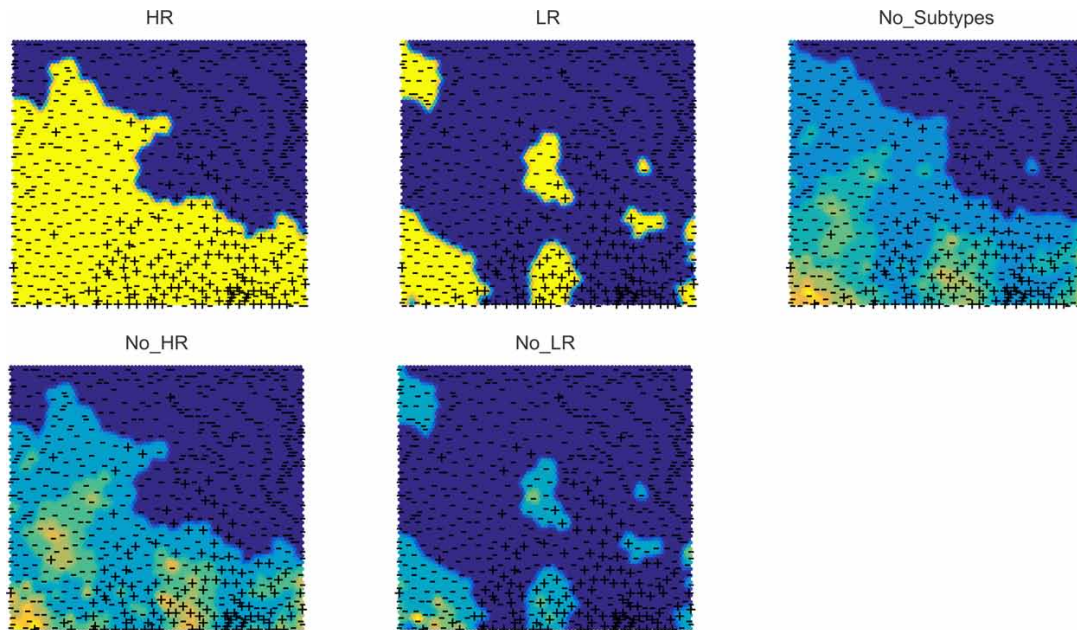
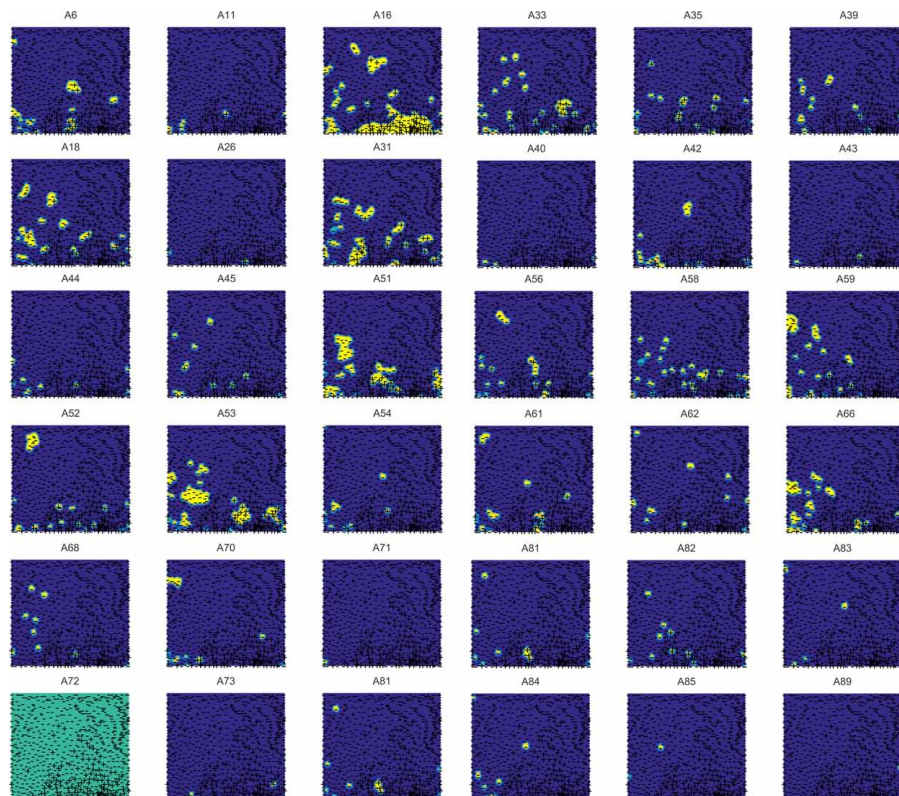
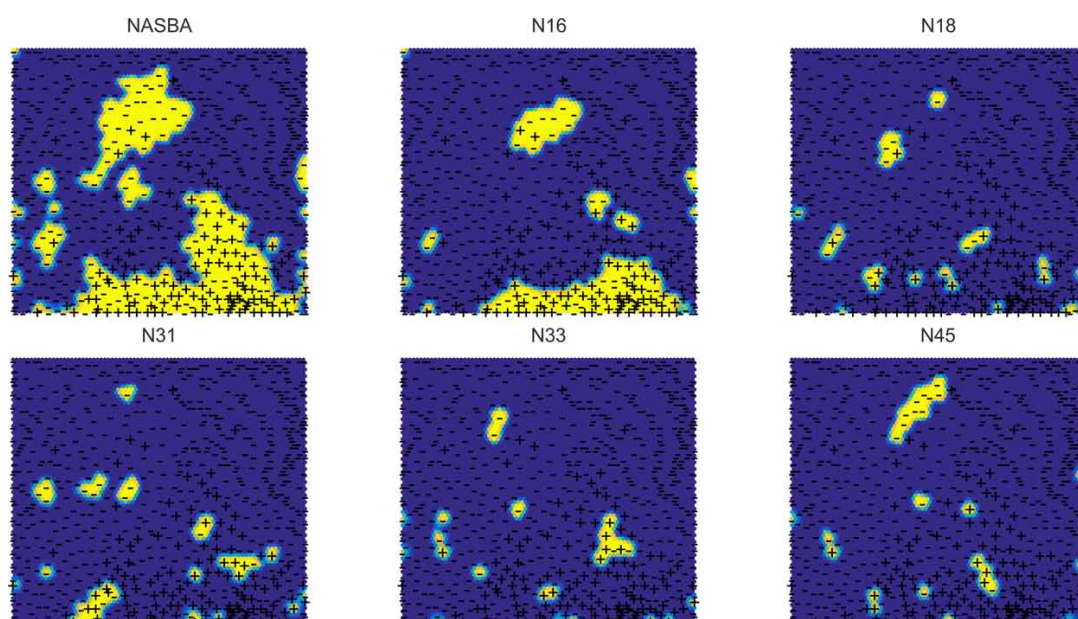


Figure 4. SOMs according to individual HPV subtypes as identified by the HPV DNA test



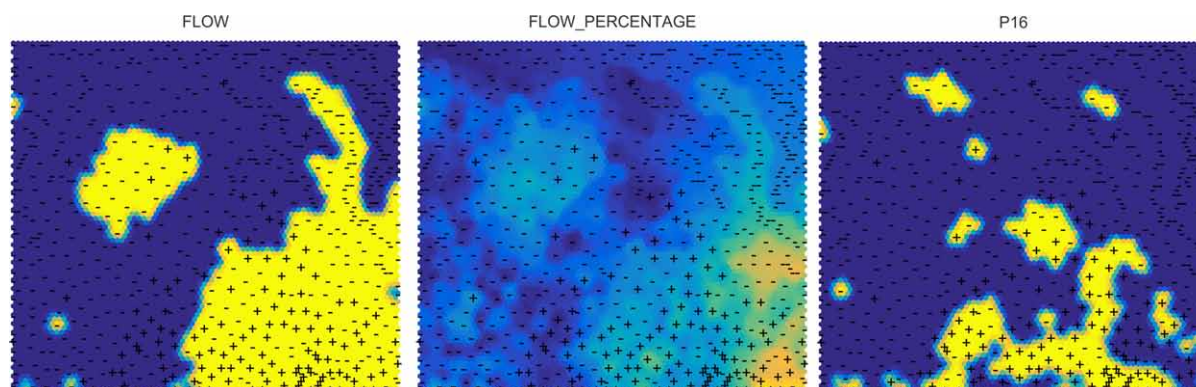
are not related to the histological status, HPV16 has a necessary coexistence with ³CIN2 cases, and additionally, there is the presence of HPV18, 31, 33, 35, 45, 51, 53 and 85. Note that these are HR subtypes being related to carcinogenesis. Finally, for HPV72, there is no mapping because there was no case identified with this subtype.

Figure 5. SOM with labelled nodes and coloring for HPV mRNA as evaluated with the NASBA technique (top left NASBA result expressed as positive/ negative, other images for specific HPV subtypes)



The final mappings are related to HPV mRNA expression as the NASBA technique identified this (Figure 5) and the FLOW cytometry technique (Figure 6), and the SOM for protein p16 (Figure 6). The NASBA technique, as expected, has similar performance with the HPV DNA identification method

Figure 6. SOM HPV mRNA as evaluated with the flow cytometry methodology (left & center), and SOM map for protein p16 (right)



(Figure 4), especially for HPV16, as the two SOMs have similar topography. This fact confirms that the SOM approach correctly identified the critical biological factors (i.e. HPV16, the genotype considered most oncogenic) related to the histological status.

Table 3. SOM results for the prediction of CIN2+

Actual Category	Predicted Category		Grand Total
	< CIN 2	³ CIN 2	
< CIN 2	1101	2	1103
³ CIN 2	6	149	155
Grand Total	1107	151	1258

After creating and labelling the SOM ANN, the next step is the analysis of its performance. For this purpose, the 1258 cases (see Table 2) were fed to the network and assigned to each category. The results are summarized in Table 3. Specifically, the SOM correctly assigned 149 from the 155 positive and 1101 from the 1103 negative cases. The performance indicators [REMOVED REF FIELD]of the final ANN system were: Sensitivity = 96.13%, Specificity = 99.82%, PPV=98.68%, NPV=99.46%, FPR=0.18%, FNR=3.87% and OA=99.36%. These results indicate a very high performance of the SOM.

DISCUSSION

For decades, the Papanicolaou Test (Diamantis, Magiorkinis, & Koutselini, 2014; Papanicolaou & Traut, 1941) has been considered the most successful CC test (Nauth, 2007) if repeatedly applied. During the last decade, several HPV related biomarkers and assays options are available for the triage of abnormal pap smears (Arbyn, Buntinx, Van Ranst et al., 2004; Arbyn, Martin-Hirsch, Buntinx et al., 2009; Kelesidis, Aish, Steller et al., 2011; Koliopoulos, Chrelias, Pappas et al., 2012; Kottaridi, Tsiodras, Spathis, Chranioti, Pappas, Kassanos, Panayiotides, & Karakitsos, 2011; Nasioutziki, Daniilidis, Dinas, Kyrgiou, Valasoulis, Loufopoulos, Paraskevaidis, Loufopoulos, & Karakitsos, 2011; Roelens, Reuschenbach, von Knebel Doeberitz et al., 2012; Spathis, Aga, Alepaki et al., 2011; Tsoumpou, Valasoulis, Founta, Kyrgiou, Nasioutziki, Daponte, Koliopoulos, Malamou-Mitsi, Karakitsos, & Paraskevaidis, 2011; Valasoulis, Tsoumpou, Founta, Kyrgiou, Dalkalitsis, Nasioutziki, Kassanos, Paraskevaidis, & Karakitsos, 2011), considered as alternatives or complementary to test Papanicolaou. However, these novel biomarker-based techniques simultaneously have high sensitivity or specificity but not high values in both performance indicators.

To the authors' knowledge, this is one of a few times that an unsupervised artificial intelligence method is used to combine such a plethora of examinations and to improve accurate diagnosis of cervical abnormalities (Salamalekis, Pouliakis, Margari, Kottaridi, Spathis, Karakitsou, Gouloumi, Leventakou, Chrelias, Valasoulis, Nasioutziki, Kyrgiou, Dinas, Panayiotides, Paraskevaidis, & Chrelias, 2019). The application of ancillary test data for the improvement of cervical intraepithelial lesions remains a hot research topic. Our group has previously presented similar innovative approaches (Bountris, Haritou, Pouliakis, Margari, Kyrgiou, Spathis, Pappas, Panayiotides, Paraskevaidis, Karakitsos, & Koutsouris,

2014; Karakitsos, Chrelias, Pouliakis, Koliopoulos, Spathis, Kyrgiou, Meristoudis, Chranioti, Kottaridi, Valasoulis, Panayiotides, & Paraskevaidis, 2012; Karakitsos, Pouliakis, Meristoudis, Margari, Kassanos, Kyrgiou, Panayiotides, & Paraskevaidis, 2011). A previously published study (Karakitsos, Pouliakis, Meristoudis, Margari, Kassanos, Kyrgiou, Panayiotides, & Paraskevaidis, 2011) CART models were applied, using data that had valid examination results for all the available ancillary tests. This approach had the disadvantage of reducing usable data volume. It is very usual that some ancillary tests cannot always have a valid result and did not capture the real-life situation (*i.e. missing values*). Later, in two other published reports (Bountris, Haritou, Pouliakis, Margari, Kyrgiou, Spathis, Pappas, Panayiotides, Paraskevaidis, Karakitsos, & Koutsouris, 2014; Karakitsos, Chrelias, Pouliakis, Koliopoulos, Spathis, Kyrgiou, Meristoudis, Chranioti, Kottaridi, Valasoulis, Panayiotides, & Paraskevaidis, 2012) supervised neural networks were applied to address the same problem; however with the same limitations. In a subsequent study, CARTs were employed to handle cases with missing data and, therefore, increase the study's power (Pouliakis, Karakitsou, Chrelias, Pappas, Panayiotides, Valasoulis, Kyrgiou, Paraskevaidis, & Karakitsos, 2015). The novelty of this approach was related to the fact that when using CARTs, it is possible to create easily understandable algorithms with a known risk of malignancy for each part of the tree. Moreover, knowledge can be represented in triage tree-like algorithms that could be useful to decision-makers.

The SOM technique presented here achieved a sensitivity of 96.13% and specificity of 99.82% in the performance comparison level. In 2011, one of the first efforts of our team to apply CART's on this classification problem (Karakitsos, Pouliakis, Meristoudis, Margari, Kassanos, Kyrgiou, Panayiotides, & Paraskevaidis, 2011) was based on 808 cases; the sensitivity, using CIN2+ as cut off, was 84.75% and specificity 91.40%, while in our study the number of cases was higher (N=1258). Moreover, our group's approach (Karakitsos, Chrelias, Pouliakis, Koliopoulos, Spathis, Kyrgiou, Meristoudis, Chranioti, Kottaridi, Valasoulis, Panayiotides, & Paraskevaidis, 2012) was based on the same data set. Another AI technique (namely the learning vector quantizer) was applied and produced similar sensitivity (85.16%) and increased specificity (98.01%) compared to the CART. A different approach by our team back in 2014 used a Clinical Decision Support System (CDSS) (Bountris, Haritou, Pouliakis, Margari, Kyrgiou, Spathis, Pappas, Panayiotides, Paraskevaidis, Karakitsos, & Koutsouris, 2014), again based on ANNs, which demonstrated increased sensitivity 89.4% and high specificity equal to 97.1% using data from significantly fewer cases (N=740), since it was not possible to apply the technique when missing values were present. Notably, in this report, specificity is higher than sensitivity in the SOM case and all other mentioned efforts. As early as 2015, the first approach to applying techniques with missing data (Pouliakis, Karakitsou, Chrelias, Pappas, Panayiotides, Valasoulis, Kyrgiou, Paraskevaidis, & Karakitsos, 2015) on the same data set as the SOM achieved sensitivity 83.28% and specificity 94.26%, a performance comparable to the first CART model. The previous paper presents comparisons of using each method (cytology and biomarker-based); as expected, no individual method could simultaneously produce balanced sensitivity and specificity. For example, cytology alone, using as cut off ASC-US, had sensitivity 97.76% and specificity 59.79%, similarly HPV DNA positivity 87.71% and 70.49%, respectively. The most exciting methods based on single biomarkers were based on flow cytometry, which achieved a sensitivity of 88.19% and specificity of 79.60%. Finally, in another approach of our team (Kyrgiou, Pouliakis, Panayiotides, Margari, Bountris, Valasoulis, Paraskevaidis, Bilirakis, Nasioutziki, Loufopoulos, Haritou, Koutsouris, Karakitsos, & Paraskevaidis, 2016), the sensitivity for prediction of CIN2 or worse was 93.0% and the specificity of 99.2%. Compared to this effort (using the SOM) illustrates improved sensitivity (96.13%). Noteworthy is that comparisons with results from other research teams

are not straightforward since the biomarkers dataset differs. The most common combinatorial techniques include Pap-test with HPV DNA typing or HPV mRNA typing or standalone biomarkers. For example, a 2014 study reported that the sensitivity and specificity of the Cobas HPV test alone, when applied in the detection of biopsy-confirmed CIN2/3 cervical lesions, was 71.7% and 25.0%, respectively (Zhou, Mody, Luna et al., 2014). This study was based on a 30,000 cases sample.

In this study, we have proposed a new methodology that combines the results of numerous biomarker-based techniques and the outcome of the Papanicolaou test to create a method that can exploit the best characteristics of each test. Regarding system performance, the results were very satisfactory and encouraging since the final specificity and sensitivity are enhanced compared to the performance of each method alone.

One of the disadvantages of the proposed approach is that the complete data set was used to train the SOM. We did not follow the traditional approach, i.e., split the data in training and test sets or into training, test and validation sets. However, the unsupervised nature of the SOMs justifies this decision since the real histological category that the cases belong to (and being the classification target) is not used during the training phase. Instead, the histological status is used after the training phase to find the labels of the SOM nodes (i.e. to mark each node and ³CIN2 or <CIN2). A potential disadvantage of applying this approach in clinical practice is the high cost of performing the complete set of examinations (i.e. Papanicolaou test, HPV DNA typing, HPV mRNA typing by NASBA, and flow cytometry and p16 staining). However, with evolution in technology, it is plausible to have cost-efficient tests that may tolerate such a system.

Moreover, the SOM topography capabilities revealed that not all tests are essential. For example, only a few of the HPV subtypes were found with the CLART-2 techniques showing a correlation with histology. Additionally, HPV mRNA typing, especially for the HPV16 subtype, produced a similar map with HPV DNA typing. Therefore, other molecular tests detecting fewer HPV subtypes can be more cost-effective.

CONCLUSION

In conclusion, the application of the unsupervised artificial intelligence technique gave encouraging results and may be helpful towards improved management of women harbouring CIN2+ lesions. Thus, it could serve as a) guide towards therapeutic decisions and personalized medicine; b) reduction of the cases referred for colposcopy and colposcopy clinics overload; c) reduction of unnecessary treatments and d) identification of a higher percentage of women genuinely being at risk of cervical precancerous lesions or cancer.

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Chapter 12

The Implementation of Clinical Laboratory Quality Indicators in the Era of the COVID–19 Pandemic

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ABSTRACT

The use of quality indicators (QIs) and risk assessment are valuable tools for maintaining the quality of laboratory tests. Both are requirements of ISO 15189: 2012 and are usually based on standard statistical and empirical data. In this chapter, the authors focus on evaluating clinical laboratory quality indicators in the era of the COVID-19 pandemic. The goal is to pose and discuss, based on the authors' experience, the quality evaluation and risk assessment through the collection, study, and analysis of quality indicators covering the pre-analytical, analytical, and post-analytical phases of the laboratory testing process. QIs were evaluated using the Six Sigma method. Moreover, FMEA risk analysis was performed, and the degree of risk priority was assessed using the Pareto method. The results show that in the analytical phase, the laboratory's performance is satisfactory, while the pre-and post-analytical phases need further preventive/corrective actions.

DOI: 10.4018/978-1-7998-9198-7.ch012

INTRODUCTION

Clinical laboratories produce test results that must be relevant, accurate and reliable for the prognosis, diagnosis, treatment, hospital admission and discharge of patients. Approximately 70-85% of clinical decisions are based upon information derived from laboratory test results. Quality in clinical laboratories is defined as the guarantee that the entire testing process is correctly performed, thus ensuring valuable decision making and effective patient care. Clinical laboratories have always been forerunners in quality. Moreover, the implementation of quality assessment programs has always been a routine in clinical laboratory work. Automated innovations have contributed to a significant improvement in the quality of laboratory results, but despite all the automation, errors, which can lead to inappropriate patient care decisions, still occur (Plebani, 2015; Najat, 2017; Lao et al., 2017).

These errors occurring may have a negative impact on patient outcomes, such as time lost, patient revisits, increased costs, erroneous therapies, diagnostic delays and increased risk of patient debility (Epner et al., 2013; Blick, 2013; Warade, 2015; Mourtzikou & Stamouli, 2017).

The ongoing new coronavirus pandemic COVID-19, caused by the SARS-CoV-2 virus, is a severe global health crisis with many social and economic consequences (Austin & Kachalia, 2020; Reeves et al., 2020).

It started in December 2019, when a cluster of pneumonia cases was observed in Wuhan City, China (Wu F et al., 2020). Since then, no country has been left untouched by the outbreak, and up to now, more than 3.5 million people have died. However, we observe a high heterogeneity in death rates among countries and between regions within a country. The World Health Organization declared COVID-19 to be a pandemic on March 11th 2020.

According to the phase of the testing process during which they are observed, clinical laboratory errors are classified as preanalytical, analytical, and post-analytical. Strategies used to reduce laboratory errors include certification and accreditation by professional bodies, internal quality control procedures, external quality assessment programs, certification of education programs, risk assessment, as well as the implementation of quality indicators for the evaluation of laboratory performance (Jones et al., 2017; Mourtzikou & Stamouli, 2017; De la Salle et al., 2017). The preanalytical phase includes all components of the laboratory testing process before specimen analysis; test ordering, specimen collection, specimen transportation to the laboratory, specimen accessioning in the laboratory centrifugation and specimen preparation for analysis. The analytical phase involves the analysis of the specimen. The post-analytical phase includes evaluation, release and report of results. According to scientific literature, laboratory errors occur mainly in the preanalytical phase, which is the most vulnerable to errors due to many non-laboratory professionals, such as physicians, phlebotomists, medical interns and nursing staff (Plebani et al., 2017; Najat, 2017). The preanalytical phase has the highest error rates, accounting for up to 70% of all errors in laboratory diagnostics.

Moreover, preanalytical and post-analytical errors account for 93% of the total errors encountered in the laboratory. Reviews on available data on laboratory errors indicate significant heterogeneity in the studies, where the data collection method is the factor that influences the prevalence and type of errors (Najat, 2017; Sushma & Shrikant, 2019; Stamouli et al., 2019). Total quality management, which encompasses all the steps involved in sample processing, beginning from test order to the final interpretation of results by the clinicians, must be evaluated periodically to reduce or eliminate the errors that may arise during the various steps (Kaul, 2020; Austin & Kachalia, 2020; Reeves, 2020).

For a patient-centered approach, there is the need to assure that every step of the entire testing process is correctly performed, that weaknesses are recognized, and that corrective and preventive actions are designed and implemented (Schneider et al., 2017; Lippi et al., 2017).

The new pandemic has required enormous changes to everyday life to reduce virus transmission, morbidity and mortality. It also resulted in a significant difference in the function of the health care system and health care procedures (Korneta et al., 2021). Along with the change of health care procedures, it is necessary to change the assessment of their quality and availability (Korneta et al., 2021; Vandenberg et al., 2021).

By ensuring the quality and accuracy of laboratory tests, the clinical laboratory services provide a valuable contribution to the management of COVID-19 disease (Tang et al., 2020; Li et al., 2020; Younes et al., 2020; Lippi & Plebani, 2020).

The working environment in clinical laboratories changes rapidly. New rules, regulations, standards, critical medical devices, diagnostic tests, and personal protective equipment are needed to offer a timely response and maintain the quality of their services. The evaluation of clinical laboratory quality indicators in the era of the COVID-19 pandemic contributes to the management of the disease.

QUALITY INDICATORS

According to ISO 15189:2012, clause 3.19, a quality indicator measures the degree to which a set of inherent characteristics fulfills requirements. Quality indicators can measure how well an organization meets the needs and requirements of users and the quality of all operational processes.

They can be measures of structure, processes, outcomes or contribution of the laboratory to the patient care (Flegar et al., 2017; Kallen & Prins, 2017) and can be expressed in different ways; as % yield, that is, the percentage within specified requirements, as % defects, which is percentage outside specified conditions, as to defects per million opportunities (DPMO) or on the Six Sigma scale (ISO 15189:2012; Sharma et al., 2018). Since quality indicators provide information about the performance of a process and help us find potential areas that need further investigation and improvement, every clinical laboratory must systematically monitor and evaluate its quality indicators. The number of quality indicators to be monitored by the clinical laboratory depends on the laboratory's size, workload, and workflow and can change with time (Sciacovelli et al., 2016).

Quality indicators evaluate critical healthcare areas, such as patient safety, effectiveness, equity, patient-centeredness, timeliness and efficiency. They are based on data related to the aforementioned essential areas and can be implemented consistently and comparably at all process steps and over time (Plebani et al., 2014). The quality indicators must be developed carefully, based on updated scientific data published in the literature, user feedback and technical specification updates, including international standards and guidelines. Moreover, they must be specific, measurable, attainable, relevant and time-bound (the SMART acronym). Quality Indicators do not provide answers but indicate potential problems and vulnerabilities in laboratory workflow (Warade, 2015).

The quality indicators selected should be designed to reflect the actual situations of the laboratory. They must be easy to measure and must provide helpful information for improving performance. Clinical laboratories must ensure that the relevant data is available, reliable and that it can be easily obtained either from the LIS or from medical records and hospital databases. They must also decide about the frequency of data collection, the means of data collection and analysis, record keeping, the acceptance

limits of the indicator, the interpretation of the indicator and the corrective actions that will be implemented in case that the result of the indicator falls out the expected values (Simundic, 2008; Simundic et al., 2010; Plebani et al., 2014). Many clinical laboratories worldwide have adopted the use of quality indicators. However, variation in processes and workflow in laboratories within countries and between countries, different approaches used to measure quality from medical records and data, differences in availability of human resources, equipment and supplies, differences in methods used for data collection processing and analysis of results underline the need for international consensus on the adoption of universal quality indicators and common terminology (Plebani et al., 2017).

SIX SIGMA

Six Sigma is a technique for process improvement whose foundations were laid by Motorola and General Electric. These two companies implementing the Six Sigma methodology achieved excellent performance and long-term success. Six Sigma is widely applied in many fields (product production, services, healthcare, etc.). Six Sigma methodology represents a more strategic business initiative than a simple quality system. The ultimate goal of Six Sigma is the elimination of errors by the so-called Define, Measure, Analyze, Improve and Control or DMAIC (specify, measure, analyze, improve, and check) method for the implementation of Six Sigma. The measure of Six Sigma level performance or six standard deviations from the mean is a statistical representation of the variation of a process compared to the acceptable tolerance limits provided by the customer/user. The standard deviation is represented by the Greek symbol sigma (σ). If we assume that the variation of a process follows the normal distribution, approximately 99.73% of the values would be within ± 3 standard deviations of the mean (Sahno et al., 2015; Kumar & Mohan, 2018). Six Sigma performance is achieved when six standard deviations of process variation fit within the product/service's tolerance specification or quality requirement for the product/service. Statistically, this is 99.9997% perfection and corresponds to an insufficient number of Defects per Million Opportunities (DPMO) (Eckes, 2000; Sahno et al., 2015; Westgard, 2015). The Six Sigma scale is indirectly proportional to the defect rate, as the higher the sigma scale, the lower the possibility of error in the process (Westgard, 2015). A 3-sigma process corresponds to 66807 DPMO, a 4-sigma process to 6210 DPMO, a 5-sigma process to 233 DPMO and a 6-sigma process to 3.4 DPMO defect rate. We measured DPMO and six sigma levels to evaluate the performance of quality indicators implemented by a Molecular Diagnostics Laboratory.

IMPLEMENTATION OF QUALITY INDICATORS

QIs evaluation was performed at the Molecular Diagnostics Laboratory of General Hospital of Nikaia "Agios Panteleimon", Piraeus, Greece. The laboratory has an extensive testing capacity and can produce results with sufficient speed to facilitate patient care. Statistical data were collected during a one year time interval. We counted the test request forms, the number of samples and the types of errors in the laboratory. Data were obtained from the Laboratory Information System.

We implemented indicators relevant to the preanalytical, analytical and post-analytical phases of the laboratory testing process, as well as to supporting processes of laboratory work, as follows:

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Preanalytical phase

- number of recollected samples due to erroneous identification
- number of recollected samples due to inappropriate sample quality
- number of rejected samples due to transportation conditions
- number of rejected samples due to transportation delay

Analytical phase

- Number of non-conformities with unacceptable performance in the internal quality control

Post-analytical phase

- Samples with prolonged Turn Around Time (TAT in minutes), from sample reception in the laboratory to the release of the result

Support Processes

- Number of incident or adverse events occurred in the laboratory concerning the health and safety of laboratory staff
- Number of training events organized for all staff per year
- Covid-19 Case Occurrence in the Laboratory Staff
- Lack of resource availability, such as equipment and materials.

All the aforementioned quality indicators are classified as priority indicators due to the pandemic and the importance of laboratory results in its management. DPMO and six sigma levels were calculated using the Westgard application <https://www.westgard.com/sixsigma-calculators.htm>.

We developed the following performance levels, which are similar to the levels established by WG-LEPS (Working Group- on Laboratory Errors and Patient Safety)–International Federation of Clinical Chemistry, based on the sigma metrics evaluation:

- Excellent: >6.0 sigma
- Very good: ³ 5.0 sigma
- Good: 4.0 to <5.0 sigma
- Poor: 3.0 to <4.0 sigma
- Unacceptable: <3.0 sigma

A total of 1200 swab specimens were analyzed with RT-PCR. Specimens were obtained from inpatients, outpatients and hospital staff members. According to our results about the preanalytical phase, out of 1200 samples, eight samples were wrongly identified (0,67%), three samples were rejected due to erroneous transportation conditions (0,25%), two samples were rejected due to delays in transportation and 134 samples were recollected due to inappropriate sample quality (11,2%). We measured the number of non-conformities with unacceptable performance in internal quality control and external quality assurance to evaluate the analytical phase. To assess the post-analytical phase, we measured the TAT for test results to estimate the delays between the patient's arrival at the hospital and the reporting of the test. Out of the 1200 specimens, 28 (2,33%) had prolonged TAT. The evaluation of the support processes is presented but not analyzed and calculated as six sigma performance. These indicators were introduced due to the pandemic and implemented for the first time. Our results are summarized in Table 1.

Table 1. Results from the implemented indicators relevant to the preanalytical, analytical and post-analytical phases of the laboratory testing process, according to the levels established by WG-LEPS

QI		SIX SIGMA
Incorrect Identification	n	8
	DPMO	6667
	s	4,0
Inappropriate Transportation	n	3
	DPMO	2500
	s	4,4
Transportation Delay	n	2
	DPMO	1667
	s	4,5
Recollection due to Sample Quality	n	132
	DPMO	110000
	s	2,8
Number of non conformities with unacceptable performance in the internal quality control	n	1
	DPMO	833
	s	4,7
Samples with prolonged Turnaround time (TAT)	n	4
	DPMO	3333
	s	4,3
Total Number of Samples		1200

DISCUSSION

Preanalytical errors are the most common problem in clinical laboratories and the leading cause for the rejection of samples worldwide. Samples with incorrect identification showed a good performance of 4,0 sigma. Since efficient and quality healthcare requires accurate patient identification, patient and sample misidentification may cause significant harm or discomfort. Causes of misidentification include homonymy, incorrect patient registration, wrong patient data, mistakes in order entry, collection of biological specimens from unfit patients, inappropriate sample labeling, tube pre-labeling before sample collection, failure to follow all patient identification procedures, and inaccurate entry or erroneous transmission of test results through the laboratory information system (Lippi et al., 2017, Corma et al., 2020). In case of misidentification, two patients are affected. At least two unique patient identifiers should be used when collecting blood samples and other specimens for laboratory testing. The best approach worldwide is the use of barcoded wristbands. Other solutions are more technologically updated, such as radio-frequency identification tags, infrared-based patient tracking, patient smart cards, and biometric technologies. However, these approaches show advantages and limitations. Errors with the wristband itself also occur (Lippi et al., 2017). A study of wristband identification errors found that the wristband absence accounts for 49.5% of wristband errors, followed by patients wearing multiple different ID wristbands and incomplete data on wristbands (Snyder et al., 2010; Salinas et al., 2013). In

our hospital, we do not use barcoded wristbands for patients. We use three patient identifiers to confirm the person's identity (name, date of birth, and unique hospital ID number). We avoid leading the patient when asking for identifiers and ask him to tell his name and date of birth, and we have a protocol in case of patients in the same unit or department with similar names. Moreover, we confirm patients' identity before labeling specimen containers, and we attach the label to the container in the patient's presence after double-checking his identification information.

According to WHO and CDC recommendations, the success of the diagnosis of SARS-CoV-2 during the COVID-19 outbreak depends mainly on the quality of the specimen and the conditions under which the specimen is transported and stored before being processed in the laboratory. For screening or diagnosis of COVID-19 infection, nasopharyngeal or oropharyngeal swabs are recommended for analysis (Kim et al., 2011; Wang et al., 2020; Patriquin et al., 2020). Nasopharyngeal swabs are better tolerated by the patient and are safer for the operator. To obtain an appropriate swab specimen, the swab must be inserted deeply into the nasal cavity, be kept in place for 10 seconds and twirled three times. Consequently, staff training is of utmost importance for sample quality. Our study samples recollection showed poor performance of 2,8 sigma (Ramdas et al., 2020; Harrington et al., 2020).

Causes for this kind of error are the lack of experience in sample collection procedure and difficulty in sampling in some patient cases (pediatric, elderly patients, or patients with debilitating diseases). Swab collection is a complex task requiring training and competency assessment of the staff involved. Moreover, the procedure carries a possible risk of transmitting the virus, so specimens must be handled cautiously to minimize the risk of infection (Druce et al., 2012).

After collection, swabs should be placed in a transport medium and transported rapidly to the laboratory. Errors in these two steps may lead to deterioration of sample quality. In our study, these two steps showed a good performance of 4,4 and 4,5 Sigma, respectively. The Viral Transport Medium allows the safe transfer of viruses for diagnostic tests and molecular biology techniques (Kim et al., 2011; Wang et al., 2020; Patriquin et al., 2020). Commercially prepared viral transport media are available in a screw cap plastic tube containing buffered proteins (serum, albumin or gelatin) and antibiotics. Antibiotics are usually incorporated into the viral transport media to suppress the growth of contaminating bacteria and fungi (Kim et al., 2011; Wang et al., 2020; Patriquin et al., 2020).

The evaluation of the analytical phase was based on the number of non-conformities in the internal quality control. Diagnostic testing without quality control can lead to wrong treatment and management decisions. Internal Quality Control is applied by the laboratory every day to assure that each step of the testing procedure is done correctly and that the procedure's output is reliable. Performing internal quality control includes an adequate number of measurements, applying correct statistical control rules, selecting appropriate control materials, calculating data, setting control limits correctly, interpreting the control data correctly, and implementing corrective actions. External Quality Assessment (EQA) compares a laboratory's testing performance to a peer group of laboratories. In this case, an external provider sends to a set of laboratories regularly biological samples treated like patient samples during testing. Then, the external provider analyzes the results and generates feedback reports. A failure of any one of these controls invalidates the test result. The test must be repeated either from stored or newly collected samples after investigating the cause of the failure. Unfortunately, due to funding reasons, our laboratory does not participate in such a scheme up to now. Moreover, it was difficult for laboratories to obtain the control materials needed in some cases due to limited air transportation. As an alternative option, our laboratory participates in an inter-laboratory comparison (Kaul, 2020).

Randomly selected samples are sent to other laboratories to confirm the results. Since the test is qualitative (positive or negative result), it is considered a good choice. In our study, the QIs for the analytical phase showed a good performance of 4,7 sigma.

The evaluation of the post-analytical phase was based on the assessment of TAT time (Turn Around Time) from sample reception in the laboratory to the release of the result in minutes. Target TAT time for the COVID-19 test in our laboratory was set at a maximum of 90 minutes, including sample preparation, analysis and report generation. Timely reporting may contribute to timely confirmation of cases, timely hospital admission and patient therapy (Ramanathan et al., 2017). Prolonged TAT may occur due to unforeseen and unavoidable problems, such as delays in the analytical phase, equipment downtime, manual documentation, lost test requisitions and lost specimens. Ricos and colleagues have estimated that approximately 11% of laboratory reports exceed the corresponding TAT (Ricos et al., 2004; Goswami et al., 2010; McKillop & Auld, 2017). However, an efficient TAT becomes irrelevant if the test result is inaccurate due to sampling quality due to hemolysis (Cadamuro et al., 2019; Simundic et al., 2020). This quality indicator showed a good performance of 4,3 sigma. Prolonged TAT is attributed to the disproportion between the patient sample workload and the number of staff members available to handle this workload.

Evaluation of Support Processes was performed with four QIs. Since they were not evaluated during the past years, we must wait for comparisons from now on. Laboratory procedures, such as centrifugation, shaking, mixing, vortexing and opening of specimen vials, can generate aerosols or droplets, so they are considered high risk for COVID-19 transmission. In our laboratory, they are always carried out in a bio-safety cabinet according to the relevant guidelines of WHO and IFCC. Wearing personal protective equipment, limiting access to the laboratory, decontamination of work surfaces, computer keyboards, phones, and frequently touched medical equipment areas, frequent hand washing and all the appropriate measures required to keep laboratory staff safe are taken.

Moreover, the physician should notify the laboratory staff when specimens from a patient with suspected or confirmed COVID-19 are submitted. Therefore, there were no such incidents or adverse events in our laboratory. As part of risk assessment, training of all personnel in the use of protective equipment, proper disposal of laboratory waste, and the implementation of safety guidelines was performed via webinars. No education program took place for the hospital staff due to the restriction measures to avoid convergence. Since there is ongoing research about COVID-19, continuous education of laboratory personnel is imperative to prevent the spread of infection. We must declare that we correctly implement good laboratory practice (GLP) (Odega et al. 2020; Wang et al., 2020).

Laboratory staff are exposed to the virus to a greater extent than the general population and might be considered at an elevated risk for infection (Wang et al. 2020; To et al. 2020).

There was only one asymptomatic case in the laboratory staff, which was managed according to the relevant guidelines (Egger et al., 2021).

There were no adverse events due to incorrect specimen handling or inappropriate laboratory procedures. Up to now, there was no lack of resource availability, such as equipment, reagents, specimen collection material, controls and personal protective equipment. There are suggestions in the literature for testing of sample pools as a solution to minimize test costs while maintaining test sensitivity and specificity, specifically in settings where the incidence of infection is low. However, since the pooling of samples may lower test traceability, we strongly disagree with such a choice.

All the quality indicators are related to critical processes and are mandatory (Burlea-Schiopoiu, & Ferhati, 2021).

The implementation of quality indicators should follow the Deming PDCA quality cycle with the four phases Plan, Do, Check, Act as follows:

- Plan: the laboratory establishes objectives and processes required to achieve the desired performance for test results
- Do: the plan from the previous step is executed
- Check: the data and results gathered from the do step are evaluated, and compared to the expected outcomes
- Act: records from the previous steps and the results of quality indicators help identify problems, non-conformities and opportunities for improvement.

Corrective and preventive actions are implemented, and eventually, the laboratory processes are improved. A new cycle follows, and quality indicators are re-evaluated, and their results are compared with the previous ones (Huang et al., 2015).

WHO highly recommends risk assessment for laboratories that analyze COVID-19 specimens. Risk assessment is a systematic process of gathering information and evaluating the likelihood and consequences of exposure to hazards, and determining the appropriate risk control measures to reduce the risk to an acceptable level (WHO 2021). Consideration must also be given to the types of equipment used by the laboratory and the procedures that will be performed. The laboratory must perform a risk assessment for each process step, such as sample collection, sample transportation, sample reception in the laboratory, sample testing and result release. In risk assessment, techniques such as FMEA, Fishbone Chart, Pareto chart, Root Cause Analysis, and Risk matrices are used to identify, analyze, and classify all risks and precisely determine the correlation between probability and severity of the risk.

CONCLUSION

Quality measurement in clinical laboratories is essential during both times of stability and times of crisis. During the last decade, the approach to errors in clinical laboratories has been shifted from focus only on the analytical phase to the entire testing process. The ongoing outbreak of COVID-19 has emphasized the importance of the laboratory diagnosis of human coronavirus infection cases to limit the spread of the disease and offer the patients the best treatment. The use of quality indicators reveals weaknesses in the laboratory procedures. In our study, we evaluated QIs for a molecular diagnostics laboratory.

Given that the laboratory environment is constantly changing due to the pandemic implementing the recommendations for improvement will require a higher level of planning and coordination than in the past. Moreover, it is necessary to ensure that quality is not compromised due to workload. Many efforts need to be made to reduce risk. In areas where non-conformity rates are higher than expected, training and communication can be targeted to improve steps. After implementing preventive and corrective actions, re-evaluation of quality indicators will prove if these interventions were effective.

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Chapter 13

Assessment of Failure Risks in Laboratories During the Pandemic

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ABSTRACT

Clinical laboratories produce test results that support the diagnosis, prognosis, and patient treatment. Test results must be relevant, accurate, and reliable for patient care. International bibliographic data estimate that approximately 62.0% of the errors made in clinical laboratories are due to errors during the pre-analytical stage. This chapter presents a failure modes and effects analysis (FMEA) to analyze potential failure risks within the pre-analytical phase and classify them according to severity and likelihood. FMEA allows molecular laboratories to lower costs and drive better outcomes through high-quality nucleic acid extraction, sensitive detection, and accurate quantification. RT-PCR technology continues to be the gold standard for the clinical detection of SARS-CoV-2 RNA in individuals suspected of COVID-19. It is essential to use highly sensitive assays to detect active infections and reduce the likelihood of false-negative results.

DOI: 10.4018/978-1-7998-9198-7.ch013

INTRODUCTION

Clinical laboratories produce test results that support diagnosis, prognosis and patient treatment. Test results must be relevant, accurate and reliable for patient care. Laboratory testing of patient samples, beginning from test order to the final interpretation of results by the clinicians, is a complex process. Every step in the total testing process must be correctly performed, thus ensuring valuable decision making and effective patient care.

Clinical laboratories have consistently been implementing quality procedures in their analytical processes, and the practices of quality assessment programs have been a routine in laboratory diagnostics. Automation innovations have also contributed to a significant improvement in laboratory science, but errors can still be translated to inappropriate patient care decisions despite all the automation. These errors are classified as preanalytical, analytical, and post-analytical. For a patient-centered approach, there is the need to assure that every step of the entire testing process is correctly performed, that eventual weaknesses are recognized, and that corrective and preventive actions are designed and implemented (Lao, García, Figuerola, Moreno, & Paraire, 2017; Lippi, Sciacovelli, Simundic, & Plebani, 2017; Roy and Das, 2019).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China, in December 2019 and since then has spread all over the world, affecting millions of people. Although the disease caused by SARS-CoV-2 in most cases occurs with mild, influenza-like symptoms, in 10 to 15% of cases may progress to severe pneumonia, acute respiratory distress syndrome and death. The most vulnerable population groups are the elderly and patients with comorbidities, such as diabetes mellitus, obesity, hypertension, cardiovascular disease and renal disorders (Sanyaolu et al., 2020; Wyper et al., 2020). SARS-CoV-2 is a single-stranded positive (+) polarity RNA virus, with an RNA genome size of 30,000 bases and a viral particle size between 70 and 90 nm. It is transmitted using large respiratory droplets, generated by coughing or sneezing, and hands, touching contaminated objects and surfaces (Coronaviridae Study Group, 2020).

In some cases, aerosol transmission is also possible using exposure to elevated aerosol concentrations within closed spaces, such as COVID-19 patient rooms or closed and narrow laboratory areas (Lippi et al., 2020). Consequently, the coronavirus outbreak may be especially hazardous to healthcare personnel, including laboratory professionals. World Health Organization provides biosafety guidance to laboratories and other stakeholders involved in diagnostics for SARS-CoV-2. According to WHO, clinical laboratories must adhere to appropriate biosafety practices. Any testing for the presence of SARS-CoV-2 or clinical specimens from suspected cases must be performed by staff trained in the relevant technical and safety procedures. Moreover, each laboratory should conduct a risk assessment to ensure that it is competent to perform the comparative tests (WHO, 2021).

Risk is defined as the probability of an error occurring in the laboratory that could harm (Yundt-Pacheco and Parvin, 2017). It can be estimated through a combination of the likelihood of harm, the severity of that harm, and the detectability, which is the probability of detecting and preventing errors before leaving the laboratory and reaching the patients (Watson 2018; Yundt-Pacheco and Parvin, 2017). Risk management is a practice developed in industrial or manufacturer settings. According to ISO 14971: 2019, risk management is described as the systematic application of management policies, procedures, and techniques to analyze, evaluate, control, and monitor risk (ISO 14971:2019). Published guidelines, such as the CLSI document EP18-A2 and the CLSI guideline EP23-A, introduce risk management to the clinical laboratory (Clinical and Laboratory Standards Institute, 2009 & 2011). Moreover, the approach to risk

reduction has been incorporated into the international standard on Medical Laboratories: Requirements for Quality and Competence ISO 15189:2012, according to which clinical laboratory staff must identify unwanted events and incidents and adopt improvements systematically to reduce or eliminate risks and minimize consequences to patient care (ISO 15189:2012; Mourtzikou&Stamouli, 2017).

Failure modes and effects analysis (FMEA) is a quality tool that identifies potential sources of failure and determines how such failures affect the operation of a system. FMEA, which is considered a bottom-up approach, involves discovering possible sources of failure, determining the probability and consequences of each failure, and outlining control measures to detect and eliminate such failures (Jiang et al., 2015; Magnesi et al., 2016).

The preanalytical phase of the testing process includes all the procedures before the start of laboratory testing and measurements. Many of these procedures are performed outside the laboratory area by non-laboratory professionals and thus without direct supervision by the laboratory staff. According to the literature, the majority of the laboratory errors (46%–68%) occur during the preanalytical phase, including inappropriate test request, wrong order entry, patient or sample misidentification, a sample collected from infusion route, sample collection errors, inappropriate container, improper handling, storage, or sample transportation, errors in sorting and routing, pour off, aliquoting, pipetting, labelling, or centrifugation time or speed (Flegar-Mestric et al., 2017; Lippi, Baird, et al., 2017; Lippi, Betsou et al., 2019).

The preanalytical phase is of utmost importance because laboratory results from inappropriate specimens are inconsistent and do not allow proper treatment nor monitoring of the patient. Moreover, they lead to increased medical costs when tests have to be repeated, or patients are misdiagnosed (Flegar-Mestric et al., 2017; Mrazek C, Lippi G, et al. 2020). In this study, we performed an FMEA analysis of the preanalytical phase of the testing process in the biochemistry laboratory of a hospital belonging to the public sector. The laboratory performs more than 5000 tests daily in serum, urine, cerebrospinal fluid and other biological specimens. Each preanalytical procedure was examined in detail to identify possible failure points and control processes that can be implemented to detect and prevent errors. All constituents of the preanalytical phase were considered in the evaluation of potential failures. FMEA analysis was divided into five subgroups: referral form production*, sample collection, sample transportation, sample centrifugation and sample preservation.*At this stage, the referral note is prepared. The doctors request the required examinations for the patient, and they complete patient data, which is necessary for the identification and the traceability of the sample. Moreover, they also meet sufficient information to analyze and interpret laboratory tests (medication, underlying disease, etc.)

FMEA ANALYSIS OF THE PREANALYTICAL PHASE

In this study, we run an FMEA to analyze potential failure risks within the preanalytical phase to classify them according to severity and likelihood, based on our experience. As a first step, we used a process flowchart to identify each process component. Then we listed each process component in the FMEA table. In the next step, we reviewed all the existing documentation and LIS data and brainstormed ideas about all the ways each process component can fail for all five subgroups. FMEA table includes columns named by terms that are of particular relevance for the analysis as follows (Mendes et al., 2013; Southard, Kumar, & Southard, 2011):

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- **Function:** short, precise and easy to explain the process to be analyzed to meet the quality requirements.
- **Possible Way of Failure:** Describes ways in which the operation fails to fulfill its purpose. Depending on the complexity of the process, the failure mode may have one or more levels.
- **Possible Implications of Failure:** Describes the results of failure and non-compliance in statutory regulations.
- **Severity-S:** evaluates the severity of a possible failure and is measured on a scale of 1 to 10, where 1 is the lowest severity and 10 is the highest.
- **Possible causes of failure:** Describes why a particular failure occurs. The more effort is made to identify the real causes, the higher the success will be to eliminate the failures and defects.
- **Occurrence-O:** the probability of occurrence of the failure cause. It is measured on a scale of 1 to 10 and results from a comparison with past data.
- **Control method:** actions that ensure adequate regulation to prevent failure.
- **Detection-D:** it is defined as assessing the ability of the procedures to detect a possible failure. It is measured on a scale of 1 to 10. The higher the value of D, the more likely the failure will not be detected.
- **Risk Priority Number (RPN)** is calculated by multiplying the degree of criticality (S), occurrence probability (O) and the probability of detection (D) ($RPN = S * O * D$). The RPN value ranges between 1 and 1000 for each failure mode. According to the RPN value, the failure modes are prioritized, and suitable corrective actions are implemented for the highest RPN value.
- **Corrective actions:** The actions required to improve and reduce the severity and incidence of failure are recorded.
- **Responsible:** the responsible department or person is responsible for the corrective actions.
- **New RPN value:** After implementing corrective actions, new S, O, D and RPN values will be calculated for each failure mode.

RESULTS

The results that concern errors identified in the preanalytical phase according to FMEA for the production of referral form showed that the overall severity (S) in all categories was 8, occurrence (O) was between 5-7, detection (D) between 1-2 and RPN between 40-112 value ranges. The lowest value, equal to 40, is observed in the category Technical problem (Table 1).

The results that concern errors identified in the preanalytical phase according to FMEA for sample collection showed that the overall severity (S) was 10 (except from the category OF incomplete result (S 8), overall occurrence (O) between 4-7, overall detection (D) between 1-3 and overall RPN between 0 and 280 value ranges. The lowest value was observed in the category Lack of sample, RPN 0 (Table 2).

The results that concern errors identified in the preanalytical phase according to FMEA for sample transportation showed that the overall severity (S) in all categories was 10, the overall occurrence (O) 6-7, detection (D) between 1-2 and RPN between 60 up to 120 value ranges, with the lowest value observed in the category Lack of sample 60 (Table 3).

The results that concern errors identified in the preanalytical phase according to FMEA for sample centrifugation showed that the severity (S) was 10, occurrence (O) between 6-7, detection (D) 1 and RPN 60 (Table 4).

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Table 1. Errors identified in the pre-analytical phase according to FMEA for the production of referral form

Function	Possible Way Of Failure	Possible Implications Of Failure	S	Possible Causes Of Failure	O	Control Method	D	Rpn	Corrective Actions	Responsible	S	O	D	Rpn
REFERRAL FORM	Improper test request in the referral form	Incomplete results	8	Uncompleted referral form	8	HIS/LIS	2	128	Inform clinicians	Laboratory secretarial support	8	7	2	112
	Improper test request in referral form	Incomplete results	8	Inappropriate request	8	HIS/LIS	2	128	Inform clinicians	Laboratory secretarial support	8	7	2	112
	Technical problem	No production of the referral form	8	Loss of data	6	HIS/LIS	1	48	Inform technical support	Laboratory secretarial support	8	5	1	40

Table 2. Errors identified in the pre-analytical phase according to FMEA for the sample collection

Function		Possible Way Of Failure	Possible Implications Of Failure	S	Possible Causes Of Failure		O	Control Method	D	Rpn	Corrective Actions	Responsible	S	O	D	Rpn
SAMPLE COLLECTION	LABELING	Inappropriate sample	Unreliable results	10	Error in sample labeling		7	USE OF BARCODE	4	280	Sample rejection-new sample collection	In charge for blood sampling	10	6	3	180
		Inappropriate sample	Unreliable results	10	Non labeled sample		7	USE OF BARCODE	1	70	Sample rejection-new sample collection	In charge for blood sampling	10	6	1	60
	QUALITY	Inappropriate sample	Unreliable results	10	Inappropriate patient preparation	Food consumption	8	INSTRUCTION FOR PATIENT PREPARATION	2	160	Sample rejection-new sample collection	In charge for blood sampling	10	7	2	140
	QUALITY	Inappropriate sample	Unreliable results	10		Under medication	8	INSTRUCTION FOR PATIENT PREPARATION	2	160	Sample rejection-new sample collection	In charge for blood sampling	10	7	2	140
	QUALITY	Inappropriate sample	Unreliable results	10		Body position	8	INSTRUCTION FOR PATIENT PREPARATION	3	240	Sample rejection-new sample collection	In charge for blood sampling	10	7	2	140
	QUALITY	Inappropriate sample	Unreliable results	10		Physical activity	8	INSTRUCTION FOR PATIENT PREPARATION	2	160	Sample rejection-new sample collection	In charge for blood sampling	10	7	2	140
	QUALITY	Inappropriate sample	Unreliable results	10		stress	8	INSTRUCTION FOR PATIENT PREPARATION	3	240	Sample rejection-new sample collection	In charge for blood sampling	10	7	3	210
	QUALITY	Inappropriate sample	Unreliable results	10	Prolonged attachment		8	INSTRUCTION FOR BLOOD SAMPLING	3	240	Repeat measurements with a new sample	In charge of blood sampling	10	7	3	210
	QUANTITY	Inappropriate sample	The results not released	10	Denial or uncooperative patient		8	INSTRUCTION FOR BLOOD SAMPLING	1	80	Inform clinicians	Laboratory secretarial support	10	7	1	70
	QUANTITY	Inappropriate sample	Incomplete results	8	Insufficient sample volume		8	USE OF APPROPRIATE TUBES	1	64	Inform clinicians	Laboratory secretarial support	8	7	1	56

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Table 3. Errors identified in the pre-analytical phase according to FMEA for the sample transportation

FUNCTION		POSSIBLE WAY OF FAILURE	POSSIBLE IMPLICATIONS OF FAILURE	S	POSSIBLE CAUSES OF FAILURE	O	CONTROL METHOD	D	RPN	CORRECTIVE ACTIONS	RESPONSIBLE	S	O	D	RPN
SAMPLE TRANSPORTATION	QUALITY	Inappropriate sample	Unreliable results	10	time	7	INSTRUCTIONS FOR SAMPLE TRANSPORTATION	2	140	Sample rejection- new sample collection	Blood collector	10	6	2	120
	QUALITY	Inappropriate sample	Unreliable results	10	temperature	7	INSTRUCTIONS FOR SAMPLE TRANSPORTATION	2	140	Sample rejection- new sample collection	Blood collector	10	6	2	120
	LACK OF SAMPLE			10	Sample loss	7	INSTRUCTIONS FOR SAMPLE TRANSPORTATION	1	70	Sample rejection- new sample collection	Blood collector	10	6	1	60

Table 4. Errors identified in the pre-analytical phase according to FMEA for the sample centrifugation

FUNCTION		POSSIBLE WAY OF FAILURE	POSSIBLE IMPLICATIONS OF FAILURE	S	POSSIBLE CAUSES OF FAILURE	O	CONTROL METHOD	D	RPN	CORRECTIVE ACTIONS	RESPONSIBLE	S	O	D	RPN
SAMPLE CENTRIFUGATION	QUALITY	Inappropriate sample	Unreliable results	10	Centrifugation time	7	INSTRUCTIONS FOR SAMPLE CENTRIFUGATION	1	70	Centrifugation using predefined program	Staff responsible for centrifugation	10	6	1	60
	QUALITY	Inappropriate sample	Unreliable results	10	speed	7	INSTRUCTIONS FOR SAMPLE CENTRIFUGATION	1	70	Centrifugation using predefined program	Staff responsible for centrifugation	10	6	1	60
	QUALITY	Inappropriate sample	Unreliable results	10	temperature	7	INSTRUCTIONS FOR SAMPLE CENTRIFUGATION	1	70	Centrifugation using predefined program	Staff responsible for centrifugation	10	6	1	60
	QUANTITY	Sample loss	Results not released	10	Break or fracture of the primary tube	7	INSTRUCTIONS FOR SAMPLE CENTRIFUGATION	1	70	Sample rejection - new sample collection	Staff responsible for centrifugation	10	6	1	60
	QUALITY	Inappropriate sample	Clot detection	10	Inappropriate serum separation	7	INSTRUCTIONS FOR SAMPLE CENTRIFUGATION	1	70	Re-centrifugation	Staff responsible for centrifugation	10	6	1	60

The results that concern errors identified in the preanalytical phase according to FMEA for sample preservation showed that the overall severity (S) was 10 in all categories, the overall occurrence (O) was found 6-7 in all categories, the overall detection (D) was 1-2. RPN was found between 60 up to 120 (Table 5).

Table 5. Errors identified in the pre-analytical phase according to FMEA for the sample preservation

FUNCTION		POSSIBLE WAY OF FAILURE	POSSIBLE IMPLICATIONS OF FAILURE	S	POSSIBLE CAUSES OF FAILURE	O	CONTROL METHOD	D	RPN	CORRECTIVE ACTIONS	RESPONSIBLE	S	O	D	RPN
SAMPLE PRESERVATION	QUALITY	Inappropriate sample	Unreliable results	10	temperature	7	INSTRUCTIONS FOR SAMPLE PRESERVATION	1	70	Sample rejection-new sample collection	Lab technician	10	6	1	60
	QUALITY	Inappropriate sample	Unreliable results	10	Frost/thaw	7	INSTRUCTIONS FOR SAMPLE PRESERVATION	1	70	Sample rejection-new sample collection	Lab technician	10	6	1	60
	QUALITY	Inappropriate sample	Unreliable results	10	Inappropriate container	7	INSTRUCTIONS FOR SAMPLE PRESERVATION	1	70	Sample rejection-new sample collection	Lab technician	10	6	1	60
	QUALITY	Inappropriate sample	Unreliable results	10	Prolonged exposure to light	6	INSTRUCTIONS FOR SAMPLE PRESERVATION	2	120	Sample rejection-new sample collection	Lab technician	10	6	2	120

DISCUSSION

Preanalytical errors constitute a significant proportion of errors in laboratory processes and contribute to considerable patient safety risks. According to ISO 15189:2012, laboratories must consider the impact of the preanalytical phase on their results. In areas such as identifying and controlling non-conformities, continual improvement, internal audit and quality indicators, laboratories must continuously collect and review data for preanalytical errors and implement corrective actions to achieve quality and improvement (ISO 15189:2012). The purpose of the present study was to evaluate the causes of preanalytical errors that occur in a Greek biochemistry laboratory. For this purpose, we run an FMEA analysis based on data, experience and relevant documentation. Moreover, laboratory personnel were asked to register the sample rejections and the causes for rejection of inpatient and outpatient samples.

FMEA analysis identifies defects or errors, potential or actual, which might occur in a process, emphasizing those affecting the customer or the end-user. FMEA prioritizes failures according to severity, occurrence and detectability. Severity describes the seriousness of failure consequences. Occurrence explains how often failures can occur, and detectability refers to the degree of difficulty in detecting failures. Moreover, FMEA includes corrective actions that prevent failures or reduce their severity and probability of occurrence and their impact and consequences (Anes, Henriques et al., 2018).

When compiling the analysis, a high degree of severity was chosen in all cases before and after the corrective actions were implemented because unreliable test results lead to inappropriate patient care. The choice of the probability of occurrence was based on evidence from daily practice. A probability of occurrence equal to 5 corresponds to once per semester, six to one per quarter, seven to once per month, and eight to once a week. Regarding the probability of detection, system design and control actions are very effective and can identify possible causes of failure.

Regarding the errors occurring during the production of the referral form, presented in Table 1, the comprehensive implementation of laboratory information systems (LIS) in the clinical laboratories has offered advanced solutions in their workflow. All steps in the total testing process have been improved, positively impacting the quality of laboratory results. LIS enables electronic requests, barcoded specimens and contributes to the prevention of identification errors. Many laboratories use structured test profiles, which are groups of tests constructed to match the clinical problems, treatments, and test ordering patterns of clinicians (profile for dialysis patients, oncology patients, cardiac risk patients, intensive care unit patients, etc.). The implementation of test profiles offers various advantages, such as appropriate test requests and rapid turnaround time (Baricchi, Zini et al., 2012). Our laboratory has implemented

such a profile for COVID-19 patients to avoid incomplete referral forms and delays in turnaround times (TAT). The examination of suspected and positive samples is completed in one round, and then samples are discarded.

Regarding sample collection presented in Table 2, the larger RPN has a value of 280 and corresponds to the wrong sample identification. That is a type of failure due to a human error; in the majority of such cases and is of utmost importance. In limited cases, it may be due to an inability to communicate with the patient due to health problems, language barriers or even deliberate deception. Labeling with barcode labels has significantly reduced failures of this type. However, they have not been eliminated. The use of a patient ID wristband, which can quickly be scanned using a barcode scanner, is a preferable option. The band provides essential health care information such as the patient's name, previous conditions, allergies, what type of medicine should be administered and medicine dosage. In our hospital, the use of this type of identification has not yet been established. In our laboratory, sample identification requires two patient identifiers, patient name and medical record number, matching the sample with the accompanying referral form. Samples not correctly identified are not tested. Many authors consider wristbands as unreliable against misidentification. Some patients have been mismatched in their care due to errors in the wristbands. Technology may contribute to reducing misidentification errors and improving patient safety. Automated systems such as radiofrequency ID, biometric technologies and smartphone facial recognition technology are possible solutions (Ferguson et al., 2019; MoutazHaddara et al., 2018).

The safety and quality of SARS-CoV-2 testing may be endangered by lack of identification or misidentification of the patient and/or sample and can lead to catastrophic outcomes. From the beginning of the pandemic, an internal directive has been issued in our laboratory, distributed to all the departments involved. This directive includes detailed instructions for all the steps of the entire testing process.

An RPN value of 240 corresponds to pre-postulate errors from body posture, stress and prolonged attachment. All these failure causes are not entirely controllable. Stress is something inevitable, especially in people severely affected by the disease. As far as the posture is concerned, some patients are catapulted for a long time, while prolonged attachment is a frequent phenomenon because they have damaged blood vessels from continuous bleeding and drug administration; thus, searching for a suitable vein for blood collection is not easy. RPN equal to 160 corresponds to an inappropriate sample due to food or medication, a factor that cannot always be avoided, despite the laboratory's recommendations, because not all patients cooperate or comply with relevant instructions (Caruso et al., 2020; Lima-Oliveira et al. 2017; Yao et al., 2017). RPN for in vitro hemolysis is equal to 80. Although the introduction of vacuum tubes and the closed blood collection system has made blood collection efficient and easy, hemolysis accounted for most rejections in our study. The laboratory has counted the number of hemolyzed samples per month for four consecutive years, but no significant change was detected. Further information and education of staff might reduce rejections due to hemolysis and maintain the integrity of samples throughout the preanalytical process (Mendoza-Benitez et al., 2019; Zhang et al., 2018).

Another failure leading to the rejection of blood samples in our study was insufficient blood volume. Clinical laboratory analyzers use minimal amounts of blood, serum or plasma. However, a minimum volume is required for processing samples automatically. Every analytical process requires a fixed volume of the specimen for analysis. Insufficient blood volume within a collection tube containing an anticoagulant will result in an incorrect ratio of blood to the anticoagulant and yield false test results (Sonmez et al., 2020). The main reasons behind this failure are ignorance of the phlebotomists, complex sampling as in pediatric patients, patients with chronic, debilitating diseases, and patients on chemotherapy whose

veins are difficult to localize. In such cases, the laboratory usually asks for a new sample, if possible, or performs the most important tests, as suggested by the clinicians.

RPN for biological variation is equal to 140. Biological variation is defined as the fluctuation of the concentration of fluid body components around the set point of homeostasis (within-subject variation) or differences in the concentration of components of biologic fluids among different persons (between-subject variation). Biological variation is an inevitable component of the preanalytical process and can be divided into two types; biological variation related to time, such as diurnal and seasonal variations, and variation related to dilution, dietary peculiarities and supplement use (Caruso et al., 2020; Kanakis et al., 2019). This type of variation will be lower with standardized preanalytical conditions. Such an example was presented by Busnardo et al. (2006) about urinary iodine in a slightly standardized study compared with the variation in non-standardized urine collections presented by Andersen et al. (2001).

In COVID-19, the role of preanalytical variables in the handling of biological samples is of utmost importance. Every step must be performed very carefully, given that the laboratories face high workloads and work under severe pressure. The collection procedure for SARS-CoV-2 molecular testing presents many difficulties. The laboratory must have clear instructions on how nasopharyngeal and oropharyngeal swabs shall be correctly collected, managed and stored. For example, the Centers for Disease Control and Prevention (CDC) in the USA recommends that nasopharyngeal and oropharyngeal material be collected using swabs with a synthetic tip and an aluminium or plastic shaft. The use of wrong swabs, collection of inappropriate or inadequate material, the use of insufficient vials, testing carried out in patients receiving antiretroviral therapy, and sample contamination may be a significant cause of diagnostic errors. Contamination can occur during sampling if the specimen swab touches a contaminated glove or surface. Sample contamination with external DNA, cross-reactions with other viruses or genetic material could also be responsible for false-positive results. A false-positive result may lead to unnecessary treatment of uninfected individuals, with many consequences including unnecessary quarantine and contact tracing, financial losses related to self-isolation, psychological damage, as well as societal problems. A false-negative result given to an infected patient contributes to disease transmission and further spread of the virus due to non-timely application of isolation and the application of restrictive measures, as well as for failure to identify other potentially infected people (Arevalo-Rodriguez et al., 2020; Hu 202; van Zyl et al., 2019; Woloshin et al., 2020). Contamination of reagents and withdrawal of testing kits has also occurred in some cases.

Transportation and preservation of biological samples are essential steps of the preanalytical phase. Specifications for sample transportation are stated in ISO standards 15189:2012 and 20658:2017. Samples must be transported as fast as possible to be measured within the established stability time of analytes and maintain turnaround times. Moreover, they must be transported under such conditions that ensure sample integrity and must not be affected by temperature, agitation, exposure to light or other influences. The impact of transportation time and requirements on test results depends on the analytes requested, time to centrifugation, and the analytical method applied (Nybo et al., 2018; Nybo et al., 2019). Samples' transportation can be either manual or automated for in-house samples. Manual transportation is, however, slow and time-consuming. Many hospitals use automated pneumatic tube transportation systems. Because of the potential for exposure to infectious aerosols or droplets, it is not recommended to transport specimens from patients with suspected or confirmed Covid-19 disease through the pneumatic tube system. These specimens are delivered by hand in our hospital in double biosafety plastic bags, placed in a solid-walled, leak-proof container.

Four variables have a considerable impact on the separation efficacy of the centrifugation process: time, temperature, the length of the sample collection vial and the relative centrifugation force (Møller et al., 2017). Given the circumstances due to the pandemic, centrifugation is performed with the sealed rotor. When a suspected specimen is centrifuged, a staff member is near the centrifuge. All samples after centrifugation are put in a biosafety cabinet to let the aerosols settle. If a tube breaks or leaks, centrifugation is stopped for at least 30 minutes to fix the aerosols. Then, the lid is opened carefully, always in a biosafety cabinet (laminar flow cabinet), and the centrifuge is sprayed and sterilized according to WHO guidelines (WHO, 2021). The centrifuge rotor with blood collection vials is then put in a biosafety cabinet to treat. The biosafety cabinet (laminar flow cabinet) is very often within day sterilized using a UV lamp.

Aerosols can be generated during centrifugation and during many normal laboratory activities such as pipetting, diluting, vortexing of laboratory vials, filling syringes, removing the supernatant, and pouring liquids resuspending pellets, homogenizing, blending etc. These activities should be handled in a biosafety cabinet to avoid contamination. According to van Doremalen et al. (2020), who evaluated the stability of SARS-CoV-2 in aerosols and on various surfaces (plastic, stainless steel, copper, and cardboard), SARS-CoV-2 remained viable in aerosols for 3 hours and was more stable on plastic and stainless steel than on copper and cardboard (van Doremalen et al., 2020). According to WHO guidelines, these observations underline the importance of personal protection of laboratory staff and proper decontamination of working surfaces regularly with standard disinfectants approved for SARS-CoV-2 infections. After centrifugation, samples are analyzed on automated analyzers. Most international organizations suggest using automated preanalytical robotic systems for decapping and recapping specimen vials. The specimens should be sealed immediately after testing (WHO, 2021).

CONCLUSION

Preanalytical errors affect the laboratory test results and occur both outside and inside the laboratory area. Test results must be relevant, accurate and reliable for patient care. The preanalytical errors on the laboratory result have consequences that can lead to the complete abolition of laboratory quality in many cases. In the present study, we performed an FMEA analysis of the preanalytical phase of the testing process of a biochemistry laboratory. FMEA is a quality tool that identifies potential sources of failure and determines how such failures affect the operation of a process or a system. Since the pandemic has affected the routine work of the clinical laboratories, we analyzed each step's errors that may affect SARS-CoV-2 results and laboratory staff safety. The concept of total quality management encompasses all the steps involved in sample processing to reduce or eliminate the errors that may arise during the various steps. Keeping records of the errors at all stages of analysis and then implementing corrective strategies for their prevention can gradually eliminate such errors.

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Chapter 14

Implementation of Static Telecytology Applications for Accreditation Purposes According to ISO 15189

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ABSTRACT

Telecytology can be defined as the process of diagnostic cytology performed on digital images. The process of diagnostic cytology performed on digital images can be used for teaching, professional examinations, obtaining expert opinions on severe cases, and routine diagnosis of the entire laboratory workload. However, little information exists about its possible use for proficiency testing purposes. The existing studies have found a high (90%–95%) concordance between telecytological and glass slide diagnoses, but they refer to a small number of cases. Thus, the purpose of the chapter is to examine the feasibility of developing a proficiency testing scheme for cytology labs wishing to be accredited according to ISO 15189:2012 by using low-cost telemedical applications.

INTRODUCTION

Modern cytopathology laboratories have to provide results of high quality and credibility. (Archondakis et al., 2009; Archondakis, 2013; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Georgoulakis et al., 2011; Green et al., 2021) Over the last decade, the practice of clinical cytopathology was dramatically influenced by the broad implementation of informatics and computer

DOI: 10.4018/978-1-7998-9198-7.ch014

sciences into the laboratory workflow. (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020) Cytopathology laboratories wishing to achieve an automated and seamless workflow process, to diminish turn-around times and improve their diagnostic accuracy have successfully adopted information technologies and automation. New types of cameras and microscopes connected to computers made possible image capture and transmission (telecytology) (Archondakis et al., 2009; Archondakis, 2013; Chantziantoniou et al., 2017). The wide implementation of telemedical systems in cytopathology became a necessity dictated by the need for real-time results for therapeutic decisions.

A telemedical application is a valuable tool for cytopathologists to manage and promote interlaboratory collaboration. The result is better cytological data management and sharing (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis, 2021; Archondakis et al., 2020; Chantziantoniou et al., 2017).

Remote cytological diagnosis can nowadays be achieved either with the use of cytological pictures viewed in real-time from the microscope (dynamic telecytological systems) or with the use of cytological images that are first captured in a digital format and then transmitted using a store-and-forward approach to distant observers (static telecytological systems) (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Caron et al., 2019).

Telecytological diagnoses should be as reliable as those made using conventional microscopy. The purpose of the adopted program should be to ensure that microscopic (cytological) findings are correctly identified and interpreted by laboratory personnel (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Caron et al., 2019; Georgoulakis et al., 2011). Accreditation is the process by which a certified organization or agency recognizes that a facility or service meets specific pre-established standards (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Pantanowitz et al., 2009; Caron et al., 2018). ISO 15189:2012 constitutes an international accreditation standard, which can be used by medical laboratories wishing to improve their quality standards (Archondakis et al., 2009; Caron et al., 2018). Its requirements consist of a group of general guidelines that will help laboratories establish and enhance their quality systems (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Brooker et al., 2019).

According to ISO 15189:2012 requirements, one of the most significant challenges facing cytology laboratories is designing and implementing a board-certified external quality control program. The purpose of the adopted program should be to ensure that microscopic (cytological) findings are correctly identified and interpreted by laboratory personnel (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis, 2021; Archondakis et al., 2020; Caron et al., 2018; Pantanowitz et al., 2009).

Telecytology can be defined as the process of diagnostic cytology performed on digital images. Telecytology can be used for obtaining expert opinions on severe cases (Archondakis et al., 2009;

Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020). Telecytology (the process of diagnostic cytology performed on digital images) can be used for teaching, professional examinations, obtaining expert opinions on severe cases, and routine diagnosis of the entire laboratory workload (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Caron et al., 2018; Georgoulakis et al., 2011). However, little information exists about its possible use for proficiency testing purposes.

Most of these studies have found a high (90%–95%) concordance between telecytological and glass slide diagnoses, but they are referring to a small number of cases (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Della Mea et al., 2000; Briscoe et al., 2000; Raab et al., 1996).

Thus, the purpose of the article is to examine the feasibility of developing a proficiency testing scheme for cytology labs wishing to be accredited according to ISO 15189:2012 by using low-cost telemedical applications.

BACKGROUND

Laboratory automation has been propelled during the last decade by the advantages of higher productivity, cost-efficacy and the capacity of integration with modern instrumental equipment that has an internet connection (Brooker et al., 2019). Laboratory information systems provide better functionality through automation in parts of the inspection procedures, permitting the lab to achieve maximum efficiency (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Brooker et al., 2019).

In the field of cytopathology, laboratory information systems have enabled Cytotechnologists and Cytolopathologists to achieve efficient, streamlined workflows, regulatory compliance, and superior reporting capabilities. Quality Control (QC) defines a service quality, imparting to it the credibility needed for its intended purpose. At the same time, Quality Assurance (QA) activities measure the degree to which desired outcomes are successful (Archondakis et al., 2020). QC may be internal or external. QC in the field of Cytology is mainly achieved by slide rescreening or by clinical-histological correlation of cytological diagnoses (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020). Many slide rescreening procedures have been proposed for QA purposes, such as rapid reviewing of smears initially reported as negative or inadequate, rapid preview/prescreening of all smears, random rescreening, targeted rescreening of specific patient groups, seeding abnormal cases into the screening pools, retrospective rescreening of negative cytology specimens from patients with a current high-grade abnormality and automated rescreening of smears initially reported as negative (Archondakis et al., 2009; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020). The laboratory managers are responsible for selecting the most appropriate

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method for QA purposes, according to the specific needs of their laboratories (Archondakis et al., 2009; Archondakis, 2013; Archondakis et al., 2020; Vavoulidis et al., 2016).

The practice of diagnostic cytopathology performed on digital images is a novel process that can be used for obtaining expert opinions on severe cases from remote laboratories (telecytology) (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020).

Telecytological diagnosis can be achieved either with the use of cytological pictures viewed in real-time with the microscope (dynamic telecytological systems), or with the help of cytological images that are first captured in a digital format and then transmitted to distant observers (static telecytological systems) (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Stamataki et al., 2008). The static telecytology systems have the advantage of considerably lower cost, but they only allow the capture of a selected subset of microscopic fields (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Pantanowitz et al., 2009). The dynamic telecytology systems permit evaluation of the cytological material present on a slide (Yamashiro et al., 2004; Vavoulidis et al., 2016). These systems may be hampered by high network traffic and their high cost of purchase and maintenance that makes them unaffordable for small laboratories wishing to participate in proficiency testing programs (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Vavoulidis et al., 2016).

The use of digital images in quality control/assurance programs eliminates the need for glass slides retrieval from the laboratory's registry (at least at the point of examination), allows annotations to be added to images, enhances the ability to transmit rapidly and remotely share images electronically for several purposes (telecytology, conferences, education, quality assurance, peer review) and protects more efficiently patient anonymity (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020).

Moreover, the use of digital images for QA programs is more practical and time-efficient. However, the conversion process of glass slides into digital image files may require some additional time. Static telecytology systems are preferred due to their low cost by laboratories that cannot afford the high cost of purchasing and maintaining dynamic systems (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis et al., 2020).

The limitations and diagnostic errors related to telecytology that some authors already mention may cause misinterpretation of digital images by less experienced participants (Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Briscoe et al., 2000). Appropriate field selection, sufficient image quality and especially diagnostic expertise are the most crucial parameters ensuring the proper function of a static telecytological system (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2020).

The most common manifestations of inter-observer discrepancy are upgrading of the telecytological diagnosis to a definitive carcinoma diagnosis or downgrading of a suspicious telecytological diagnosis to a relatively benign lesion because of image deficiencies (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2020).

Proficiency testing (PT) is a well-recognized method for evaluating actual laboratory performance, usually employing inter-laboratory comparisons (Archondakis, 2013). Proficiency testing results can be used as an independent indication of a laboratory's diagnostic competence and can be integrated into the normal process of the laboratory's assessment and accreditation (Archondakis, 2013). According to ISO 15189:2012, all accredited laboratories should conduct proficiency tests following their standard patient testing and reporting procedures (Archondakis et al., 2009). The latest revision of ISO 15189, published in 2012, proposes alternative methods to evaluate laboratories technical competence, where accredited PT schemes are not available (Vavoulidis et al., 2016).

Proficiency testing (PT) checks actual laboratory performance, usually using interlaboratory data comparisons (Woodhouse et al., 1999; Cramer et al., 1991; Caron et al., 2018). Results from proficiency testing indicate a laboratory's competence and consist an integral part of the assessment and accreditation process (Woodhouse et al., 1999; Cramer et al., 1991; Brooker et al., 2019). According to ISO 15189:2012, all accredited laboratories must conduct proficiency tests following their normal patient testing and reporting procedures (Caron et al., 2018; Pantanowitz et al., 2009). The practice of diagnostic cytology performed on digital images is a novel process that can be used for obtaining expert opinions on severe cases from remote laboratories (telecytology) (Archondakis et al., 2009; Pouliakis et al., 2014; Pouliakis et al., 2015; Brooker et al., 2019). Telecytological diagnosis can be achieved either with the use of cytological pictures viewed in real-time from the microscope (dynamic telecytological systems) or with the use of cytological images that are first captured in a digital format and then transmitted to distant observers (static telecytological systems) (Archondakis et al., 2009; Stamataki et al., 2008; Pouliakis et al., 2014; Pouliakis et al., 2015;) Pouliakis et al., 2020; Pouliakis et al., 2021). As a result, many studies have focused on the possible role of telecytology as a tool of diagnosis and consultation in the everyday workflow (Archondakis et al., 2009; Brooker et al., 2019)

The practice of diagnostic cytopathology performed on digital images is a process by which remote laboratories can obtain expert opinions on severe cases (telecytology) (Archondakis et al., 2009; Pouliakis et al., 2014; Pouliakis et al., 2015;) Pouliakis et al., 2020; Pouliakis et al., 2021). Telecytological diagnosis can be achieved either with the use of cytological pictures viewed in real-time from the microscope (dynamic telecytological systems), or with the help of cytological images that are first captured in a digital format and then transmitted to distant observers (static telecytological systems) (Archondakis, 2013; Stamataki et al., 2008; Pouliakis et al., 2014; Pouliakis et al., 2015;) Pouliakis et al., 2020; Pouliakis et al., 2021). Hybrid systems have also been developed. The majority of relevant articles have focused on the possible use of telecytology for diagnostic and consultation purposes (Archondakis, 2013; Pouliakis et al., 2014; Pouliakis et al., 2015;) Pouliakis et al., 2020; Pouliakis et al., 2021).

Diagnostic agreement and reproducibility between the same (intra-observer) and different (inter-observer) observers are the main parameters monitored and recorded during telecytology programs (Stamataki et al., 2008; Pantanowitz et al., 2009). The agreement is the total or the proportional number of cases in which the same diagnosis was issued between or within observers, including the part of the agreement that may be attributed to chance (Landis & Koch, 1977). The kappa statistic measures reproducibility, which is part of the agreement that cannot be explained purely by chance (Landis & Koch,

1977). Within the positive kappa values and in accordance with the study by Landis and Koch (1977), the agreement was interpreted as follows: a range of 0.00–0.20 indicates slight agreement, a range of 0.21–0.40 indicates fair agreement, a range of 0.41–0.60 indicates moderate agreement, a range of 0.61–0.80 shows very good agreement, while a range of 0.81–1.00 indicates excellent or almost perfect agreement (Landis & Koch, 1977).

Cytopathology laboratory's quality assessment is achieved by continuous monitoring of interobserver or intraobserver diagnostic reproducibility and concordance between histological and cytological diagnosis. Internal and external quality control programs focus on the constant monitoring of interobserver and intraobserver diagnostic agreements (Chantziantoniou et al., 2017; Pouliakis et al., 2014; Pouliakis et al., 2015; Pouliakis et al., 2020; Pouliakis et al., 2021).

Telecytology is the interpretation of cytology material at a distance using digital images. The routine practice of telecytology may take place between a Cytopathologist and another cytopathologist in a remote location (Caron et al., 2019). Static telecytology systems capture cytologic pictures in a digital format followed by transmission to a distant observer. In its purest form, a static system comprises a digital microscopic workstation consisting of a microscope attached to a camera and a computer with high processing capacity and internet connection. The same static telecytology systems can capture representative images from selected fields during microscopy. Digital images can be stored in different directories, transferred via file transfer protocol to specific password-protected accounts, or shared via web and cloud applications (Brooker et al., 2019; Caron et al., 2019). In our laboratory, digital images include captured areas of interest at 100× and 400× magnifications with 1,124 × 1,120 resolution at 16-bit color depth and 300 dpi. This quality can ensure proper diagnostic interpretation of selected fields by all participants with adequate experience in diagnostic cytopathology.

A modern cytopathology laboratory is electronically tracking QC/QA indicators either within the LIS and/or by exporting data from the LIS (via spreadsheet software) (Brooker et al., 2019; Caron et al., 2019; Pouliakis et al., 2014; Pouliakis et al., 2015; Pouliakis et al., 2020; Pouliakis et al., 2021).

THE USE OF STATIC TELEMEDICAL APPLICATIONS OF CYTOPATHOLOGY FOR PROFICIENCY TESTING

The current study was carried out on 248 thyroid fine-needle aspiration specimens from patients preoperatively aspirated under ultrasonography guidance and on 208 pap smears with histological confirmation, retrospectively selected from the department's registry. One cytopathologist collected all 456 glass slides and imaged ten representative fields from each case. Images were captured with a Hamamatsu C4742-95 digital camera (Hamamatsu Photonics, Herrsching am Ammersee, Germany) mounted on a Leica DMLB microscope (Leica Microsystems, Wetzlar, Germany). The camera was connected via SCSI to a 1,200-MHz Pentium CPU running Windows XP (Microsoft, Redmond, WA). The fields selected provided valuable information routinely used in cytological diagnoses, such as background, cellularity, and nuclear and cytoplasmic details. All areas of interest were imaged at 100× and 400× magnifications. Images were captured at 1,124 × 1,120 resolution at 16-bit color depth and 300 dpi. JPEG compression was applied to all pictures. Each case's pictures were segregated and stored into separate directories.

All 4,560 representative images were transferred via file transfer protocol to specific password-protected accounts and were reviewed remotely by three (3) cytopathologists on workstations using Microsoft's Internet Explorer Web browser. The diagnostic approach of digital images concerning diagnosis criteria,

terminology of lesions, requirements of adequacy, and recommendations for further management was similar to those applied in conventional cytology. Primarily, the cytological reports were classified into three basic diagnostic categories. “Benign,” “malignant,” and “intermediate” diagnoses were adopted. Cohen’s kappa statistic was used to calculate interobserver and intraobserver reproducibility (Friedman & Wyatt, JC.1997).

Mean intraobserver reproducibility was calculated as the weighted average of the individual kappa values. To determine the significance of the intraobserver kappa values, we used the Svanholm formula (Friedman & Wyatt., 1997).

To confirm the reproducibility of the telecytology diagnosis and to study the interobserver agreement further 6, 12 and 18 months after the first initial round, the same representative digital images were transferred in random order to the same cytopathologists and were reviewed again by them. The intraobserver variability was studied among initial and review rounds. At the same time, the diagnostic agreement was analyzed for intraobserver agreement by using the diagnosis given by the same cytopathologist between the two separate diagnostic rounds. The interobserver agreement was interpreted using the diagnoses given by different cytopathologists on each of the diagnostic rounds.

Intraobserver reproducibility between light microscopy diagnoses and telecytology diagnoses was calculated among all cytopathologists and ranged from perfect (for the more experienced cytopathologist) to nearly perfect (for the other less experienced cytopathologists) with the corresponding overall kappa values ranging from 0.805 to 0.854.

Cytological diagnoses based on digital images and glass slides were compared with histological diagnoses. Both light microscopy and telecytology diagnoses did not present any significant discordance compared to the respective histological diagnoses. Furthermore, the reviewers also commented on overall digital image quality. Reviewers’ opinions of image quality ranged from very good to excellent.

During the initial round, the diagnostic agreement was nearly perfect among all cytopathologists. Interobserver agreement improved slightly during the following review rounds. The kappa statistic was also used to analyze the intraobserver agreement of the diagnosis by the same cytopathologist in the different diagnostic review rounds based on the three main diagnostic categories and their subcategories. More specifically, the diagnostic agreement among all diagnostic rounds for the three cytopathologists ranged from perfect (for the more experienced cytopathologist) to nearly perfect (for the other less experienced cytopathologists) with the corresponding overall kappa values ranging from 0.85 to 0.92.

Issues, Controversies, Problems

The slides collected to produce the digital material from the Cytology Department’s registry were coming from already histologically confirmed cases. The histological examination consists of the best way cytology slides can be validated (Brooker et al., 2019; Chantziantoniou et al., 2017; Pantanowitz et al., 2009). Inadequate validation of test slides could lead to indiscriminate failure of qualified, competent personnel participating in external quality control programs (Chantziantoniou et al., 2017; Pantanowitz et al., 2009)

The scoring system and reporting terminology were simplified and possibly inappropriate and unfair. Specific scoring systems and reporting terminologies should be established for each kind of cytological specimen to ensure that the cytological diagnoses reflect the clinical implications associated with this terminology in modern practice, particularly regarding recommended follow-up (Pouliakis et al., 2014; Pouliakis et al., 2015;) Pouliakis et al., 2020; Pouliakis et al., 2021; Williams et al., 2001).

Implementation of Static Telecytology Applications

Furthermore, in our external quality control program, testing is directed at the level of individuals instead of the laboratory level as in all other proficiency testings. As a result, the personal participation of all laboratory personnel is encouraged by the use of individual password-protected electronic accounts.

The static telecytology systems have the advantage of considerably lower cost, but they only allow the capture of a selected subset of microscopic fields (Caron et al., 2018; Pantanowitz et al., 2009; Pouliakis et al., 2014; Pouliakis et al., 2015;) Pouliakis et al., 2020; Pouliakis et al., 2021). On the other hand, the dynamic telecytology systems permit evaluation of the cytological material present on a slide (Caron et al., 2018; Yamashiro et al., 2004). However, these systems may be hampered by high network traffic, and their high cost of purchasing and maintaining may be unaffordable for small laboratories wishing to participate in proficiency testing programs.

Cytology quality assessment is not very similar to clinical laboratory proficiency testing. While clinical laboratory testing results are very dependent on instrument calibration and reagents, less frequent evaluation is appropriate for the well-trained cytology professional assessing slides regularly (Caron et al., 2018; Williams et al., 2001). Since there is no evidence to suggest that cytology screening and interpretive abilities deteriorate after one year, we recommend that the suggested proficiency testing interval may be lengthened to three years rather than the current one-year test interval.

Criteria for interlaboratory static telecytological comparisons are not established yet. Still, there is enough evidence that an adequate number of alternative answers is available to participants, that participants must respond in the correct series at least 90% of the time and that the standard error of this percentage is less than 0.05 (Pantanowitz et al., 2009; Caron et al., 2018; Chantziantoniou et al., 2017).

The most common manifestations of interobserver discrepancy are upgrading the telecytology diagnosis to a definitive carcinoma diagnosis or downgrading a suspicious telecytology diagnosis to a relatively benign lesion because of image deficiencies (Vooijs et al., 1998; Caron et al., 2018). In our research, the majority of discrepant cases were down-grading. Observers were diagnostically deliberated in some cases due to the limited adequacy of selected fields. In our study, the picture quality was very good and did not allow any significant disagreement among participating cytopathologists (Archondakis et al., 2009; Chantziantoniou et al., 2017).

Still, using digital images for diagnostic purposes in the absence of a conventional slide was a new experience for all participants. Some of them needed some additional time to familiarize themselves with the whole process (Archondakis et al., 2009).

On the other hand, the person appointed to pictures' capture and transmission is of paramount importance for the success of a static telecytology system. In our study, the person who captured and transmitted the digital images was an already certified cytopathologist with adequate experience in conventional cytological diagnosis. Less specialized personnel, such as inexperienced screeners, may endanger the acquisition of representative images from each cytological slide (Archondakis et al., 2009; Chantziantoniou et al., 2017).

In conventional cytology, specific diagnostic criteria and pitfalls are already described. During static telecytological diagnosis, the cytopathologist uses the same diagnostic criteria and avoids the same pitfalls. What makes the telecytological diagnosis more demanding is uncertainty about the actual specimen's adequacy or the representativity of the selected images (Archondakis et al., 2009; Chantziantoniou et al., 2017). The person appointed to capture and transmit images is of paramount importance for the success of a static telecytological system. In our study, the person who captured and shared the digital images was an already certified cytopathologist with adequate experience in the cytological diagnosis

of cervical smears. Our study suggests that cytological diagnoses based on digitized images can be as reliable as those of conventional cytology (Archondakis et al., 2009; Tsilalis et al., 2012).

Solutions and Recommendations

Besides histological examination, other cytology slide validation measures should be adopted to avoid possible indiscriminate failure of qualified, competent personnel participating in external quality control programs (Nagy et al., 2006; Chantziantoniou et al., 2017). Such measures could be the verification of cytological diagnosis by board-certified, well trained scientific personnel, the establishment of the specific scoring system and reporting terminology for all kinds of cytological specimens, and finally capturing of a significant number of representative images by certified, well-trained personnel (Nagy et al., 2006; Hanna et al., 2019; Vavoulidis et al., 2016).

Telecytology may be challenging to integrate into daily workflow. Distant cytopathology departments with high needs for assistance in the form of expert consultation can rarely afford the high cost of buying and maintaining dynamic systems (Raab et al., 1996). Static telecytological systems are affordable by all cytology departments and allow all scientific personnel to participate in proficiency testing programs, even when there is a significant time difference among participating laboratories (Raab et al., 1996; Hanna et al., 2019). Moreover, laboratory management should encourage the personal participation of all scientific personnel in such proficiency testing programs (Pinco et al., 2009; Hanna et al., 2019; Vavoulidis et al., 2016).

Cytology scientific societies should focus on cytology proficiency testing particularities and define particular technical aspects such as images' size and analysis, suggested testing intervals, diagnostic categories and methodology used for the statistical evaluation of the proficiency testing results (Nagy et al., 2006; Caron et al., 2018; Tsilalis et al., 2012; Yao, 2018).

Finally, proficiency testing providers should ensure that the personnel appointed to pictures' capture and transmission have adequate experience in conventional and image-based diagnosis. Previous experience in that field should be well-documented and recorded (Nagy et al., 2006; Hanna et al., 2019; Chiou, 2020; Tsilalis et al., 2012; Yao, 2018).

Last but not least, digital images storage and transmission must follow strict regulations in order to avoid any unauthorized alteration or improper use (Mun et al., 1995; Hanna et al., 2019; Chiou, 2020; Vavoulidis et al., 2016). Current standards of electronic medical data handling are still informative, yet the need for a secure electronic environment, especially in the field of static telecytology, continues to grow.

FUTURE RESEARCH DIRECTIONS

Telecytology, when integrated into the daily workflow, can provide exceptional consultation and professional testing opportunities to distant laboratories. Static telecytology systems are preferred by laboratories that cannot afford the high cost of buying and maintaining dynamic systems. In any case, the cost of participation in a running telecytology program is inexpensive for small cytology departments (Archondakis et al., 2009; Nagy et al., 2006; Yao, 2018). Provincial hospitals where close scientific collaboration and support are necessary can take advantage of this excellent opportunity to improve their cytology services (Archondakis et al., 2009; Chantziantoniou et al., 2017; Yao, 2018).

Future research must focus on the details of the implementation of a static telecytological application for proficiency testing purposes, that is, determining the required testing interval, elucidating the validation criteria applied to electronic material used for proficiency testing purposes, and possibly changing the focus of the test from individuals to laboratory level testing.

The diagnostic reliability of static telecytology provides the potential for further amelioration of the laboratory services by producing digital educational material for web-based training systems (Stergiou et al., 2009; Hanna et al., 2019). Those programs can improve the professional skills of the participating medical staff and make them feel more confident in their daily work (Stergiou et al., 2009; Vavoulidis et al., 2016; Yao, 2018).

In Greece, the accreditation of the first private cytology laboratory, according to ISO 15189:2012, is already completed by the National Accreditation Board. Digital material from histologically confirmed cases is collected in cooperation with National Anticancer Hospital. The first static telecytology program will soon apply for accreditation as an individual proficiency testing provider. By the end of the year, this first proficiency testing program on clinical cytology is expected to have given many answers to many unresolved problems on healthcare quality and is expecting scientific support and collaboration by local and distant cytology labs.

CONCLUSION

During the last decades, the absence of an integrated laboratory quality control program was making cytological diagnosis reliability subjective to various factors, and self-assessment was the only way to prove each cytopathology's diagnostic proficiency (Caron et al., 2019; Gutmann, 2019; Green et al., 2021; Yao, 2018).

Telecytology images can be used in the years to come for external or internal audits and quality assurance programs. Furthermore, digital images can be used in proficiency testing programs in order to assess the laboratory's medical staff diagnostic expertise, according to ISO 15189:2012 requirements (Archondakis et al., 2009; Chantziantoniou et al., 2017; Hanna et al., 2019; Senel, 2020; Yao, 2018).

Telecytology, when integrated into the daily workflow, can provide exceptional consultation and professional testing opportunities to distant laboratories. Static telecytology systems are preferred due to their low cost by laboratories that cannot afford the high cost of buying and maintaining dynamic systems. In any case, the cost of participation in a running telecytology program is inexpensive for small cytopathology labs (Archondakis et al., 2009; Nagy et al., 2006; Vavoulidis et al., 2016). Provincial hospitals where close scientific collaboration and support are necessary can take advantage of this excellent opportunity to improve their cytology services (Archondakis et al., 2009; Vavoulidis et al., 2016).

Cytological images' transmission and remote evaluation allow reproducible diagnoses. Diagnoses made using telecytological systems can be as reliable as those made by using conventional microscopy on the condition that representative images are taken and that the standard cytological diagnostic criteria are applied.

Telecytological systems diagnostic reliability is a *sine qua non* for further implementing this method in external or internal audits and quality assurance programs. Furthermore, digital images can be used in proficiency testing programs for assessing the laboratory's medical staff diagnostic expertise. More specifically, the implementation of telecytology practices in the everyday laboratory workflow meets ISO 15189:2012 requirements.

Future research must focus on the details of the implementation of a static telecytological application for proficiency testing purposes, that is, determining the required testing interval, elucidating the validation criteria applied to electronic material used for proficiency testing purposes, and possibly changing the focus of the test from individuals to laboratory level testing.

The diagnostic reliability of static telecytology makes its use to further ameliorate the laboratory services by producing digital educational material for web-based training systems (Stergiou et al., 2009; Green et al., 2021; Senel, 2020; Yao, 2018). These programs can improve the professional skills of the participating medical staff and make them feel more confident in their daily work (Stergiou et al., 2009; Green et al., 2021; Senel, 2020).

Adopting standards for an image file format that meets the needs of applications in cytopathology will enable the growth of these diagnostic applications shortly (Gutmann, 2019). Standardization of the equipment used for image storage and transmission among distant cytology laboratories is indispensable for further implementation of such applications for consultation, analysis or conferencing purposes (Archondakis et al., 2009; Chantziantoniou et al., 2017; Gutmann, 2019; Hanna et al., 2019; Green et al., 2021; Senel, 2020).

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Chapter 15

Implementation of Videos Captured by Static Telecytological Applications for Obtaining Expert Opinions

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ABSTRACT

Published studies compare static and dynamic telecytology systems. Still, no study has focused on implementing short videos captured by static telecytology stations for telemedical applications. The chapter aims to evaluate the diagnostic reproducibility of telecytology in thyroid fine-needle aspiration specimens prepared using liquid-based cytology among four cytopathologists using representative short duration videos captured by a static telecytology station. It also examines the agreement between the contributor's and the reviewer's diagnoses.

INTRODUCTION

Modern cytopathology laboratories have to provide results of high quality and credibility. Cytopathology laboratories wishing to achieve an automated and seamless workflow process, diminish turnaround times and improve their diagnostic accuracy have successfully adopted information technologies and automation. New types of cameras and microscopes connected to computers made possible image capture and transmission (telecytology) (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Chantziantoniou et al., 2017; Yao et al., 2018).

DOI: 10.4018/978-1-7998-9198-7.ch015

Telecytological diagnoses should be as reliable as those made using conventional microscopy. The purpose of the adopted program should be to ensure that microscopic (cytological) findings are correctly identified and interpreted by laboratory personnel (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Caron et al., 2019; Yao et al., 2018).

Telecytology can be defined as the process of diagnostic cytology performed on digital images. Telecytology can be used for teaching, professional assessment, auditing, archiving, quantitative cytology and research, obtaining expert opinions on complex cases, and routine diagnosis of the entire laboratory workload. (A Archondakis et al., 2009; Archondakis, 2013 ; Archondakis, 2014 ; Archondakis et al., 2014 ; Archondakis, 2015 ; Archondakis et al., 2016 ; Archondakis et al., 2019 ; Archondakis, 2020 ; Archondakis et al., 2021 ; Archondakis, 2021 ; Archondakis et al., 2020; Pouliakis et al., 2014; Pouliakis et al., 2015; Pouliakis et al., 2020; Pouliakis et al., 2021; Vavoulidis et al., 2016). Telecytological diagnosis can be achieved using cytological pictures viewed in real-time from the microscope (dynamic telecytological systems) or using cytological images captured in a digital format and then transmitted using a store-and-forward approach to distant observers (static telecytological systems). (Archondakis et al., 2009; Archondakis, 2013 ; Archondakis, 2014 ; Archondakis et al., 2014 ; Archondakis, 2015 ; Archondakis et al., 2016 ; Archondakis et al., 2019 ; Archondakis, 2020 ; Archondakis et al., 2021 ; Archondakis, 2021 ; Archondakis et al., 2020; Pouliakis et al., 2014; Pouliakis et al., 2015; Pouliakis et al., 2020; Pouliakis et al., 2021; Vavoulidis et al., 2016 ;Yao et al., 2018)

Remote cytological diagnosis can nowadays be achieved either with the use of cytological pictures viewed in real-time from the microscope (dynamic telecytological systems) or with the use of cytological images that are first captured in a digital format and then transmitted using a store-and-forward approach to distant observers (static telecytological systems) (Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Pouliakis et al., 2014; Caron et al., 2019; Yao et al., 2018).

Diagnoses made using telecytology should be as reliable as those made using conventional microscopy. The purpose of the adopted program should be to ensure that microscopic (cytological) findings are correctly identified and interpreted by laboratory personnel (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2020; Pouliakis et al., 2014; Pouliakis et al., 2015; Pouliakis et al., 2020; Pouliakis et al., 2021; Vavoulidis et al., 2016; Caron et al., 2018; Pantanowitz et al., 2009).

The existing studies which focused on the possible impact of static telecytology in the everyday laboratory's workflow have found a high (90–95%) concordance between telecytological and glass slide diagnoses.

Since now, all available studies compare static and dynamic telecytology systems, but there is no study available that has focused on the alternative implementation of short videos captured by static telecytology stations for telemedical applications. (Archondakis et al., 2019 ; Archondakis, 2020 ; Archondakis et al., 2021 ; Archondakis, 2021 ; Archondakis et al., 2020;) The present study aims to evaluate the diagnostic reproducibility of telecytology in thyroid fine-needle aspiration specimens prepared by means of liquid-based cytology among four cytopathologists using representative short duration videos captured by a static telecytology station. The study also examined the agreement between the contributor's and the reviewer's diagnoses.

BACKGROUND

Cytopathology laboratory's quality assessment is achieved by continuously monitoring specific indicators, such as turnaround times, interobserver or intraobserver diagnostic reproducibility, and concordance between histological and cytological diagnosis. (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021 ; Archondakis et al., 2020; Pouliakis et al., 2014.)

Diagnostic agreement and reproducibility between the same (intra-observer) and different (inter-observer) observers are the main parameters monitored and recorded during telecytology programs (Stamataki et al., 2008; Pantanowitz et al., 2009). The agreement is the total or the proportional number of cases in which the same diagnosis was issued between or within observers, including the part of the agreement that may be attributed to chance (Landis & Koch, 1977). The kappa statistic measures reproducibility, which is part of the agreement that cannot be explained purely by chance (Landis & Koch, 1977). Within the positive kappa values and in accordance with the study by Landis and Koch (1977), the agreement was interpreted as follows: a range of 0.00– 0.20 indicates slight agreement, a range of 0.21–0.40 indicates fair agreement, a range of 0.41–0.60 indicates moderate agreement, a range of 0.61–0.80 shows very good agreement, while a range of 0.81–1.00 indicates excellent or almost perfect agreement (Landis & Koch, 1977).

Cytopathology laboratory's quality assessment is achieved by continuous monitoring of interobserver or intraobserver diagnostic reproducibility and concordance between histological and cytological diagnosis. Internal and external quality control programs are focusing on the constant monitoring of both interobserver and intraobserver diagnostic agreements (Chantziantoniou et al., 2017; Pouliakis et al., 2014; Pouliakis et al., 2015; Pouliakis et al., 2020; Pouliakis et al., 2021; Yao et al., 2018).

In our study, the intraobserver κ mean value was 0.81 (very good). As long as the number of mistakes committed during specimen collection, preparation, and diagnostic interpretation diminishes, all monitored quality assessors continue to improve, and vice versa (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Pouliakis et al., 2021; Vavoulidis et al., 2016).

The practice of diagnostic cytology performed on digital images is a novel process that can be used for obtaining expert opinions on severe cases from remote laboratories (telecytology) (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Brooker et al., 2019). Telecytological diagnosis can be achieved either with the use of cytological pictures viewed in real-time from the microscope (dynamic telecytological systems) or with the use of cytological images that are first captured in a digital format and then transmitted to distant observers (static telecytological systems) (Archondakis et al., 2009; Stamataki et al., 2008). As a result, many studies have focused on the possible role of telecytology as a tool of diagnosis and consultation in the everyday workflow (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Brooker et al., 2019)

REMOTE EVALUATION OF SHORT VIDEOS CREATED BY STATIC TELEMEDICAL APPLICATIONS FOR OBTAINING EXPERT OPINIONS

The current study was carried out on 124 thyroid fine-needle aspiration specimens from patients pre-operatively aspirated under ultrasonography guidance, retrospectively selected from the department's registry. One cytopathologist collected all 124 glass slides and captured two representative videos from each case. Videos were captured with a Hamamatsu C4742-95 digital camera (Hamamatsu Photonics, Herrsching am Ammersee, Germany) mounted on a Leica DMLB microscope (Leica Microsystems, Wetzlar, Germany). The camera was connected via SCSI to a 1,200-MHz Pentium CPU running Windows XP (Microsoft, Redmond, WA). The two videos selected from each cytology slide were of 40 seconds duration each. They provided valuable information routinely used in cytological diagnoses, such as background, cellularity, and nuclear and cytoplasmic details. More specifically, the criteria usually adopted for selecting the captured areas were high cellularity, absence of obscuring factors, excellent preservation and visualization of nuclear and cytoplasmic details of follicular cells, background details, reactive cellular changes, cytological atypia, or dysplasia (when present). The number of two representative videos was adopted as a minimum quality standard for all 124 slides to ensure that the captured areas were adequately representative of the characteristic cytological changes of each smear that was included in our study. The study intended to provide all participating cytopathologists with adequate digital material for making an accurate diagnosis without any methodological bias that could compromise the results of our research. All videos captured areas of interest at 100× and 400× magnifications with $1,124 \times 1,120$ resolution at 16-bit color depth and 300 dpi. Each case's short videos were compressed, segregated and stored into separate directories.

All 248 representative videos were transferred via file transfer protocol to specific password-protected accounts and were reviewed remotely by four (4) cytopathologists on workstations using Microsoft's Internet Explorer Web browser. The diagnostic approach of digital videos concerning diagnosis criteria, terminology of lesions, requirements of adequacy, and recommendations for further management was similar to those applied in conventional cytology. Primarily, the cytological reports were classified into three basic diagnostic categories. "Benign," "malignant," and "intermediate" diagnoses were adopted. Cohen's kappa statistic was used to calculate interobserver and intraobserver reproducibility (Friedman & Wyatt, JC.1997).

Mean intraobserver reproducibility was calculated as the weighted average of the individual kappa values. To determine the significance of the intraobserver kappa values, we used the Svanholm formula (Friedman & Wyatt., 1997).

To confirm the reproducibility of the telecytology diagnosis and to study the interobserver agreement further 6, 12 and 18 months after the first initial round, the same representative digital videos were transferred in random order to the same cytopathologists and were reviewed again by them. The intraobserver variability was studied among initial and review rounds. At the same time, the diagnostic agreement was analyzed for intraobserver agreement by using the diagnosis given by the same cytopathologist between the two separate diagnostic rounds. The interobserver agreement was analyzed using the diagnoses given by different cytopathologists on each of the diagnostic rounds.

Intraobserver reproducibility between light microscopy diagnoses and telecytology diagnoses was calculated among all cytopathologists and ranged from perfect (for the more experienced cytopathologist) to nearly perfect (for the other less experienced cytopathologists) with the corresponding overall kappa values ranging from 0.825 to 0.864.

Cytological diagnoses based on digital videos and glass slides were compared with histological diagnoses. Both light microscopy and telecytology diagnoses did not present any significant discordance compared to the respective histological diagnoses. Furthermore, the reviewers also commented on overall digital image quality. Reviewers' opinions of image quality ranged from very good to excellent.

During the initial round, the diagnostic agreement was nearly perfect among all cytopathologists. Interobserver agreement improved slightly during the following review rounds. The kappa statistic was also used to analyze the intraobserver agreement of the diagnosis by the same cytopathologist in the different diagnostic review rounds based on the three main diagnostic categories and their subcategories. More specifically, the diagnostic agreement among all diagnostic rounds for the four cytopathologists ranged from perfect (for the more experienced cytopathologist) to nearly perfect (for the other less experienced cytopathologists) with the corresponding overall kappa values ranging from 0.82 to 0.89.

Issues, Controversies, Problems

The slides collected to produce the digital material from the Cytology Department's registry were coming from already histologically confirmed cases. The histological examination constitutes the golden standard for cytology slides validation (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Brooker et al., 2019; Chantziantoniou et al., 2017; Pantanowitz et al., 2009). Inadequate validation of test slides could lead to indiscriminate failure of qualified, competent personnel participating in teleconsultation programs (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Chantziantoniou et al., 2017; Pantanowitz et al., 2009).

The static telecytology systems have the advantage of considerably lower cost, but they only allow the capture of a selected subset of microscopic fields (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Pouliakis et al., 2014; Pouliakis et al., 2015; Pouliakis et al., 2020; Caron et al., 2018; Pantanowitz et al., 2009). In diagnostically non-challenging cases, bias in the selection of representative fields may have no implications. However, in difficult cases, the potential bias of inexperienced personnel in acquiring and sending representative images may endanger accurate telecytological diagnosis. On the other hand, the dynamic telecytology systems permit evaluation of the cytological material present on a slide (Caron et al., 2018; Yamashiro et al., 2004). However, these systems may be hampered by high network traffic, and their high cost of purchasing and maintaining may be unaffordable by small laboratories wishing to take advantage of such systems for teleconsultation purposes.

With the widespread availability of imaging technology and telecommunication, access to global expert pathologists is no longer a limiting factor. The recent advances in computer technology allow inexpensive personal computers, cameras, and smartphones to capture, store, edit, and transmit digital videos, further reducing the cost of video production. This form of static telecytology is technically straightforward, produces small manageable files that can easily be stored—retrieved, sent, reviewed and shared.

However, disadvantages of static telepathology relate to the fact that the consulting telepathologist has no remote control of the microscope or imaging device/ camera; their interpretation is limited to only captured field of view. Static telecytology systems are used to evaluate highly selected static images focusing only on few cells that may not show the entire evidence required for cytologic diagnosis. The

short pre-captured videos ensure continuity of cytological observation and provide substantial evidence of the representativeness of the selected fields. (Archondakis et al., 2019 ; Archondakis, 2020 ; Archondakis et al., 2021 ; Archondakis, 2021 ; Yao et al., 2018)

Telecytology by means of short pre-captured videos, when integrated into the daily workflow, can provide special consultation opportunities to distant laboratories (Archondakis et al., 2009; Archondakis, 2021; Archondakis et al., 2020; Caron et al., 2018; Pouliakis et al., 2014; Pouliakis et al., 2015; Pouliakis et al., 2020; Pouliakis et al., 2021; Vavoulidis et al., 2016; Vooijs et al., 1998). We suggest that static telecytology systems are preferred because of their low cost by laboratories that cannot afford the high cost of buying and maintaining dynamic systems. In addition, the telecommunication costs for the operation of static systems is lower as the usual standard ADSL Internet connection is adequate to operate a static system.

The most common manifestations of interobserver discrepancy are upgrading of the telecytology diagnosis to a definitive carcinoma diagnosis or downgrading of a suspicious telecytology diagnosis to a relatively benign lesion because of image deficiencies (Archondakis et al., 2009; Archondakis, 2021; Archondakis et al., 2020; Caron et al., 2018; Pouliakis et al., 2014; Pouliakis et al., 2015; Pouliakis et al., 2020; Pouliakis et al., 2021; Vavoulidis et al., 2016; Vooijs et al., 1998). In our research, the majority of discrepant cases were down-grading. Observers were diagnostically deliberated in some cases due to the limited adequacy of selected fields. In our study, the video quality was very good and did not allow any significant disagreement among participating cytopathologists (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Chantziantoniou et al., 2017).

Still, the use of digital videos for diagnostic purposes in the absence of a conventional slide was a new experience for all participants, and some of them needed some additional time to familiarize themselves with the whole process (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Yao et al., 2018).

On the other hand, the role of the person appointed to videos' capture and transmission is of paramount importance for the success of a static telecytology system. In our study, the person who captured and transmitted the digital videos was an already certified cytopathologist with adequate experience in conventional cytological diagnosis. Less specialized personnel, such as unexperienced screeners, may endanger the acquisition of representative images from each cytological slide (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Chantziantoniou et al., 2017).

In conventional cytology, specific diagnostic criteria and pitfalls are already described. During static telecytological diagnosis, the cytopathologist uses the same diagnostic criteria and avoids the same pitfalls. What makes the telecytological diagnosis more demanding is uncertainty about the actual specimen's adequacy or the representativity of the selected images (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Chantziantoniou et al., 2017; Yao et al., 2018).

The person appointed to capture and transmit videos is of paramount importance for the success of a static telecytological system. In our study, the person who captured and shared the digital videos was an

already certified cytopathologist with adequate experience in the cytological diagnosis of cervical smears. Our study suggests that cytological diagnoses based on digitized images can be as reliable as those of conventional cytology (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Chantziantoniou et al., 2017; Yao et al., 2018).

Solutions and Recommendations

Telecytology may be challenging to integrate into daily workflow. Distant cytopathology departments with high needs for assistance in the form of expert consultation can rarely afford the high cost of buying and maintaining dynamic systems (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Pouliakis et al., 2014; Pouliakis et al., 2015; Pouliakis et al., 2020; Pouliakis et al., 2021; Vavoulidis et al., 2016; Raab et al., 1996). Static telecytological systems are affordable by all cytology departments and allow all scientific personnel to participate in telecytology programs, even when there is a significant time difference among participating laboratories (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Hanna et al., 2019; Yao et al., 2018). Moreover, laboratory management should encourage the personal participation of all scientific personnel in such telecytology programs (Pinco et al., 2009; Hanna et al., 2019).

Cytology scientific societies should focus on teleconsultation particularities and define particular technical aspects such as optimal videos' size and analysis, suggested diagnostic categories and methodology used for the statistical evaluation of the participants' diagnoses (Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Nagy et al., 2006; Caron et al., 2018).

Finally, all participating laboratories should ensure that the personnel appointed to pictures' capture and transmission have adequate experience in conventional and image-based diagnosis. Previous experience in that field should be well-documented and recorded (Archondakis, 2015 ; Archondakis et al., 2016 ; Archondakis et al., 2019 ; Archondakis, 2020 ; Archondakis et al., 2021 ; Archondakis, 2021 ; Archondakis et al., 2020; Pouliakis et al., 2014; Pouliakis et al., 2015; Pouliakis et al., 2020; Pouliakis et al., 2021; Vavoulidis et al., 2016; Nagy et al., 2006; Hanna et al., 2019).

Last but not least, digital videos storage and transmission must follow strict regulations in order to avoid any unauthorized alteration or improper use (Archondakis et al., 2009; Archondakis, 2013; Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis, 2021; Archondakis et al., 2020; Mun et al., 1995; Hanna et al., 2019; Pouliakis et al., 2014; Pouliakis et al., 2015; Pouliakis et al., 2020; Pouliakis et al., 2021; Vavoulidis et al., 2016; Yao et al., 2018). Current standards of electronic medical data handling are still informative, yet the need for a secure electronic environment, especially in the field of static telecytology, continues to grow.

FUTURE RESEARCH DIRECTIONS

Telecytology, when integrated into the daily workflow, can provide exceptional consultation opportunities to distant laboratories. Short videos produced by static telecytology systems can be used by laboratories that cannot afford the high cost of buying and maintaining dynamic systems. (Archondakis, 2014 ; Archondakis et al., 2014 ; Archondakis, 2015 ; Archondakis et al., 2016 ; Archondakis et al., 2019 ; Archondakis, 2020 ; Archondakis et al., 2021 ; Archondakis, 2021 ; Archondakis et al., 2020; Nagy et al., 2006; Yao et al., 2018). Provincial hospitals where close scientific collaboration and support is necessary can take advantage of this great opportunity in order to improve their cytology services (Archondakis, 2014; Archondakis et al., 2014; Archondakis, 2015; Archondakis et al., 2016; Archondakis et al., 2019; Archondakis, 2020; Archondakis et al., 2021; Archondakis, 2021; Archondakis et al., 2020; Chantziantoniou et al., 2017).

Rapid telecytological diagnosis by means of short videos can dramatically diminish turnaround time, a quality indicator that refers to the time between specimen collection and final cytological report submission.

The diagnostic reliability of this method enables its use for further upgrading of the static telecytology stations services by producing virtual digital videos for educational purposes. Based on pre-captured and archived short videos simulating actual diagnostic processes, education programs can dramatically improve the participating medical staff's professional skills and make them feel more confident in their daily work. (Archondakis, 2014 ; Archondakis et al., 2014 ; Archondakis, 2015 ; Archondakis et al., 2016 ; Archondakis et al., 2019 ; Archondakis, 2020 ; Archondakis et al., 2021 ; Archondakis, 2021 ; Archondakis et al., 2020; Stergiou et al., 2009; Yao et al., 2018).

The use of telecytology for teleconsultation purposes in the laboratory's daily workflow will further ensure the accuracy of preoperative cytological diagnoses. It will contribute to cytopathologists continuous education and a better understanding of the criteria applied in thyroid gland lesions cytomorphological diagnosis.

CONCLUSION

The practice of diagnostic cytopathology performed on digital videos is a novel process that can be used for obtaining expert opinions on severe cases from remote laboratories (telecytology).

Cytological videos' transmission and remote evaluation allow reproducible diagnoses. Diagnoses made by using short videos created by static telecytological systems can be as reliable as those made by using conventional microscopy on the condition that representative videos are taken and that the standard cytological diagnostic criteria are applied.

Short telecytology videos can be used in the years to come for external or internal audits and quality assurance programs. Furthermore, digital videos can be used in proficiency testing programs in order to assess the laboratory's medical staff diagnostic expertise, according to ISO 15189:2012 requirements.

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Chapter 16

A Light Into the Current COVID–19 Pandemic in the Context of the Ancient Indian Science

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ABSTRACT

Ancient science relating to plants has always been a source of drug discovery, and in ancient times, people used medicinal plants to fight against pandemics. Researchers suggest ancient medical practices like Ayurveda, Unani, and traditional herbal medicine as a potential source to cure or prevent diseases like COVID-19. The internet of things (IoT) aims to help solve real-world problems by connecting all modern-day devices. An internet of healthcare things (IoHT), a branch of IoT, is creating a revolution in medicine. We can incorporate ancient knowledge into the IoT system and help people worldwide fight this pandemic by spreading the knowledge of Ancient Indian medicinal practice.

INTRODUCTION

IoT is the latest technological evolution that is helpful in the transmission of data over the defined network without having any human involvement at any level. Although IoT is transforming the world, we cannot deny the importance of ancient science. By 31st May 2021, more than 170 million COVID-19 cases were confirmed, and there were 3.5 million deaths in over 150 countries and regions worldwide. Although vaccination is going on, it could not be able to prevent the outbreak. Ancient science relating to plants is always a source of drug discovery, and at old times people had used medicinal plants to fight against pandemics. Researchers suggest ancient medical practices like Ayurveda, Unani, and traditional herbal

DOI: 10.4018/978-1-7998-9198-7.ch016

medicine as a potential source to cure or prevent COVID-19. India and China are integrating medicinal plants with western medicine to boost the immunity power of COVID-19 patients (Khadka et al., 2021). IoT is creating a revolution on the Internet. The world has entered into an extraordinary period in which the Internet connects company products and electrical devices. An Internet of Healthcare Things (IoHT) is creating a revolution in medicine, healthcare delivery, and consumer health. Smart medical devices, including watches, smartphones, and other biological-based wearables connected in an IoHT, provide improved, pervasive, cost-effective and personalized medical care and wellness (Alur et al., 2015). Internet of Things-enabled services do not replace the need for health professionals but can play a vital role in remotely tracking and monitoring symptoms which is beneficial in this pandemic of COVID-19, where the disease spreads due to contact with the virus particle. So, if we can incorporate the ancient science of plants into IoT systems, it can help fight this pandemic in an advanced way.

SARS-COV-2 VIRUS AND COVID -19

Severe Acute Respiratory Syndrome Corona Virus 2, the etiological agent of COVID-19, is part of a large family of viruses; it is a positive-sense single-stranded RNA virus that causes diseases in humans and animals has a typical crown-like appearance under an electron microscope (Gennaro et al., 2020). The Severe Acute Respiratory Syndrome (SARS) pandemic of 2002-2003 and the Middle East respiratory syndrome (MERS) outbreak in South Korea in 2015 are due to this virus. In 2019, the Centres for Disease Control and Prevention had started examining the outbreak of a new coronavirus variant, SARS-CoV-2, which was causing a respiratory illness later named COVID-19. Coronavirus has an envelope, which is round or oval and sometimes pleomorphic. The diameter of this virus is about 50–200nm. SARS-CoV-2 consists of 30 kb long RNA and has a unique club-shaped spike projection on the virus's surface. That makes the virus look like a solar corona. The coronavirus encoded four major structural proteins: the spike, membrane, envelope, and nucleo-capsid proteins. The spike protein is the most important structure that can bind with the receptor, which is the primary antigenic structure in the virus (Nugraha et al., 2020).

The World Health Organization (WHO) announced COVID-19 as a pandemic in December 2019. By 31st May 2021, more than 170 million COVID-19 cases were confirmed, and there are 3.5 million deaths in over 150 countries and regions worldwide. The first outbreak of the virus was documented in Wuhan, China. The virus is generally transmitted from person to person primarily through respiratory droplets containing viable virus particles. However, the report shows that the viruses can also be transmitted through contact with contaminated surfaces, objects etc. (Gholipour et al., 2020). The clinical description of COVID-19 includes asymptomatic or pauci symptomatic forms and clinical conditions characterized by severe respiratory failure that necessitate mechanical ventilation and support in an intensive care unit; it causes multi-organ and systemic failure in terms of septic shock, sepsis and multiple organ dysfunction syndromes. The main symptoms are fever, cough, headache, dyspnoea, sore throat and rhinorrhea (Gennaro et al., 2020). The rapid spread of SARS-CoV-2 has caused massive harm to public health and the economy to this date. In India, black, white and yellow fungi are currently infecting patients along with the coronavirus.

THE VACCINE OF COVID-19 AND ITS CONSEQUENCES

India's top drug regulator issued approval for two vaccines against COVID-19- Covaxin and Covishield. Covishield is considered better among the two vaccines approved. It is a version of the Oxford University-AstraZeneca vaccine with an average efficacy of 70.4% in various studies. The Serum Institute of India made the vaccine Covishield which is an Indian version of AstraZeneca. Covaxin is India's first home-produced vaccine against COVID-19. It was developed by Bharat Biotech in collaboration with the National Institute of Virology and the Indian Council of Medical Research. Cadila Healthcare, Ahmedabad produced another domestic COVID-19 vaccine, ZyCoV-D, based on the new plasmid DNA vaccine technology. Gam-COVID-Vac, a trade-name of Sputnik V, is a COVID-19 vaccine developed by the Gamaleya National Center of Epidemiology and Microbiology of Moscow, Russia. Sputnik V is a two-vector viral vaccine based on human adenoviruses (Kumar et al., 2021). India's biotech companies are expected to produce 300 million doses of Russia's Sputnik V vaccine. This may help to preserve the powdered version of the vaccine at refrigerator temperatures which is suitable for India's climate to preserve it for a longer time. It puts India in a prime position to benefit from the world's vaccine need and provide for its citizens. The latest COVID-19 vaccine, which was granted conditional permission for the 1st and 2nd phase trial, is the mRNA vaccine developed by the Pune-based Genova Biopharmaceuticals Ltd in collaboration with HDT Biotech Corporation USA (Kumar et al., 2021).

Fever, headache, pain or swelling at the injection site and irritability are the main side effects after vaccination. Death, acute leukoencephalopathy are some consequences faced during the vaccination trial period. Other reports of adverse events during the 1st and 2nd phases of a clinical trial are fatigue, nausea, vomiting, body aches, chills, diarrhoea etc. According to another report, a person with allergies to the vaccine's ingredients may develop symptoms like difficulty in breathing, swelling of face and throat, rapid heartbeat, dizziness, weakness, rashes throughout the body etc.

ANCIENT SCIENCE

In the recent past, even though there had been magnificent development in the field of science and technology as well as medical science, the importance of ancient methods of preventing diseases could not be neglected even in the 21st century. Developing and administering vaccines for all the infective pathogens is technically and economically challenging, especially in developing countries like India. There is also the chance of mutations and emergence and re-emergence of infective agents. Therefore, the world is looking forward to an alternative solution and knowledge available in Ayurveda. Unani texts may help us find a solution, as ancient science like Ayurveda and Unani turn out very beneficial during the COVID-19 pandemic.

Ayurveda and Its Role during Pandemic

Ayurveda, often called "Mother of All Healing", originated in India more than 5,000 years ago. It has a holistic approach to preventing and managing diseases, broadly classified as communicable and non-communicable, depending upon their mode of transmission. Ayurveda interventions become more pertinent because there is a detailed description for causation and management of epidemic (*Janapadodhwamsa*) in Ayurveda. There are two concepts in Ayurveda to prevent the infection- one is focusing upon patho-

gen (*beeja*) related to vaccine development, and the other focuses upon host (*kshetra*) for modulation of innate immunity. *Sthanatyaga*, which means ‘leaving the place where Ayurveda rambles, recommends a measure to prevent the spread of infectious diseases. If one cannot leave the place, it is advisable to maintain distance from the infected person and community as a protective measure. Rasayana (rejuvenative therapy) increases *oja* (the essence of *dhatu*s, i.e., the structural elements of the body), which boosts the immune system. Rasayana, like pippalirasayana, can be used to prevent infective diseases by strengthening our body’s natural defence mechanism. The three branches of Ashtang Ayurveda, Bhoot Vidya, Rasayana Vigyan and Vajikaran Vigyan are pertinent in managing epidemic diseases. The three branches cover both the psychological and physical health of a person. Just after the delivery of a child by the mother, there is the provision of *sutakakala* days (10 days for a female child or 20 for a male child) to avoid contact with the persons of the society, which probably helps the newborn as well as the mother to protect from getting infected. It is advised during defecation to cover the nose, mouth and head with some cloth. Bathing is recommended after going to the place of cremation, vomiting or shaving. One should take food after washing hands, mouth and foot with water. Measures to prevent infectious and communicable diseases include improved vaccination services, sanitation, safe water, hygienic conditions, health promotion activities, surveillance, and health education, which are also suggested by the World health (Dubey et al., 2020).

YOGA AND ITS ROLE DURING THE PANDEMIC

Thousands of years ago, Yoga was developed in ancient India as a spiritual practice. One of the best ways available for stress management is Yoga. It accentuates the unifying mind with body and soul to promote mental, spiritual and physical wellbeing. Even during COVID-19, Yoga will improve lung capacity and stabilize mental health to overcome the stress and depression associated with the pandemic (Tiwari et al., 2020). Since Yoga combines physical exercise, controlled breathing and mental concentration, it improves the immune system. Among the many yoga *asanas*, *shavasana* and *sasakasana* reduce stress and increase the immune system’s efficiency. Breathing techniques like *pranayama* enhance the respiratory system’s functioning—*Trikonasana* improves blood circulation, which benefits all vital organs. Patients with mild symptoms of COVID-19 and who have been advised to isolate at home could benefit from practicing yoga *asanas* and breathing exercises with proper caution, as suggested by several medical practitioners and experts.

The anxiety and uncertainty about the trajectory and course of illness among the COVID-19 positive patients and those suspected and being in quarantine can lead to psychological distress that can down-regulate their immune defences and increase the chance and severity of infection communities during the pandemic. The accompanying psychological distress and sequelae in COVID-19 patients are often ignored. There are reports of anxiety and acute depression leading to suicides during home isolation and in covid care hospitals. Social isolation has led to fear and severe mental health issues in pre-existing anxiety or depression disorders. Providing psychological treatment and support may reduce the burden of mental health conditions and ensure those affected. There is some evidence that enhancing general physical and mental health can reduce the burden of acute respiratory illness. In the war against Covid, several doctors and yoga therapists are deployed in Covid care hospitals to teach and practise Yoga with the patient. Simple yoga practices involving respiratory effort and lung capacity have improved oxygen saturation in those with respiratory distress. *Bhujangasana* breathing, *sulabhamatsyasana* breathing, *shashankasana*

breathing and yoga breathing have been found helpful in this situation. Inducing relaxation response using pranayama like Nadishodana and Bhramari and yogic relaxation response using pranayamas such as Nadishodana and Bhramari and yogic relaxation techniques has shown to reduce psychological stress, anxiety, depression, distress and stress in these hospitalized patients. Yoga is also known to improve duration and quality of sleep with lesser waking episodes and more deep sleep as assessed using novel sensor technology. Several practices like yogic breathing, chair breathing and shashankasana breathing are also known to improve oxygen saturation levels independently (Ministry of AYUSH). Approximately 10 percent of people diagnosed with COVID-19 experience prolonged symptoms, including trouble breathing, headaches, nausea, blood clots, muscle pain and fatigue that last weeks, months and years after testing positive for the coronavirus. Yoga teachers and yoga therapists have been working with these Covid long-haul patients to help them ease stress and pain, maintain mobility, and breathe easier. Researchers of Loma Linda University, School of Medicine, in California performed a meta-analysis of effective pulmonary lung rehabilitation treatments. They determined that breathing exercises that strengthen the diaphragm and stretching are essential for recovery. Their study published in the journal of Physical Medicine & Rehabilitation recommends a series of breathing exercises (Eichinesher, 2021).

UNANI AND ITS ROLE DURING PANDEMIC

The Unani system of medicine has its roots in the teachings of Hippocrates. As per Unani classical wisdom, improving immunity with immune boosters is critical for preventing disease and maintaining health (Khan et al., 2020). Many herbal-mineral drugs have been practiced for various acute infectious diseases from ancient times in the Unani system. The Unani concept has mentioned healing an epidemic fever (Humma Wabaiya) that resembles the present COVID-19. Unani Medicine gives great emphasis on the prevention of disease and promotion of existing health through six principles and essential factors, which are Hawa(Pure air), Ma” Kul-o-Mashrub (Healthy Food and Drink), Harakat-o-Sukun Badani (Active Body movement and Repose),Harkat-o-Sukun Nafsani (Peaceful Psychi movement and Repose), Nawmwa Yaqza (Proper Sleep and Wakefulness) and Istifraghwalhtibas (Needful Evacuation and Retention). It emphasizes maintaining a proper ecological balance and keeping water, air and food free from all possible pathogens. According to Zakariyya al Razi, people who regularly remain physically active and exercise are less susceptible to epidemic diseases (Parvez et al., 2016). Patients with a weak constitution and those suffering from underlying illnesses are more vulnerable during epidemics. Razi wrote details about quarantine and explained that public transportation must be stopped during an epidemic (Razi, 1991). Also,the Unani classical books mentioned the prevention of epidemic diseases by gargling with lemon juice, washing the surroundings with rose or sandal and fumigation with camphor. In the Unani system of medicine, most of the classical books mentioned preventive measures of epidemics by the use of Tiryqaqafeni (Antidote) and bukhoor (fumigation) with other antiviral herbal substances, itre (perfume) like Sandalwood (*Santalum album*), Rose (*Rosa damascena*), Musk (*Moschus moschiferous*) and Sirka (Vinegar). As per Unani literature, improving immunity with immune boosters enhances immunity and provides symptomatic relief in upper respiratory tract infections. Unani medicine emphasized that ghiza (food) is an essential supporting pillar of life that improves vitality, strength and immunity during epidemics. It is advised to avoid meat, sweets and fruits with high water content. These restrictions were placed because the zoonotic spread of infections was speculated. It is also recommended to consume citrus and sour fruits, especially grapes, apples, lemon etc. Ancient physician Jurjani stated

in his book *Zakhera-e-Khwarizam Shahi* that “Lying face down is better for the lungs”. A recent study has proved that for patients hospitalized with coronavirus disease, lying face down was better for the lungs, according to a research letter published in the American Thoracic Society’s *American Journal of Respiratory Critical Care Medicine* (Farzana and Sultana, 2021).

AAROGYA SETU

The Government of India has launched a smartphone application named Aarogya Setu to overcome and make civilians more aware of the COVID-19 pandemic. It aims to enable Bluetooth-based contact tracing, mapping hotspots and spreading essential and relevant information about COVID-19. Aarogya Setu is designed to develop a connection between the critical possible healthcare services and the people of India. In the application, the users will be asked if they have any symptoms of COVID-19 or have recently travelled internationally. The App tries to determine the risk if one has been near (within 6 feet) of a COVID-19 infected person by scanning a database of known cases across India. Arogya Setu is open-source, which allows people to modify and share because its design is publicly available. The significance of this App is to expand collaboration among the talented youth and citizens through open source, which will help build a robust and secure technology that will further support the frontline health workers in fighting this pandemic together.

MEDICINAL PLANTS THAT CAN HELP TO FIGHT COVID-19

The immune status of patients plays an essential role in COVID-19 infection, so some herbal medicine that has an immunity-boosting effect can act as a preventive measure and therapeutic agent for patients with COVID-19 infection. There was a recent trend in the community, the consumption of herbal infusions containing certain active compounds, which have antimicrobial, anti-inflammatory, anti viral and immune-stimulatory activities. As India has a rich history of ancient knowledge about medicinal plants, for example, *Curcuma longa*, *Ocimum sanctum*, *Azadirachta indica*, *Allium sativum*, *Tinospora cordifolia*, *Syzygium aromaticum*, *Panaxquin quefolius*, *Piper betel*, *Pipe rnigrum*, *Black cumin L.*, *Withania somnifera*, *Astragalus glycyphyllos*, *Curcuma domestica*, *Sambucus nigra*, etc. has been used traditionally as a drug or supplement because of its anti-inflammatory, antioxidant, anticancer, and antimicrobial effects. So much research has shown that herbal medicine can be helpful to treat COVID-19 (Nugraha et al., 2020). Plants have always been a source of drug discovery, and in ancient times, people had used medicinal plants to fight against pandemics. Researchers are suggesting herbal medicine as a potential source to cure or prevent COVID-19. India, along with China, is integrating medicinal plants with western medicine to boost the immunity power of COVID-19 patients (Khadka et al., 2021). Crude extract of plants like *Astragalus membranaceus*, *Artemisia annua*, *Agastache rugosa*, *Cassia alata*, *Gymnema sylvestre*, *Ecklonia cava*, *Glycyrrhizae uralensis*, *Houttuynia cordata*, etc. has shown promising inhibitory effects against corona virus (Adhikari et al., 2020). Song et al. (2014) demonstrated that six cinnamic amides extracted from *Tribulus terrestris* L. fruits could inhibit SARS-CoV- 2 viruses in a dose-dependent manner. Park et al. (2016) have studied the inhibitory potential of nine alkylated chalcones (isobavachalcone, xanthoangelol D, xanthoangelolE, 4-hydroxyderricin, xanthoangelol, xanthoangelol F xanthoangelol B, xanthoangelol G, xanthokeistal A) and furocoumarins extracted from the ethanolic extract of *Angelica*

keiskei (Miq.) Koidz, and the alkylated chalcones inhibited SARS-CoV-2 in a dose-dependent manner. From the ethanolic extract of brown Alga *Ecklonia cava*, Park et al. (2013) isolated nine phlorotannins effective against SARS-CoV-2.

Herbal medicines can prevent or help in the treatment of COVID-19 patients like *Echinacea purpurea*. This plant can be used in the form of extracts, tinctures, teas, and sprays. It contains several bioactive compounds like chicoric acid and caffeic acids, alkylamides, and polysaccharides. *Cinchona* sp. has bioactive compounds that can heal fever. The bark of the trees produces quinine alkaloids, which were also an effective treatment of malaria for more than several centuries (Abolghasemi et al., 2012). Quinine has a similar mode of action that of chloroquine, a synthetic antimalaria agent to treat malaria. The quinine sulphate has become a wanted drug for COVID-19 treatment. *Curcuma xanthorrhiza* Roxb. or Java curcumin is a herbal plant that is widely used in Southeast Asian countries. The most common compound in java turmeric is xanthorrhizol. A study shows that xanthorrhizol, the active compound of *Curcuma xanthorrhiza*, inhibits proinflammatory cytokines. Patients with COVID-19 who are susceptible to CRS can use xanthorrhizol, which may lower the proinflammatory response in a patient with COVID-19 (Nugraha et al., 2020). 6-Shogaol obtained from ginger (*Zingiber officinale* Rosc.) strengthens the body's defence mechanism by improving the antioxidant property and cures many chronic diseases and disorders; this important compound helps relieve the patient's respiratory issues. The alkaloid irritant taste from ginger also aids in clearing respiratory problems; thus, it is also known to help prevent COVID-19.

Curcumin's (*Curcuma aromatica*) anti-thrombotic properties help clear the mucous in the lungs, which helps relieve the oxygen supply to the entire body. The natural compound, Withaferin A, isolated from Ashwagandha (*Withania somnifera*), helps treat many diseases such as the common cold. It possesses antiviral activity against many viral infections, and it is effective against COVID-19. Liquorice (*Glycyrrhiza glabra*) contains glycone metabolite 18 β glycyrrhetic acid, which treats respiratory, is potent against the COVID-19 disease. Giloy (*Tinospora cordifolia*) contains alkaloid components like Neosporin, tetrahydropalmatine, choline, palmatine, and magnoflorine help to improve our immune system to fight against infectious diseases. A herbal formulation containing this *Tinospora cordifolia* is found to help prevent and cure COVID-19. Neem (*Melia azadirachta* L.) has a strong bitter taste known to cure many health disorders and is taken orally on an empty stomach to flush out the toxins and kill worms in the stomach. The bitter taste of neem helps in clearing the mucous of the lung, and therefore it is taken as preventive medicine for COVID-19. Tulsi (*Ocimum sanctum* L.), used in traditional medicine to cure various ailments, can heal. It is reported in a study that the tulsi plant has the binding property to destroy Corona virus causing the COVID-19 disease (Logeswari et al., 2020).

MINISTRY OF AYUSH (GOVERNMENT OF INDIA)

The Ministry of Ayush includes Ayurveda, Yoga, Naturopathy, Unani, Sidha and Homeopathy, abbreviated as AYUSH, which has the purpose of the development in education, research, and propagation of indigenous people alternative medicine system in India. The Ministry of AYUSH has included the seven most critical traditional methods of healthcare in India. This Ministry is headed by a Minister of State (Rathee, 2021). The Ministry of AYUSH recommends some self-care guidelines for preventive health measures and boosting immunity with particular reference to respiratory health, needed during this COVID 19 pandemic. Both Ayurvedic literature and scientific publications support these guidelines. The recommended measures are drinking warm water throughout the day; daily practise of Yoga and

meditation for at least 30 minutes; spices like Turmeric, Garlic, Cumin, Coriander are recommended in cooking; taking Chyavanprash (a dietary supplement) in the morning, helps people with diabetes; drinking herbal tea or decoction made from Basil, Black pepper, Cinnamon, dry Ginger and Raisin, once or twice a day, we can add jaggery (natural sugar) or fresh lemon juice to it; drinking Golden Milk which contains half teaspoon turmeric powder in 150 ml hot milk, once or twice a day; Applying sesame oil or coconut oil or Ghee in both the nostrils in the morning and evening; Oil pulling therapy once or twice a day - Taking one tablespoon sesame or coconut oil in the mouth, swish in the mouth for 2 to 3 minutes and spit it off and rinse with warm water. During dry cough or sore throat, use steam inhalation with fresh mint leaves or caraway seeds, which can be practiced once a day; Clove powder mixed with natural sugar or honey can be taken 2-3 times a day in case of cough or throat irritation. These measures generally treat normal dry cough and sore throat. However, it is best to consult doctors if these symptoms persist.

The hospitals follow these different approaches as per their specialization and modern medicine, potentially relevant for COVID-19 treatment. The Ministry of AYUSH recommends using AYUSH kwath, a ready-made formulation for the health promotion of the people. The formulation is made of four herbs *Cinnamomum verum* J. Presl. Stem, barks, *Zingiber officinale* Roscoe rhizomes, *Ocimum sanctum* L. leaves, and *Piper nigrum* L. fruits. The formulation is sold in the market with 'AYUSH Kwath', 'AYUSH Joshanda' or 'AYUSH Kudineer'. The formulation is available in powder and tablet forms on the market. These herbs are reported to boost immunity by Niphade et al. (2009); Alsuhaibani and Khan (2017) and are active remedies to various viral diseases, which are reported by Mair et al. (2016); Pruthvish and Gopinatha (2018) and Ghoke et al. (2018). Another product, the AYUSH-64 tablet, comprises *Alstonia scholaris* (L.) R. Br. bark, *Swertia chirayita* (Roxb.) H. Karst whole plant, *Picrorhiza kurroa* Royle ex Benth. rhizomes and *Caesalpinia crista* L. seed pulp. As it possesses anti malarial activity, AYUSH-64 is used as an effective medicine among the high-risk coronavirus population (Ahmad et al., 2020). Sharma et al. (1994) have reported that each of its constituents is effectively antiviral, antiasthmatic, and immune-boosting. Samshamani Vati is an Ayurvedic formulation used in all types of fevers. It is also used as an antipyretic and anti-inflammatory remedy, used and reported by Patgiri et al. (2014). Samshamani Vati is made of an aqueous extract of *Tinospora cordifolia* (Willd.) Miers is an immune-modulator by More and Pai, 2011 due to the synergistic effect of the various compounds present in various viral diseases. Agasthaya Hareetaki is used in the management of various respiratory infections and comprises nearly 15 herbal ingredients. Most of its ingredients have antiviral, anti asthmatic, anti-inflammatory, and immune-modulatory activities reported by Patel and Asdaq (2010); Kumar et al. (2011). *Leptadenia reticulata* (Retz.) Wight and Arn are reported to be effective in an allergic response, treatment of asthma, bronchitis, and throat trouble by Mohanty et al. (2017); *Sesamum indicum* L. oil for dry cough, asthma, migraine, and respiratory infections is reported by Nagpurkar and Patil (2017). Therefore, Anuthailacan is used in corona virus pandemic conditions. Ayush recommends Unani medicines like Triyaq-e-Araba, an important Unani formulation used as a detoxifying agent which contains *Laurus nobilis* L. berries, *Aristolochia indica* L. roots *Bergenia ciliate* (Haw.) Sternb. stem and *Commiphora myrrha* (Nees) Engl. It has been reported as a potent antiviral agent that is also effective against SARS-CoV-2 (Loizzo et al., 2008). Therefore, Ahmad et al. (2020) suggested that Triyaq-e-Araba could be an effective antiviral that can be used against COVID-19. Ahmad et al. (2020) suggested Roghan-e-Baboona which, an Unani remedy used to treat inflammatory complaints. The medicinal formula consists of flowers of *Matricaria chamomilla* L., which is found effective for acute viral naso-pharyngitis. Ahmad et al. (2020) described sharbat-e-sadar which as Unani poly-herbal syrup used for the common cold and respiratory diseases. *Trachyspermum ammi* (L.) Sprague, an important ingredient of the drink, was reported to neutralize

antibodies for the Japanese encephalitis virus, reported by Roy et al. (2015); *Bombyx mori* increases immune responses against viral infection, which was reported by Lu et al.(2018). Other ingredients such as *Ficus carica* L., *Glycyrrhiza glabra* L., *Onosma bracteatum* Wall., and *Ziziphus jujuba* Mill. also possess antiviral and immune-modulatory activities. Ahmad et al. (2020) described Arq-e-Ajeeb which as a liquid preparation that contains thymol, menthol, and camphor. They are reported as an antiviral agent, anti-inflammatory agent (Zaia et al., 2012). Unani physicians have a successful history of treating Nazla wabai (Swine flu) using Arq -e-Ajeeb, which supports Arq-e-Ajeeb for the COVID-19 disease. Khameera Marwareed is a sugar-based compound, semi-solid Unani formulation used as an immune-modulator (Ahmad et al., 2020). It has been reported to stimulate the immune system through cytokine response. It maintains the body in a healthier position to fight against the viral infections reported by Khan et al. (2009). Its ingredients have shown powerful antiviral activities by inhibiting replication (Ahmad et al., 2020). Habb-e-Bukharis, a polyherbal tablet formulation of the Unani system of medicine, is prescribed in malarial fever. Cinchona bark is the main ingredient of Habb-e-Bukhar. Some countries are using its active constituent quinine as a drug with a promising profile against COVID-19 (Ahmad et al., 2020); *Tinospora cordifolia* is (Willd.) Miers is another constituent of the formulation reported as a potent antiviral agent against HSV by Pruthvish and Gopinatha (2018). it is also suggested by Rastogi et al. (2020) to have immune-enhancing activity. Therefore, Ahmad et al. (2020) have suggested Habb-e-Bukhar in the treatment of COVID-19.

IoT AND THE COVID-19 PANDEMIC

The Internet of Things (IoT) is a part of Operations Research (OR), an applied discipline that aims to help solve real-world problems. OR includes many mathematical tools, techniques and systems thinking and consists of qualitative and quantitative tools. The large amount of data obtained from the IoT can support quantitative tools and techniques like data analysis. IoT is regarded as the next phase in the evolution of the Internet. It will enable all our daily use devices to be connected to the Internet to achieve many goals. It is estimated that only 0.6% of the objects that can be part of the IoT are currently connected. By 2020, there are up to 50 billion devices connected to the Internet worldwide (Ryan and Watson, 2017). The world has entered into an extraordinary period in which company services or products and electrical devices are connected. These devices communicate with each other without any human interaction. Smart sensors in traffic and road control structures collect information about traffic status and roads, weather conditions, etc. actually, the potential advantages of the IoT are virtually unlimited. Today's IoT-based applications are changing the way we live by saving time and organizational resources. They also bring new opportunities for development, innovation and knowledge formation (Albishi et al., 2017).

An Internet of Healthcare Things (IoHT) is creating a revolution in medicine, healthcare delivery, and consumer health. Smart medical devices, including watches, smartphones, and other biological-based wearables connected in an IoHT, provide improved, pervasive, cost-effective and personalized medical care and wellness (Alur et al., 2015). The marketplace for e-health monitoring devices is present, having precise solutions that are equally non-interoperable and designed based on various architectures and platforms (Albishi et al., 2017). An IoHT can also improve hospitals, nursing homes, assisted living, and care in retirement communities of our society in many ways. In hospitals, automated caregiver reminders, locating devices, handwashing systems, and automatic linking of device-produced medical data with medical records can improve our hospitals' operation and safety systems. Internet of Healthcare Things

can monitor, intervene, and assist plug-n-play devices, usable interfaces, help senior adults and people with disabilities, and techniques to handle large volumes of data to avoid overwhelming caregivers. An actual global IoT infrastructure can revolutionize the practice of medicine and transform the way people manage their health (Alur et al., 2015).

Medical applications of the Internet of Healthcare Things can reach areas hard for health professionals to reach. Here, the Internet of Things-enabled services do not replace the need for health professionals but can play a vital role in remotely tracking and monitoring symptoms which is beneficial in this pandemic, where the disease spreads due to contact with the virus particle. Thus, IoHT can easily recognize conditions patterns and supports people to play a more empowered role in their healthcare. MobiSante48 has developed a smartphone-based ultrasound device that allows healthcare workers to perform ultrasounds anywhere and share images with diagnostic teams via a secure networking system. This kind of system can replace access to health care, could serve to provide another tier of health care, disrupting the previous situation of people having access to medical care when it is available nearby. This system has particular potential for rural areas where the nearest hospital or doctor is challenging to reach or hours away (Coll and Simpson, 2016). To avail of low-cost services efficiently, our current healthcare systems experience massive changes, and challenges like limited resources in some cities make it challenging to obtain a proper healthcare system. That is why the existing healthcare systems require changes to transform into intelligent healthcare systems. Several tools and mechanisms like sensors and wearable devices together make intelligent healthcare systems. A competent healthcare system includes innovative emergency systems and smart hospitals using tools used in operations, such as smartphones and cloud computing. In Saensuk city of Thailand, an intelligent healthcare system was launched in January 2016 with Intel and Dell Company. The patients wear smart Bluetooth-enabled devices which collect and investigate the data related to walking, sleeping, and movements. The collected data is sent to the city central cloud system. Medical practitioners prepare an appropriate report, and necessary action is performed on an urgent basis of the data (Din et al., 2019). The IoT is about extending the power of Internet connectivity beyond computers to a whole range of other things, processes, and environments.

IoT interrelates all computing, mechanical and digital technologies to transfer the data through the Internet without human interaction. In the health sector, IoT has changed the lives of both the young and elderly drastically. Due to the COVID-19 pandemic, the role of the IoT landscape has been significantly changed. Some use is directly related to mitigating the spread of the virus (e.g., contact tracing, temperature screening etc.). In contrast, others seek to facilitate the new standard created by the pandemic (homeschooling, working from home etc.) (Yousif et al., 2021). Many wearable light weight IoT devices could be used to limit contagious viruses, such as the coronavirus and ameliorate healthcare offerings. Some symptoms can be monitored with the use of IoT devices without any effort. IoT can also work as a mapping network that shows places with an increased number of cases and a higher risk of infection. The Internet of Things (IoT) enabled the healthcare system to monitor COVID-19 patients by employing an interconnected network adequately. This technology helps to increase patient satisfaction and reduces the readmission rate in the hospital. (Singh et al., 2020).

Many devices are developed using IoT in the health sector like Pocket ECG, which has a diagnostic technology for cardiac arrhythmia detection, access to a full ECG signal for physicians, diagnostic reports with complete statistical analysis. Philips e-Alert has rapid insight into key MRI parameters; automatic alerts via mobile messaging.

CONCLUSION

There are examples of ancient medicinal practices to boost the immunity of COVID-19 patients. In Ayurvedic, Unani systems, traditional medicinal plants have shown healing and preventive properties against COVID-19. In India, we incorporate various ancient practices like Yoga to strengthen the respiratory system, such as taking an immunity boosting drink daily in hospitals and home isolation, vaccination, and other modern-day treatments. In India, we incorporate Arogya Setu, Ministry of AYUSH App, into every Indian person's mobile device. Although IoT in the healthcare system is still evolving, we need more innovative technologies to incorporate all this information into IoT systems. We suggest incorporating this knowledge into IoT systems like remote contact devices, some search engines from where everyone can access the knowledge and take care of themselves at home and office. Thus, we can help people worldwide fight this pandemic, spread the knowledge of our ancient medicinal practice and make people immune against the virus.

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Chapter 17

Electrical, Magnetic Radiation and Power Density Analysis of Electronic Gadgets During Yajna

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ABSTRACT

All of us are aware that the modern mechanical and electrical systems in collaboration with AI, CPS, and IoT have affected our lives drastically. At one end, they have provided ease and comfort. On the other end, the electrical and magnetic radiations emitted by them have threatened the mental and physical fitness. Surprisingly, the Asian Agnihotra process effectively reduces the electrical, magnetic radiations emitting from electronic devices. The chapter deals with the computational analysis of electrical, magnetic radiation, and power density measurement of environmental effects and gadgets after the Homa therapy. In the gap of a specific time, readings were recorded, and it was observed that drastic reduction occurred at the place where Yajna was performed. This gap was curtailed gradually as time increased. The phenomenon can undoubtedly be used to address human health threats due to electronic gadgets in the 21st century. Also, it supports the concepts of smart cities where one can quickly identify the numerous effects of the Yajna process.

DOI: 10.4018/978-1-7998-9198-7.ch017

INTRODUCTION

The world is suffering nowadays with unprecedented technical progress and enormous use of electronic gadgets. There is a guess that around every human being is using 3.5 gadgets emitting high radiation levels, and it is causing different health threats to them. Anxiety, depression, mental fitness breach, lack of decision-making, and insomnia are general symptoms due to this problem. The science community is worried about this threat and searching for alternative therapies (Fig. 1).

Figure 1. Human Life full of different electronic gadgets

(Source URL: <https://www.shutterstock.com/image-vector/brain-radiation-electronic-devices-201727895>)



The Indian Vedic sciences and especially the Mantra and Homa therapy have been effective tools in this direction. Researches have proclaimed that Yajna and its positive vibrations diminish the threats described above up to a substantial level. The manuscript reveals the experimental facts to validate this statement.

Characteristics of Electromagnetic Fields

EM fields propagate as waves and travel at the speed of light (c). The wavelength is inversely proportional to the frequency.

$$\lambda \text{ (wavelength)} = c \text{ (speed of light)} / f \text{ (frequency)}$$

If the distance to the field source is less than three wavelengths, then we are usually in the near field. If the distance is more than three wavelengths, the far-field conditions usually hold.

In near field conditions, the magnetic field value can not be calculated from the electric field value. This EMR meter is designed for reliable far-field measurements only (As per Fig. 2).

This electromagnetic radiation meter is used to indicate EM pollution generated artificially. Electric (E) and magnetic (H) fields arise wherever there is a voltage or a current. All types of Radio broadcasting and TV transmitters produce EM fields, and they also occur in the industry, business and the home. They affect us. Even our sense organs perceive nothing (Gupta, S. et al., 2012; Oprea, M. et al., 2011).

Figure 2. EMR Radiations emitted by electronic gadgets

(Source URL: <https://www.shutterstock.com/image-vector/brain-radiation-electronic-devices-201727895>)



Electric Field Strength (E)

A field vector quantity that represents the force (F) on an infinitely small unit. Positive test charge (q) at a point divided by that charge. Electric field strength is expressed in units of volts per meter (mV/m). This meter measures Electric field strength directly (Karatzas, K. et al., 2010; Romana, R.K. et al., 2015).

Magnetic Field Strength (H)

A field vector that is equal to magnetic flux density divided by the permeability of the medium. Magnetic Field Strength is expressed in units of amperes per meter (A/m). In far fields' situations, one can calculate the magnetic field from the electric field value. This meter can display the calculated magnetic field strength (Limaye, V.G. et al., 2019; Saxena, M. et al., 2018).

Power Density(s) of a Gadget

Power per unit area normal (perpendicular) to the direction of propagation, usually expressed in units of watts per square meter (W/m^2) or, for convenience, units such as milliwatts per square centimeter (mW/cm^2) (Ghosh et al., 2015; Ritchie et al., 2019).

Yajna and Humans

The young generation loves this for all materials used in this is easily portable, can carry wherever we go, and most appealing part is its time consumption. Hardly has it taken 10 to 15 minutes to complete the whole process. Then sit and inhale the mild fumigations with a sweet herbal fragrance that enters your respiratory system and reaches every cell. Feels completely stress-free and energetic (Apte, K. et al., 2016; Chauhan, P. et al., 2015).

Sound Energy in Yajna

Sound energy can alter our mood and improve our general well-being. Nevertheless, the key to understanding mantra lies in the relationship between our physical selves and our spiritual physiology, which many teachers of metaphysics refer to as a subtle body, and this body interpenetrates our physical body (Cortes, U. et al., 2000; Dev, M. et al., 2017).

Mantra and Effects

The chanting of Mantras during Yagyopathy kneads the flesh of the body with sound energy. The delicate cells of the elaborate bundles of nerves are subjected to constant hammering, a seizure of the flesh by the vibrations of the sacred sound that raises the subtle energies of the body (physical, mental and psychic) to cosmic levels and enhance the brain's capacity working with our endocrine system in producing memory-boosting hormones plus positivity. Doer feels mental, physical health, and happiness, due to which the positivity in the atmosphere increases in many folds. Society becomes healthy, happy and prosperous (Devender, K. 2et al., 2019; Ghorani, Azam et al., 2016).

BACKGROUND

Thukral and his team, in their research work, found that sound energy has immense frequencies; we all have a magnetic field around us, connected to Mooladhar Chakra, also storage of karma. As per Meta Physics, the sound energy that soothes you or makes you sad works deeply, creating patterns in the blood

and plasma of our body. Sound energy works with the magnetic field (aura) of our body and creates thought patterns. Here the song is identical, and patterns are different, actually as per my knowledge different sound creates different patterns. Hair follicles have the highest vibrations. That is why we get Goosebumps. In this video, some original sound has changed, the standard song is repeated (Thukral et al., 2020).

Naren and his team established that the Yajna experiment was done in Copper Kund 7.6” sides with GomaySamidha (cow dung sticks) as usual. Ghee (clove) was Madhusudan Ghee (clove), and zero PM was achieved even during Havan, towards the end, i.e. after 20 minutes of lighting fire. The levels were low before, but they had never achieved zero PM (Naren et al., 2020).

To check the effects of different pollutions, many researchers have done various experiments.

Ritchie experimented that electromagnetic radiation is resulted due to the current modern westernized lifestyle. Mobile, laptop, microwave, television and all electronic gadgets emit radiations. Long term exposure to these instruments can cause a tumor in the neck or head parts of the body. IARC (International Agency for Research on Cancer) has done analysis and research to check the possibility of correlation between head or neck cancer using phones by adults. It harms the ozone layer and causes cosmic radiation. (Ritchie et al., 2019).

The data was collected and calculated after analysis which was recorded from 13 countries, and it was found that more than ten years of usage of mobiles increases the risk of brain or nervous cancers (McCoorron, G. et al., 2018).

Nautiyal and his team and Sharma and his colleagues found in their experiments that there were high radiations of gadgets which were decreased up to zero after the Yajna activity. The experiments were conducted in the Vipin garden extension, New Delhi, India. Usually, the radiation ranges are up to 3 to 12 feet, varied from electrical/ electronic instruments. In the places where Yajna/Havan are performed regularly, the radiations are curtailed and diminished up to 3 to 5 inches only(Nautiyal et al., 2007; Sharma et al., 2019).

EXPERIMENTAL SETUP AND METHODOLOGY

HTC (High Tech. Computer Corporation) Application

Maintenance and service work must be done in areas where active electromagnetic fields are present in the broadcasting stations. Additionally, other employees may be exposed to electromagnetic radiation. In such cases, personnel must not be exposed to dangerous levels of electromagnetic radiation, such as:

- High frequency (RF), Electromagnetic wave field strength measurement.
- Mobile phone base station antenna radiation power density measurement.
- Wireless communication applications (CW, TDMA, GSM, DECT).
- RF power measurement for transmitters.
- Wireless LAN (Wi-Fi) detection, installation.
- Spy camera, wireless bug-finder.
- Cellular/ cordless phone radiation safety level, microwave oven leakage detection.
- Personal living environment EMF safety.

The Decive EMF-523 was used to measure the electrical and magnetic radiations and power density measurements. Readings were recorded after the Yajna activity at 6:40 am, 7:15 am, 7:30 am, 1:30 pm, 6:00 pm, daily average, after the day of Yajna and Before Yajna.

Figure 3. EMF-523 Device for Measurement of Radiation



This device is used to monitor the high-frequency radiation in the range of 50MHz to 3.5GHz. It has a non-directional electrical field antenna and high sensitivity, allowing electric field strength measurement in TEM cells and absorber rooms. It is also used to indicate the electromagnetic pollution generated artificially. It has many significant applications, i.e. high-frequency electromagnetic wave field strength measurement, wireless communication application, mobile phone base station, antenna-radiation, power-density measurement, and RF-power measurement for transmitters (Fig. 3).

EMF-523 is a high tech sensor-based device with the following components in its configurations.

RF-3 Axle sensor, Liquid Crystal LCD, Record/Time/ L Button, Unit/ Enter Switch button, Hold/ up button, Backlight/ set,XYZ/ Mem/ Down button, Tripod Mounting Screw, Battery Cover

EMF-523 Features

- Measurement method: Digital, triaxial measurement
- Directional characteristic: Isotropic (triaxial)
- Measurement range selection: One continuous range
- Display resolution: 0.1mV/m, 0.1 pA/m, 0.001 pW/m², 0.001 pW/cm²
- Setting time: typically 1.5s (0 to 90% measurement value)
- Sample rate: 3 times per second
- Units: mV/m, Vim, pA/m, mA/m, pW/m², mW/m², pW/cm²

- The meter is the broadband device for monitoring high-frequency radiation in the range from 50 Mhz to 3.5 GHz
- The non-directional electric field antenna and high sensitivity also allow measurements of electric field strength in TEM cells and absorber rules.
- The auto-ranging units of measurements and the measurement types have been selected to be expressed in electrical and magnetic field strength and power density units.
- At high frequencies, the power density is of particular significance. It provides the measure of the power absorbed by a person exposed to the field. This power level must be kept as low as possible at high frequencies.
- The meter can be set to display the instantaneous value, the max or average value measured.
- Non-directional (isotropic) measurement with three-axis measurement sensors.
- High dynamic range due to three-channel digital result processing
- Configurable alarm threshold and memory function.
- Easy and safe to use
- Low battery detector
- Overload Indication

EMF-523 Specifications

- Frequency Range: 50Mhz ~ 3.5 GHz
- Specified measurement range:
- CW signal ($f > 50\text{MHz}$)
- $0.01\text{V/m} - 20.0\text{V/m}$
- $0.01\text{mA/m} - 532.6\text{mA/m}$
- $0.01\text{W/m}^2 - 106.94\text{mW/m}^2$
- Dynamic range: Typically 75dB
- Absolute error at 1V/m and 2.45GHz : $\pm 1.0\text{ dB}$.

EMF-523 Frequency Response

- Sensor taking into account the typical CAL facto:
- $\pm 2.4\text{ dB}$ (50MHz to 1.9 GHz)
- $\pm 1.0\text{ dB}$ (1.9GHz to 3.5GHz)
- Isotropy deviation: Typically $\pm 1.0\text{ dB}$ ($f > 2.45\text{GHz}$)
- Overload limit: 0.42 mW/cm^2 (11 V/m) per axis
- Overload Limit: (0 to 500C): $\pm 0.2\text{dB}$

RESULTS AND DISCUSSION

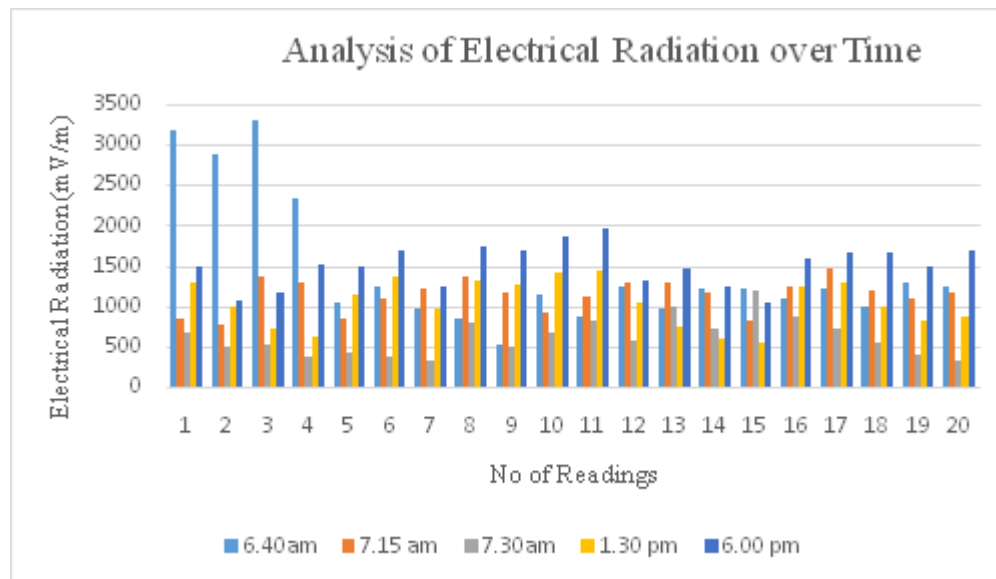
Electrical Radiation

Electrical radiation (mV/m) readings by the device are below in Table 1.

Table 1. Data Measurement and Readings for Electrical radiations in Different Time Intervals

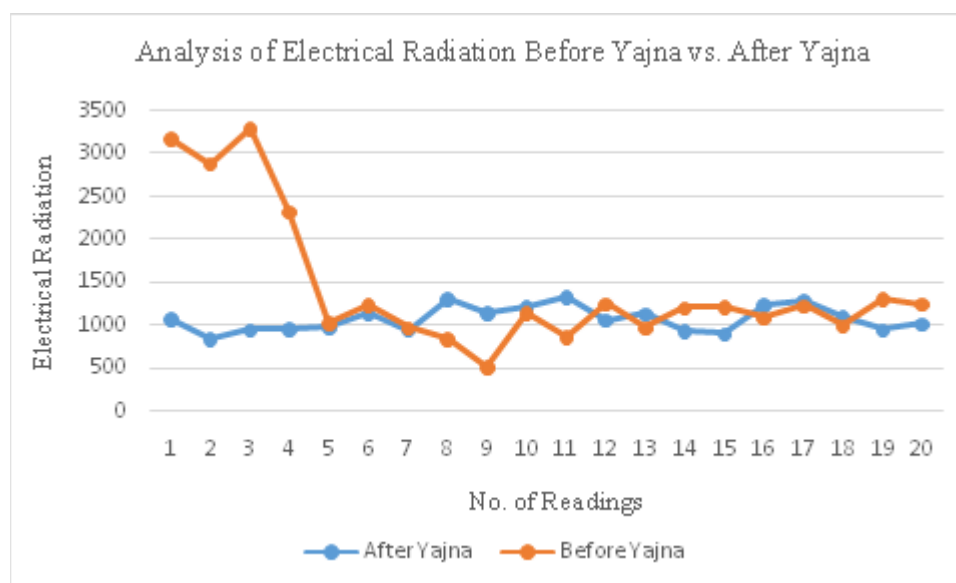
Electrical radiation (mV/m) millivolt per meter								
Time	6.40am	7.15 am	7.30am	1.30 pm	6.00 pm	daily Avg	After Yajna	Before Yajna
1	3175	855	676	1289	1485	1496	1076.25	3175
2	2884	762	506	996	1058	1241.2	830.5	2884
3	3297	1376	516	716	1159	1412.8	941.75	3297
4	2327	1288.5	377	617	1524	1226.7	951.625	2327
5	1032	832	417	1150	1489	984	972	1032
6	1244	1103	364	1374	1683	1153.6	1131	1244
7	968	1206	333	965	1245	943.4	937.25	968
8	845	1356	787	1320	1745	1210.6	1302	845
9	510	1157	485	1265	1678	1019	1146.25	510
10	1139	925	666	1412	1854	1199.2	1214.25	1139
11	863	1114	820	1437	1958	1238.4	1332.25	863
12	1248	1284	578	1032	1324	1093.2	1054.5	1248
13	973	1300	1005	749	1468	1099	1130.5	973
14	1204	1159	732	585	1236	983.2	928	1204
15	1219	808	1184	553	1035	959.8	895	1219
16	1088	1231	857	1249	1578	1200.6	1228.75	1088
17	1226	1457	726	1301	1654	1272.8	1284.5	1226
18	995	1185	541	1000	1658	1075.8	1096	995
19	1302	1081	404	815	1478	1016	944.5	1302
20	1247	1165	324	875	1695	1061.2	1014.75	1247
Time	6.40am	7.15 am	7.30am	1.30 pm	6.00 pm			
mean	1439.3	1132.2	614.9	1035.0	1500.2			
median	1211.5	1162.0	559.5	1016.0	1506.5			

Figure 4. Analysis of Electrical radiation over time



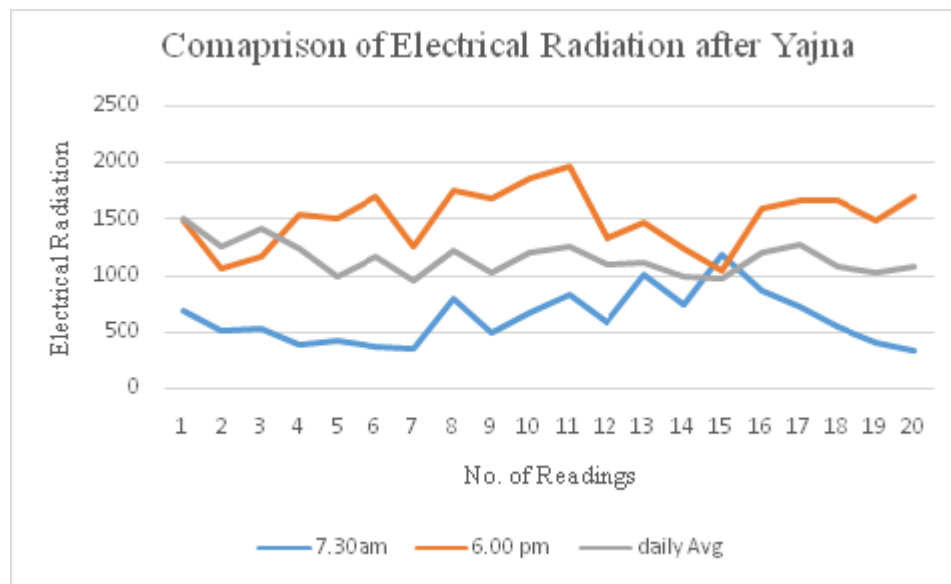
The above graph represents the whole data that describes the effects of Yajna on electrical radiation over time. The team had performed Yajna for 20 days and measured the electrical radiation. That is a bar chart, having different bars denoting different times. The above graph shows that at 6:00 pm, readings are very high and at 7:15 am, readings are significantly less. So, in the evening, electrical radiation increases drastically because the effect of Yajna decreases (Fig. 4).

Figure 5. Analysis of electrical radiation before Yajna vs After Yajna



This graph describes that in the starting days of Yajna, before Yajna, readings are very high. However, after few days of daily Yajna practices, readings are drastically decreasing. In the end, Before Yajna and After Yajna readings are almost similar. So, it can be quickly concluded that performing Yajna daily reduces radiation from electronic devices. The orange line shows the average of readings after Yajna, and the blue line indicates before Yajna (Fig. 5).

Figure 6. Comparison of Electrical radiation after Yajna



This graph compares readings just after Yajna, average daily readings and after 10 hours of Yajna. One can observe from the above chart that just after Yajna, electrical radiation is very low. Still, after 10 hours of Yajna, Electrical radiation is very high compared to the daily average and after Yajna readings. It can be concluded that the effect of Yajna decreases as time increases. The orange line displays readings at 6:00 pm (10 hours after Yajna), the blue line indicates readings at 7:30 am (Just after Yajna), and the grey line shows the daily average (Fig. 6).

Magnetic Radiation

Magnetic radiation readings by the device (Table 2).

This graph describes the gist of the experiment, which represents the effects of Yajna on magnetic radiation over time. The author team had performed Yajna for 20 days daily and recorded the magnetic radiation of electronic devices at different times. There is one reading before Yajna and four readings after Yajna. It can be concluded that just after Yajna (7:15 am), readings are significantly less, and before Yajna (6:40 am), readings are very high. That is a line chart where one can observe that different colored lines show other readings (Fig. 7).

Electrical, Magnetic Radiation and Power Density Analysis of Electronic Gadgets During Yajna

Table 2. Data Measurement and Readings for Magnetic radiations in Different Time Intervals

Magnetic radiation unit in Joule						
Time	6.40am	7.15 am	7.30am	1.30 pm	6.00 pm	After yajna AVG
1	1159	647	956	1015	1758	1094
2	1154	658	954	1056	1738	1101.5
3	2341	745	1045	1545	2068	1350.75
4	1049	576	889	1017	1542	1006
5	3300	845	1378	1754	2457	1608.5
6	2408	757	1032	1505	2087	1345.25
7	2881	765	1089	1565	2014	1358.25
8	2751	898	1075	1585	2065	1405.75
9	2148	746	1087	1515	2073	1355.25
10	1740	648	987	1330	1859	1206
11	5765	989	1697	1965	2512	1790.75
12	3409	869	1383	1718	2235	1551.25
13	3509	858	1400	1701	2568	1631.75
14	2737	778	1054	1560	2011	1350.75
15	1947	625	997	1308	1890	1205
16	1543	568	923	1363	1858	1178
17	1519	578	947	1304	1841	1167.5
18	3903	754	1585	1766	2401	1626.5
19	2610	734	1078	1575	2047	1358.5
20	1910	724	912	1475	1805	1229
mu	2519.6	738.1	1123.4	1481.1	2041.5	
median	2374.5	745.5	1049.5	1530.0	2030.5	

Figure 7. Analysis of Magnetic radiation w.r.t. Different Time

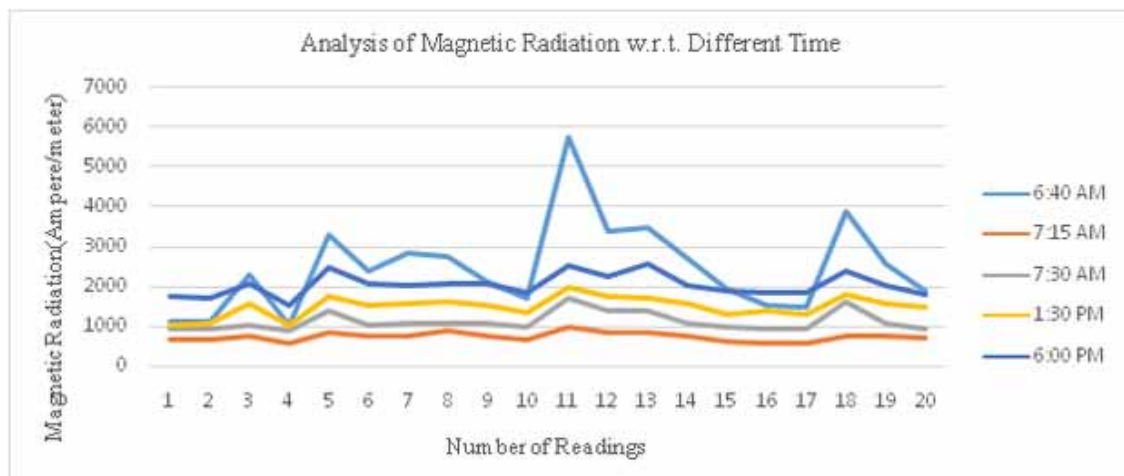
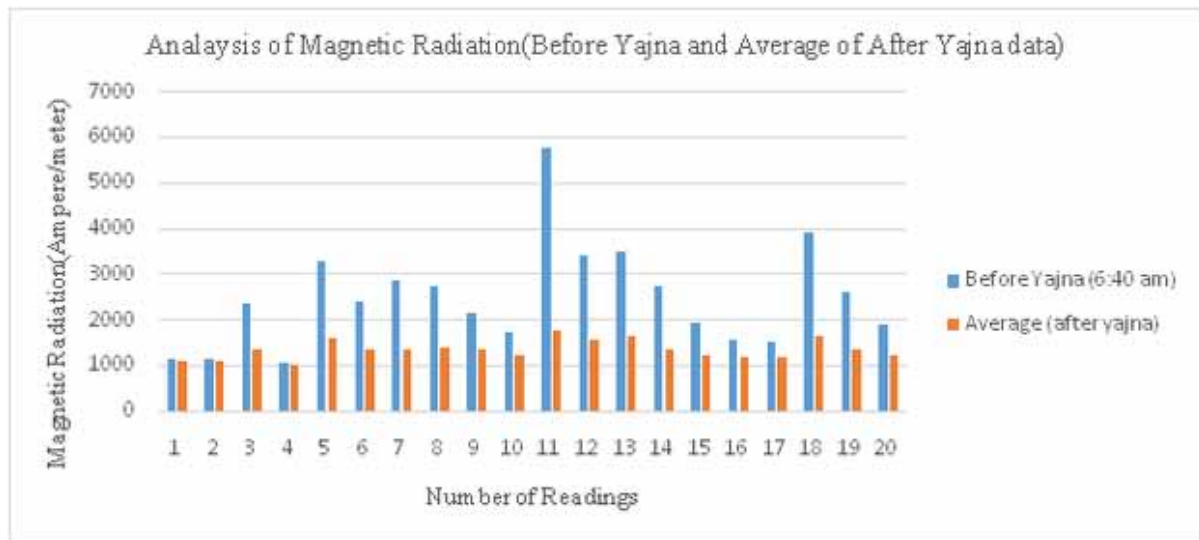
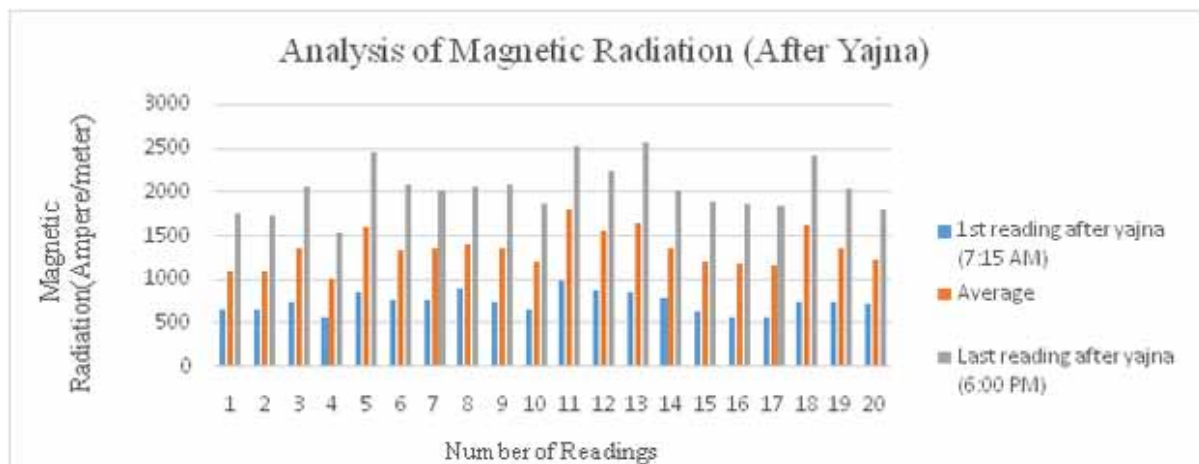


Figure 8. Analysis of Magnetic radiation (Before Yajna and Average of After Yajna data)



The above bar chart represents data that describes the effect of Yajna on Magnetic radiation before and after the Yajna. The blue bar represents the data of Magnetic radiation before the Yajna, and the red bar represents the average of the readings of Magnetic radiation taken after the Yajna. It can be observed from the above graph that the readings are very high before Yajna and get low after the Yajna (Fig. 8).

Figure 9. Analysis of Magnetic radiation (After Yajna)



The above bar chart represents data that describe the effects of Yajna on magnetic radiation after the Yajna. The blue bar represents the 1st reading of magnetic radiation at 7:15 am, and just after the Yajna, the red bar represents the average of the readings of magnetic radiation after Yajna. The green bar represents the last reading of magnetic radiation at 6:00 pm after Yajna. The above graph shows that the

Electrical, Magnetic Radiation and Power Density Analysis of Electronic Gadgets During Yajna

1st reading after Yajna is very low compares to the average because of the effect of Yajna on Magnetic radiation, and the last reading after Yajna is very high compared to the average because of the impact of Yajna decreases over time (Fig. 9).

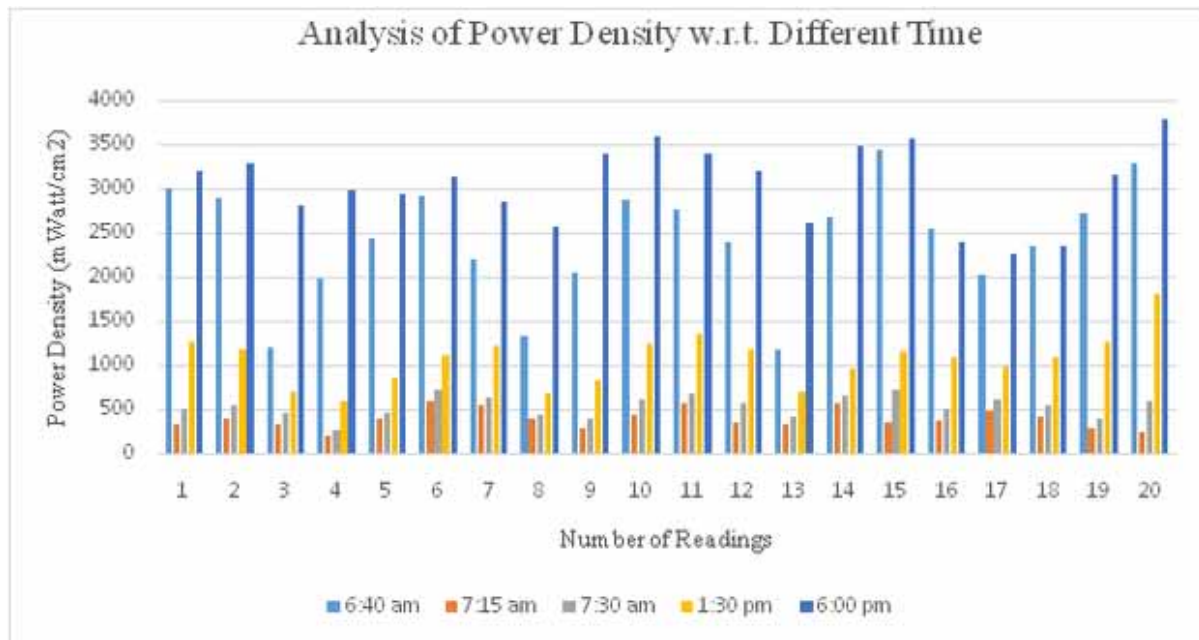
Power Density

Power density readings by device are below (Table 3).

Table 3. Data Measurement and Readings for Power density in Different Time Intervals

Power density (Unit in mW/ m ²)						
Time	6.40am	7.15 am	7.30am	1.30 pm	6.00 pm	After Yajna AVG
1	2998	320	508	1263	3206	1324.25
2	2893	395	536	1169	3293	1348.25
3	1205	335	464	703	2802	1076
4	1988	190	268	589	2970	1004.25
5	2435	391	459	842	2940	1158
6	2905	579	721	1108	3134	1385.5
7	2204	541	637	1222	2846	1311.5
8	1319	382	426	677	2558	1010.75
9	2042	283	397	828	3397	1226.25
10	2859	441	616	1241	3594	1473
11	2769	565	675	1352	3389	1495.25
12	2394	349	558	1168	3200	1318.75
13	1165	330	416	698	2615	1014.75
14	2683	560	661	960	3475	1414
15	3443	352	728	1155	3565	1450
16	2549	372	506	1086	2396	1090
17	2014	485	598	974	2262	1079.75
18	2337	416	541	1088	2342	1096.75
19	2720	276	401	1252	3151	1270
20	3276	248	589	1798	3775	1602.5
mu	2409.9	390.5	535.3	1058.7	3045.5	
median	2492.0	377.0	538.5	1098.0	3142.5	

Figure 10. Analysis of Power density w.r.t. Different Time



The above graph represents the whole data that describe the effects of Yajna on power density coming from a. mobile phone, which was used as a source. Yajna was performed for 20 days, and the power density was measured. So, this bar chart has different bars denoting different times. The team measured power density before Yajna at 6:40 am and measured power density after Yajna at 7:15 am, 7:30 am, 1:30 pm and 6:00 pm. It can be observed from the above graph that at 6:40 am, the readings are very high, and after the Yajna at 7:15 am, the readings drastically decrease because of the effects of Yajna. At 6:00 pm, readings get very high. So, it can be interpreted that in the evening, power density increases because the impact of Yajna decreases (Fig. 10).

The above bar chart represents data that describe the effect of Yajna on power density before and after Yajna. The blue bar represents the power density data before the Yajna, and the red bar represents the average of the readings of power density taken after the Yajna. One can observe from the above graph that the readings are very high before Yajna and get very low after the Yajna (Fig. 11).

The above bar chart represents data that describe the effect of Yajna on power density after the Yajna. The blue bar represents the 1st reading of power density at 7:15 am, just after the Yajna. The red bar represents the average power density readings after Yajna, and the green bar represents the last reading of power density at 6:00 pm after Yajna. The above graph shows that the 1st reading after Yajna is very low compared to the average because of the effect of Yajna on power density, and the last reading after Yajna is very high compared to the average because of the impact of Yajna, which decreases over time (Fig. 12).

Figure 11. Analysis of Power density(Before Yajna and Average of data After Yajna)

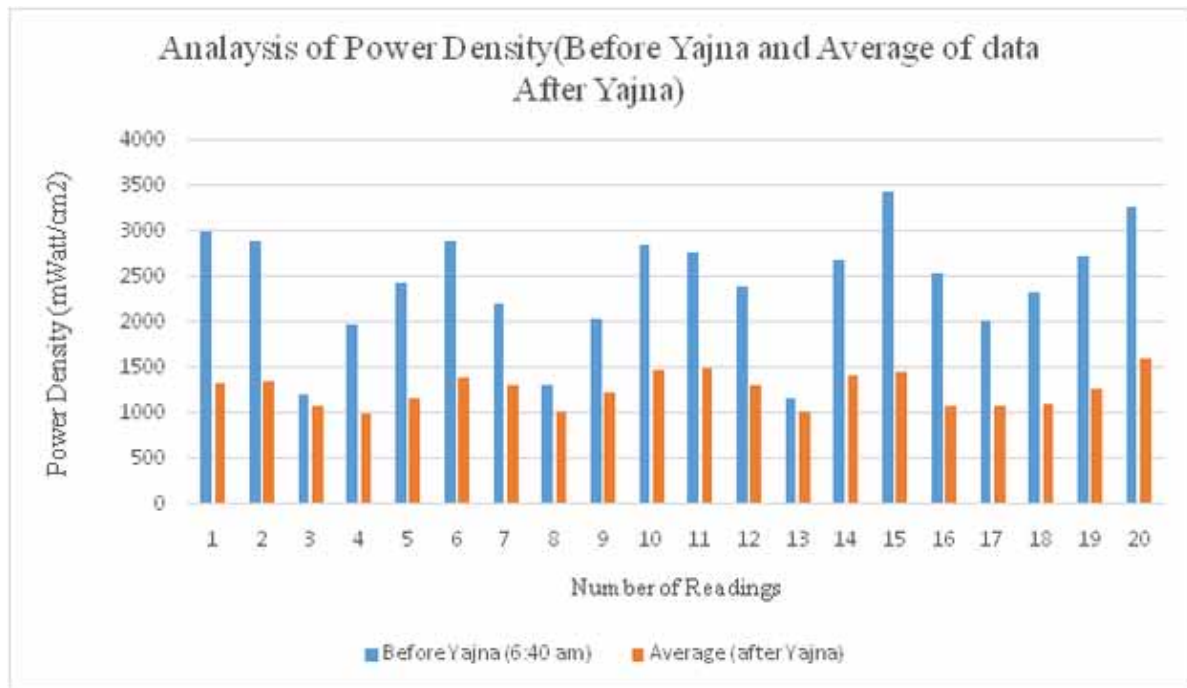
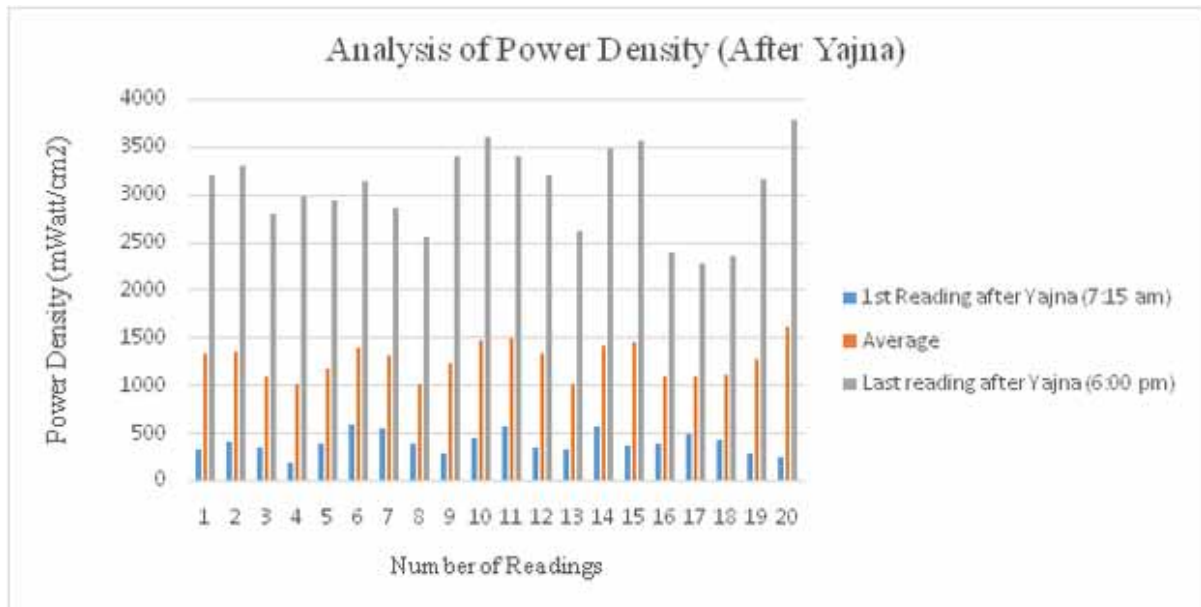


Figure 12. Analysis of Power density (After Yajna)



RECOMMENDATIONS AND NOVELTY

The Yajna experiments were conducted, and research results have been compiled for different human life and environmental aspects. The experiments were done on various diseases and symptoms and the effect of Yajna therapy on them. Effects of Yajna on the Psycho-Physical domain have been demonstrated.

Pollution due to electromagnetic radiation and the effect of Homa on it. Expansion and movement of Pranic Energy are continued here (Sharma et al., 2019; Singh et al., 2019).

Yagyopathy is now being treated as a therapy to cure diseases, and Gayatri Parivaar organizations volunteers and researchers are being honored for spreading awareness of this ancient Indian Vedic wisdom.

It is rather hard to believe that any spiritual process can reduce electromagnetic radiation in the western world. The human brain has an electromagnetic method to operate. However, the various signals are so weak that it is hard to admit that such effects can occur and cause EMI. However, the present author's experiments and this approach could be available for other researchers to repeat and validate the results.

The Yajna experiments were conducted, and researches results have been compiled for different aspects of human life and the environment related to health. The experiments were done on various diseases and symptoms and the effect of Yajna therapy on them. The impact of Yajna on the Psycho-Physical domain have been explored here.

FUTURE RESEARCH DIRECTIONS AND APPLICATIONS

Further research on Homa can be done in one of the following areas:

- Cosmic Energy Movement through Yajna.
- The research team may explore results after measuring through Energy Measurement.
- Energy increase at the time duration of Mantra Chanting.
- Energy increase if practitioners chant in a louder voice.
- Ordinary people do Yajna (reflects a minor energy increase).
- Three minutes of Yajna process completion (energy increases).
- After around 120 minutes (energy increases at completion).

CONCLUSION

Technological aspects of Yagyopathy are a more straightforward form of Kund in which Yajna activities were performed with medicinal herbs in minimal quantity. It is the subtler form that has a powerful impact on health and the environment. Offerings of medicinal herbs with Vedic mantras (the mystic syllable of sound energy) chanting produces the necessary changes in the mental plain of the doer at a higher level. Change of thoughts is a shift in reality through which they find a creative path for business, study or endeavors in any aspect of life, and move towards the righteous path, uplifting self and society.

The Above results and discussion section clearly illustrates the effect of Yajna activity on Radiation control, and there is a significant improvement over the pollution by radiation. The various gadgets and the effect of Homa on their radiation shows that it is highly useful to use gadgets in the Agnihotra environment so that the mal effects of radiation are curtailed, and it is safe and valuable for human health.

ACKNOWLEDGMENT

The team of authors would love to pay our deep sense of gratitude to the ABES Engineering College, Ghaziabad & Amity International Business School, Amity University, and Noida for arranging us all the facilities, the direct-indirect supporters for their timely help and valuable suggestions and the almighty for blessing us throughout. We would also like to extend the vote of thanks to IIT Delhi, IIT Roorkee, Dev Sanskriti Vishwavidyalaya, Haridwar, Patanjali Foundation and Ayurveda Institute, Dehradun for their support and guidance in accomplishing our research paper.

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Chapter 18

Facets of the Evolving Healthcare Management Model

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ABSTRACT

The pandemic represents an opportunity to reimagine future healthcare and rethink healthcare management unbound by preconceived notions based on the following three main drivers that emerged during the pandemic. These include transformed business models, new care delivery models disrupted by ubiquitous data and technology, intelligent spaces, and digitally-enabled hospitality. In this context, it is imperative to reexamine all facets of healthcare management, considering that applying linear models to healthcare management has improved our understanding of their system structure and function. However, such models often fall short of explaining experimental results or predicting future abnormalities in complex nonlinear systems. Nonlinear models may better explain how the individual components collectively act and interact to produce a dynamic system in constant flux. They also assist in filling in some of the results which linear models do not adequately explain. Finally, chaos theory might provide new insights into standard as well as abnormal behavior within systems.

INTRODUCTION

Management is defined as all the tasks and activities undertaken for achieving goals by planning, organizing, leading and controlling. It is also a process of reaching its objectives efficiently and effectively by:

- Planning.
- Decision making.
- Organizing.
- Leading.
- Motivating and controlling an organization's resources.

DOI: 10.4018/978-1-7998-9198-7.ch018

Overall, we might summarize a threefold concept of management. In this context, management is an economic factor, one of the factors of production together with land, labor, and capital. Management is also a system of authority that arose through the paternalistic approach and constitutional management towards a participatory process.

Moreover, sociologists view management as a class and status system, as the complexity of relationships demands the elite of the brain and education. At the same time, an entry into the profession depends on excellence in education and knowledge.

Thus, we might define the nature of management as:

- A systematic process of planning, organizing, staffing, leading and controlling.
- The concepts and activities that are applied to all levels and all types of organizations and activities.
- The creation of surplus.
- A unique group of people who direct the effort and activities of other people.
- The fulfillment of the objectives of the interested parties.

As a result, management could be considered as the art and science of getting the work done, and also encompassing the following features:

- Team efforts.
- Purpose (the achievement of something definite).
- Goal orientation (urge for accomplishment).
- Indispensability (neither be replaced nor substituted by anything else).
- Intangibility (unseen force).

On the other hand, healthcare management is the overall management of a healthcare facility, such as a clinic or hospital. It is an umbrella term encompassing clinical directors, healthcare supervisors, health coordinators, and nursing home facilitators. It is worth noting that the terms healthcare management and healthcare administration are often mistakenly used interchangeably. However, they are two different things, as healthcare administration takes care of the staff and employees, and healthcare management is in charge of the entire healthcare organization.

Furthermore, we should take into account the key differences between the healthcare industry and other industries (Moumtzoglou, 2020), which include the following features:

- **High-Risk Industry**
The healthcare industry impacts individuals to a greater extent than any other industry.
- **Highly Regulated**
Numerous regulations govern the provision of healthcare.
- **Multiple stakeholders**
There is a large number of interested parties in the healthcare industry. That includes the patients, the physicians, the nurse practitioners, the hospitals/clinics, their administrative staff members, the payers/ insurance companies, employers, pharmaceutical companies, technology vendors, device manufacturers, government bodies, and so on.

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- **Slow Pace of Adoption**

The healthcare industry has traditionally been slow to adopt IT, especially the smaller clinics and individual physician practices.

- **Small and Large Providers**

The small providers typically do not have the resources to evaluate or experiment with advanced IT systems. On the other hand, there are several large multi-specialty hospitals whose IT requirements are distinctly different from those of office practitioners.

- **Long-Term Relationships**

Changing IT systems often is not easy, and there is an assumption that any product adopted would be advantageous to use for several years. This hypothesis does not follow the need for both the IT systems and individuals to adapt.

Considering the management's features and the COVID-19 situation, we will explore the facets of management that unfold or unfold in the pandemic aftermath.

BACKGROUND

The establishment of managerialism in the public sector is associated with the New Public Management (NPM) movement of the 1980s. However, in the private sector, managerialism marked the beginning of the twentieth century (Fleischman and Tyson, 2006). Performance measurement and management are not recent phenomena. Recording information on commercial transactions is a long-standing practice, as ancient civilizations used bookkeeping records engraved in stone tablets (Johnson and Kaplan, 1991). However, it is worth noting that performance measurement and management only became vital management practices in the mid-eighteenth century. Until that time, the putting-out system was the dominant business model adopted in a primarily agriculture-based economy. Within this model, workers were paid for the work done (piece work), and production took place at home (Mokyr, 1998). Moreover, the economic units had a simple structure, and there were no shareholders. In the period between about 1760 and 1830, a series of changes occurred in the following four areas (Mokyr, 1998):

- Economic growth.
- Technological change.
- Structure and scale of firms.
- The characteristics of financial transactions.

These changes, which later became known as the Industrial Revolution, led to the substitution of the agricultural-based economy by a mercantile and manufacturing-orientated setup (Day, 2000). The industrial organization model marked the beginning of modern mass production, mass marketing and mass distribution, replacing traditional local markets with a new regional economy (Chandler, 1994).

With this new dominant business model, the simple structure of monetary units was gradually replaced by large capital-intensive and complex firms. By contrast to the putting-out system used in the past, the factory system relied on hiring workers on long-term employment contracts, and their work was closely supervised using command and control structures (Hudson, 2004).

As a result of these changes, factories became too large for the individual owner-entrepreneur to manage. That led to the creation of intermediate levels of management and the consequent adoption of a hierarchical organizational structure (Johnson and Kaplan, 1991).

Besides leading to internal organizational changes, the adoption of the industrial model also influenced the way companies interact with the external environment. In conjunction with new performance measurement tools, more detailed and redefined accounting practices were gradually enforced by law (Matthews, 2006). The principle of managing companies along scientific lines was pioneered by the US engineer Frederick W. Taylor and became known as Taylorism. Through training and development provided by managers, employees would learn how to perform their tasks following a uniform 'scientifically' designed approach. This scientific approach contrasted with previous generations' rule-of-thumb methods (Taylor, 1911). As a result of the implementation of 'scientific' strategies, workers began to receive detailed written instructions about tasks to be carried out, how to execute them and the duration of each task. Overall, it is evident that the human resource management practices associated with scientific management significantly differ from those that govern the putting-out system. This divergence was particularly noticeable in reducing employees' autonomy, which a corresponding power gain by managers accompanied. Furthermore, the focus on increasing the market share and profitability, coupled with newly acquired functional improvements and strategic management skills, encouraged firms in the early twentieth century to progressively develop into (Chandler, 1994):

- Large.
- Complex.
- Multiproduct.
- Multimarket multidivisional corporations.

This organizational design significantly differed from the one adopted by large companies created during the Industrial Revolution. Based on Taylor's scientific management principles, Du Pont created performance measures such as the return on investment (ROI). In the 1920s, the multidivisional organizational model developed by Du Pont was introduced in other corporations, as it became common for companies to use four main strategies to grow. These included (Chandler, 1994):

- Acquiring or merging with similar firms in terms of product, production processes, and markets.
- Incorporating companies whose activity focused on other stages of the chain of production.
- Entering into other geographical markets and
- Producing new products using the company's existing technology.

The evolution of the organizational landscape into more complex enterprises in the early twentieth century increased the focus on performance management. Alongside the rise of large corporations, the twentieth century saw the establishment of management as a critical recognized function within organizations. That led to a subsequent proliferation of new management tools, including innovative measuring performance (e.g., benchmarking, ISO quality standards, and balanced scorecard). The new centrality of managers was closely associated with the possibility of managers monitoring other staff's performance through outcome indicators. That bolstered the belief that everything that could be measured could also be managed. That opened a pathway to the intellectual growth of what we would describe as 'managerialism'. In line with this new management philosophy, there was a sequence whereby performance

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measurement tools focusing on financial performance (e.g., ROI and ROCE) were gradually augmented by several other management tools with a broader scope during the twentieth century. These included (Sibbet, 1997):

- Management by objectives (1950s).
- Statistical quality control for acceptable defect levels (1950s).
- Management by numbers (1960s).
- Managerial grid (1960s).
- Critical path method (1960s).
- Statistical process control for quality (1980s).
- ISO standards (1980s).
- Benchmarking (1980s).
- Balanced scorecard (1990s).

While this increase in regulation has shaped the day-to-day management of organizations, the behavior of organizations also affected the nature of the regulatory activity. Additional challenges arose from ongoing processes of globalization, which accelerated during the latter part of the twentieth century.

Another area of significant change during the twentieth century was the relationship between companies and their stakeholders. Accordingly, corporate social responsibility encompasses the expectations that companies operate within the legal framework and follow ethical principles.

Changes in the organizational contexts, more significant stakeholders, and the demand for analyzing companies' information have led to a gradual widening of performance concepts. In this context, more emphasis was attributed to dimensions other than finance, which has transformed the idea of performance into a multidimensional concept, including aspects such as:

- Marketing (Neely, 2007).
- Operations management (Neely, 2007).
- Supply chain management (Neely, 2007).
- Innovation (Neely, 2007).
- Employees, systems and organizational procedures (Kaplan and Norton, 1996).
- Corporate social performance and environment (Stanwick and Stanwick, 1998).

In particular, the second half of the twentieth century has been marked by the rise of quality as a critical dimension of performance (Sibbet, 1997). During the twentieth century, as part of progressively more comprehensive management control systems, companies started to adopt instruments and policies targeting the improvement of specific areas of performance. One of these critical areas was quality. Since the 1950s, several tools initially aimed at improving the quality of manufactured goods and more recently aimed at the quality of services provided. Amongst the most influential instruments are (Sibbet, 1997):

- The statistical quality control for acceptable defect levels (the 1950s).
- The project evaluation and review technique (1950s).
- Critical path method (1960s).
- Robotics and numerical control (1980s).
- Statistical process control for quality (1980s).

- Lean manufacturing (1980s).
- Benchmarking (1980s).
- ISO standards (1980s).
- Process re-engineering (1990s).
- Supply chain management (1990s).

However, notwithstanding the interest in managing quality during the 1950s, quality came to be recognized as a critical area of performance only in the 1980s. Finally, the rise of the New Public Management movement within healthcare is associated with the leading healthcare models of industrialized countries which include:

- The Beveridge model.
 - The National Health Insurance model.
 - The Out-of-Pocket model.
- as well as the rise of healthcare expenditure across these models.

Despite evidence of the escalation of health expenditure within the overall budgets of welfare states observed throughout most of the twentieth century, the issue gained significant political attention only in the 1980s. Until then, the financing of healthcare systems had only sporadically been a topic of discussion. This focus on healthcare expenditure in the 1980s arose when public expenditure started to become a matter of concern. This trend, coupled with the increase of citizens' demand for welfare services, eventually led to claims in the 1970s and 1980s that the welfare state was in crisis.

The New Public Management model replaced the 'Progressive Public Administration' (PPA) concept of public accountability (Hood, 1995), the leading public sector management framework that governed the period from the end of the Industrial Revolution to the beginning of the twentieth century. The PPA has based on the premise that politicians were inherently corrupt and would attempt to use their position to obtain personal benefits (Hood, 1995). As a result of this assumption, the PPA framework advocated two critical principles for the governance of public services (Hood, 1995):

- Public and private sectors were to be distinct.
- Public managers' discretion was to be reduced through detailed procedures and rules.

The NPM was characterized by new forms of public accountability and public administration, which differed from the underlying principles of the PPA framework. It advocated a convergence between the private and the public sectors, including their management styles. Additionally, under the NPM, results and not processes were the basis of accountability. By comparison, the NPM considered markets as functioning entities and thus favored pro-market ideologies and the management methods used in private organizations.

Although many of the changes that were introduced in the 1980s into public sector management are frequently referred to as NPM, it should be noted that the NPM movement encompassed a series of different initiatives. Thus, Ferlie et al. (1996) present four models of NPM:

- The efficiency drive, downsizing and decentralization, in search of excellence and public service orientation.

Facets of the Evolving Healthcare Management Model

- Downsizing and decentralization, in line with the ‘post-Fordist’ model of organization. Associated with this model were the development of quasi-markets and the contracting out of non-strategic functions.
- Strong emphasis on organizational culture in shaping employees’ performance and focusing on managing change processes and innovation. In so doing, it attached relevance to the creation of ‘learning organizations’.
- Prioritizing service quality and user concerns and expectations.

In conclusion, the NPM can be understood as a radical ‘reinvention’ of the welfare state. In healthcare systems following the Beveridge model, reforms initiated in the 1980s led to the introduction of significant changes in healthcare financing and organization. One key distinction that marked the difference between the old ethos and the new paradigm of organizing healthcare systems was that the new paradigm advocated a separation between the financing and provision of care functions.

Another central theme was the shift from professionalism to managerialism, meaning that power was associated with the possession of expertise by a professional group in the past. At the same time, in the latter, the capacity to manage healthcare organizations is attributed to managers as experts in organizational management (Clarke, Gewirtz, and McLaughlin, 2000).

HEALTHCARE QUALITY MANAGEMENT

Interest in the quality of healthcare provision is probably as old as the origins of medicine itself. It is assumed that standards, restraining the influence who was allowed to practice medicine in Egypt and parts of India and China, date back to the first century AD (Zineldin, 2006). In Europe, medical practice licensing can be traced to Italy in 1140 (Zineldin, 2006). These scenarios of professional self-regulation changed in the 1950s, and even more so since the 1980s, as healthcare quality management gradually became a significant area of concern in the provision of care (Komashie, Mousavi, and Gore, 2007). As previously discussed, several interrelated factors contributed to this phenomenon, which ultimately led to various approaches to improving care quality.

One of the conclusions drawn from the thoughtful analysis of the demand and supply of quality of care is that until the middle of the twentieth century, patients were not exerting pressure to improve the quality of healthcare provision. Modest perceptions of the scope of healthcare institutions, the lack of choice and the limited information on health issues available to patients until the beginning of the twentieth century have often been identified as the main reasons for this limited demand in terms of quality of care.

Until the middle of the nineteenth century, medical knowledge was still in its infancy, and there was universal ignorance concerning the causes of disease (Breslaw, 2012).

At that time, it was thought that ‘miasmas’ present in the air and patients’ sinful behavior was the causes of diseases (Koblenz, 2013). Based on the Hippocratic treatise *Airs, Waters, Places* which were part of the Greek tradition (Bynum, 1994), environmental factors such as the wind, climate, temperature, soil or humidity were alternatively seen as an explanation of disease and epidemics.

Despite an increased interest in environmental factors as causes of diseases, a sense of powerlessness of medicine dominated the discourses on healthcare in many countries as late as the beginning of the twentieth century. This fatalistic view of healthcare, which deviates from modern attitudes, profoundly impacted early developments in healthcare management and initiatives to improve its quality.

That manifested in several ways. Firstly, due to the absence of patients and other external stakeholders exerting pressures for quality improvement (Komashie, Mousavi, and Gore, 2007). Secondly, although environmental projects possessed some credibility, their general acceptance by the clinical community depended on how they fit within the underlying assumptions held at that time about diseases, quality of care, and its contributing factors.

At the beginning of the twentieth century, hospitals began to perform an increasingly important function for society. Ideas of organization and standardization of hospitals started to be seen as timely (Hornsby, 1913). That contrasted with the past when quality assurance initiatives only had a limited influence in terms of scope and breadth of improvement. The widespread adoption of comprehensive hospital standardization programs continued. By 1951, the American College of Surgeons' program for hospital standardization led to the Joint Commission on Accreditation of Hospitals (JCAH)¹ (Hanlon, 2003).

The broad dissemination of quality assurance frameworks led to what Palmer and Adams (1993) described as the transition from the 'professional' model to the 'bureaucratic' model that characterized health systems between the 1960s and 1980s. The two models relate to different measures to improve quality and are underpinned by other concepts of quality of care. Within the professional model, quality of care was defined as the absence of defects (until the 1920s), and from the 1920s to the 1960s, as the capacity to meet set quality standards in care provision.

In the bureaucratic model (1960s-1980s), quality started to be perceived as a goal beyond the minimum standards defined in the professional model. The bureaucratic model was thus characterized by escalating the regulations associated with care provision (Graham, 1995).

In the 1970s, healthcare quality frameworks started to take into consideration issues such as 'optimal achievable results, medical necessity, negative indices, unnecessary disease and death or disability' (Graham, 1995) as well as the degree of adherence to standards of clinical practice and expected outcomes (Graham, 1995).

The rise of the New Public Management (NPM) movement in the 1980s challenged the supremacy of quality assurance, giving place to what is known as the 'quality improvement approach'. Within the quality improvement philosophy, the emphasis was put on the analysis of processes and on the expectations of customers (Carey and Lloyd, 1995), which further increased the level of expectations about the quality of care provided.

Two seminal articles published by the US medical doctors Donald M. Berwick (1989) and Glenn Laffel and David Blumenthal (1989) supported applying industrial-quality models to healthcare. Since then, there has been a proliferation of publications advocating quality initiatives into healthcare organizations.

The shift from the quality assurance framework of the bureaucratic model to the continuous quality improvement initiatives entailed in the industrial model implied a change in the philosophy and methodology of quality initiatives in healthcare. The industrial quality improvement model encompassed new quality improvement methodologies and ways of measuring quality and a new underlying definition of quality. Within the industrial model, quality of care was defined as a much more inclusive concept, encompassing dimensions such as (Legido-Quigley et al., 2008):

- Effectiveness.
- Efficiency.
- Access.
- Safety.
- Equity.

Facets of the Evolving Healthcare Management Model

- Appropriateness.
- Timeliness.
- Acceptability.
- Patient responsiveness or patient-centeredness.
- Satisfaction.
- Health improvement.
- Continuity of care.

This new concept of quality of care could be summarized as ‘meeting the expectations’ of a series of healthcare systems actors, which, among others, included the general public, governments, healthcare providers, suppliers, healthcare professionals and patients; the latter being seen as customers within the industrial model. A comparison of this model with the ‘minimum standards’ perspective of the professional model (which was widely used until the 1960s), or with the ‘quality as meeting requirements’ view of the bureaucratic model (which was the mainstream approach between the 1960s and 1980s), introduced a sea change in the concept of quality of care during the 1980s (Graham, 1995).

Healthcare quality improvement came to be considered a continuous process in industry rather than a series of one-off efforts. Additionally, the development object started to be the entire organization, instead of just the quality of the products produced or the services provided.

The implementation of new performance measurement tools affected the adoption of systemic quality improvement approaches in several ways. The introduction of Diagnosis-Related Groups (DRGs) is an example of this interdependency (Lighter and Fair, 2004). Specifically, the use of DRGs supported the opening in the healthcare of methods such as Statistical Process Control (Atkinson, 1994). As a result of adopting these new performance measurements and quality improvement methodologies in healthcare under the industrial model, there was some level of convergence in terms of the management of health systems which, like industrial management, also became more complex.

In line with developments in the industrial sector, the new models saw a decline in clinicians’ authority about managerial cadres. That led to claims that healthcare quality improvement methods under the industrial model supported managerialism in healthcare quality management. Given the chasm between what the professional and bureaucratic healthcare management models entailed, authors such as Shine (2002) have argued that the introduction of the industrial model marked a paradigm change in the governance of health systems (Shine, 2002).

THE LESSONS FROM THE COVID-19 PANDEMIC

The COVID-19 pandemic exerts tremendous stress on management, the formal training of healthcare professionals, their creed to no harm (Siddiqui, 2020), as well as the patient safety movement. So far, we have explicitly been teaching healthcare professionals that the best way of treating a patient is through its vicinity with multiple providers. Moreover, we argue that healthcare education requires a pack of healthcare workers from varied educational backgrounds and training levels for the nuances of a disease. However, the novel coronavirus (COVID-19), a respiratory disease that has spread to many countries around the world, affects not only all aspects of daily life but also the organizational culture and values of healthcare. In this context, healthcare institutions experience absenteeism, change in patterns of com-

merce, and interrupted supply/delivery. In this context, we have given healthcare professionals intellectual, moral, and social instructions to (OSHA, 2020):

- Use ‘hierarchy of controls’ in selecting ways to control workplace hazards.
- Control a hazard by removing it from the workplace systematically.

On the other hand, during the pandemic, healthcare professionals are also in danger as they rank at a very high exposure risk according to the four exposure risk levels of the Occupational Risk Pyramid, which represents the probability distribution of risk. There is also collateral damage of COVID-19 that reaches much farther than those who get the virus (Love, 2020). Specifically, there are ripple effects related to the delay or avoidance of healthcare from fear of the virus leading to complications in surgeries or creating disease burdens that we have to deal with after the pandemic is over. Overall, a broad overview of the implications first includes concerns about national security (McIntosh, 2020). The pandemic took countries by surprise, despite its drumbeat being heard across the globe. As a result, we must invest in health as we do in security. That means rethinking national budgets to dedicate strategic resources to research, development, and training in the medical sector and purchasing and producing materials. The key to success in resisting pandemic attacks is logistics. Second is the crucial importance of collaboration between citizens and official institutions and understanding that the idea of a public good is interrelated with personal autonomy ideas. In Western democracies, there is a constitutional limit to the obligations imposed on citizens, hence the importance of personal responsibility. The third element is mobilizing technology, while the fourth challenge is retaining and building upon the changes in delivery, particularly remodeling service delivery. New roles have emerged that have the potential to enhance independence and increase health autonomy for practitioners. These maxims have come to the fore with the medical and health professions fulfilling the goals of the value-based agenda through integrated provision (Bromley and McIntosh, 2016). The fifth element is combining big data and creating operational models of a national learning health system. There is a data-driven transformation of health policy and planning, service delivery and evaluation, and provision. A multidisciplinary effort is also essential to design, characterize, and evaluate interventions shaping behavior, especially self-management (Cottom, 2020). Self-management can be defined as a set of steps that aim to enable individuals to feel that they can live well with a long-term condition on their terms. Such methods include a spectrum of support to help patients learn about their condition, acknowledge its impact on their lives, make changes, and identify areas where they require additional support. One of the mechanisms responsible for these improvements in health status is self-efficacy (Moumtzoglou, 2019). Adherence to medical treatment is closely linked to the patient’s ability to self-manage their chronic pain and is shown to be an essential factor in increasing self-efficacy (Nicholas, 2007). Furthermore, looking towards the post-pandemic future, it is clear that chronic disabilities could be an outcome for those who have survived COVID-19 infection. Ultimately, this will cause additional pressure on pain management clinics, many of which are already months or years behind, as they begin to look at the resources such as waiting lists. Following on from this, there is certainly a growing need to provide a more diverse service for chronic pain patients. It is also imperative to ensure that future service delivery includes continuing monthly supported self-management sessions containing face-to-face and online service provision elements. It must also be highlighted that not everyone experiencing chronic pain needs a referral to a secondary care chronic pain clinic. It is also of decisive importance to take proactive steps in building emotional resilience and minimizing workplace stress. That means being good role models by looking after ourselves, supporting

individual emotional needs and acting to ensure our organizations adapt working practices where needed. That is best done when models of supervision are holistic and feed upwards to information systems. To facilitate a resilient organization and workforce and avoid mass burnout, line managers must have the expertise and time to undertake high-quality supervision and enable debrief. Moreover, we must not forget the potential for burnout and prioritize meaningful, well-articulated supervision to continue supporting and building the staff. Finally, as hospitals and health systems respond to and recover from the impact of COVID-19, their strategic and financial plans will inevitably change. Similarly, the organization's available capital capacity and the prioritization of projects in its allocated capital portfolio will need adjustment. Nonetheless, the underlying process of capital allocation and management should stay the same, relying on the fundamentals of structure, discipline, rigor, and skill to accommodate necessary changes. Last but not least, the COVID-19 pandemic has created unique challenges for the healthcare systems due to the staggering mismatch between capacity and patient demand. The healthcare industry adopts digital innovation slowly due to the conventional belief that humans need to be at the center of healthcare delivery tasks. However, in the setting of the COVID-19 pandemic, artificial intelligence (AI) is used to carry out specific tasks such as pre-hospital triage and enable clinicians to deliver care at scale. A summary of worldwide technological efforts during the pandemic in 2020 included (Meskó, B., Dhunnoo, P., 2020; Moutzoglou, 2020):

- Microsoft launched an interactive Bing map, which details the number of active, recovered and fatal cases globally and countrywide.
- BlueDot, which first sounded the alarm back in December 2019, uses artificial intelligence (AI)-based algorithm that identifies the trend, which epidemiologists then analyze.
- Alibaba developed a new AI algorithm that detects COVID-19 infections from CT scans of patients' chests with 96% accuracy.
- The UAE collaborates with telecom companies to set up the first virtual hospital in the Middle East, while the CDC and WHO advocate telemedicine to monitor patients and reduce risks.
- In Italy, Paginemediche launched an online chatbot developed to support remote triage of potential COVID-19 cases.
- South Korea's authorities used data from CCTV footage, bank transaction and phone use to locate people exposed to COVID-19 in managing the outbreak.
- Singapore launched the TraceTogether app., as a community-driven means for contact tracing.
- Headspace was offering its Premium option of the mental wellbeing app. for free, through 2020, to healthcare professionals working in the US public health.
- Owners of wearables from companies like Apple, Fitbit and Garmin can help spot viral outbreaks and aid healthcare authorities to take prompt actions by opting for the DETECT study.
- The WHO to raise awareness about the coronavirus among younger audiences used TikTok.
- Open-sourced masks and mechanical ventilators for milder symptoms were 3D-printed in Spain. Moreover, in Italy, a 3D-printing startup supplied hospitals with valves required to connect respirators to oxygen masks as the company making those had trouble keeping up with the demand. In a similar vein to open-sourcing designs for 3D-printing medical equipment, other communities are leveraging the power of the community to fight COVID-19 with free resources.
- Foldit is an online computer game where players can solve puzzles by folding protein structures without prior biochemistry knowledge. The University of Washington Institute for Protein Design in Seattle will test and manufacture the best ones.

- In China, e-commerce giant JD.com deployed self-driving robots to deliver medical goods to Wuhan. Moreover, the startup Shanghai TMIRob sent robots to disinfect wards, intensive care units and operating rooms in hospitals. Back in January, doctors in a US hospital used a robot to assist them in taking vitals of a patient infected with the COVID-19 virus. Robots are repurposed in Thailand to measure patient fever and allow physicians to communicate with patients via video call. The Belgian robotics company ZoraBots provided their robots, free of charge, to care centers to assist elderly contact remotely.
- Researchers working with the gene-editing tool CRISPR were taking an interest in the COVID-19 fight. Scientists from the New York Genome Center and New York University have recently published their findings on a new technique using CRISPR to suppress gene expression.

Furthermore, during the COVID-19 pandemic, several countries developed makeshift hospitals by converting public venues to medical facilities, aiming to substantially upgrade the health system's capacity in very little time. This change management capability is among the fundamental elements of infrastructure futureproofing. Finally, Medical 4.0, which is now emerging as the fourth medical revolution (Haleem & Javaid, 2020), represents:

- The applications of electronically supported information technology.
- Microsystem.
- High level of automation.
- Personalized therapy.
- Artificial Intelligence (AI).

Moreover, robotics is evolving in healthcare and allied areas with unique concerns relating to managing and controlling the spread of the COVID-19. The prime utilization of robots is to reduce person-to-person contact and ensure cleaning, sterilization and support in hospitals and similar facilities such as quarantine.

Taking heed of the previous processes, we argue that:

- Leadership style becomes a critical aspect of management after the pandemic.
- There is a need for wise motivation, as professionals should appreciate their work.
- The proper and balanced workload for employees should be redefined.
- Peer support should be encouraged.
- Wellness and mental health should be ensured.
- Exemplary teamwork should be built.
- Employee control over their work should be increased.
- Achievements should be reviewed regularly.
- Unnecessary gatherings at work should be cancelled.

Overall, shared leadership will play a fundamental role in improving healthcare performance through social capital.

HEALTHCARE MANAGEMENT AND COMPLEXITY SCIENCE

The Covid-19 pandemic prompts us to consider that we live in a highly unpredictable and complicated world. It has presented many challenges, including managing the supply chain for personal protective equipment (PPE) and adjusting workforce capacity to cope with financial loss. Amid these challenges lies healthcare leaders' opportunity to better position and transform their organizations for a future of unpredictable surprise.

The Covid-19 pandemic is a clear demonstration of the ability of a minor, surprise event in one part of the world to influence the daily operations of medical practices and hospitals around the globe. Three dimensions can characterize a surprise event (Begun & Jiang, 2020):

- The complexity of its source.
- The speed of its spread, and
- The unpredictability of its scale and impact.

Faced with these acute challenges, health care organizations can find guidance in complexity science which is the multidisciplinary study of complex systems composed of interacting agents and units within a boundary. These systems are complex because the agents and teams within the system are highly interdependent, heterogeneous, and dynamic.

Complexity science studies how complex systems change over time or adapt to external environmental changes. From a complexity science perspective, the external environment is interrelated to and coevolves with the organization instead of being independent of it. The environment is highly unpredictable because of the complex and nonlinear relationships among many of the environmental elements. A complex system's adaptation to a sudden change in the environment is hastened when agents and units are qualified and empowered to react to external events and supply real-time feedback to decision-makers. Complex adaptive systems manifest feedback loops between agents and the environment through which information travels and leads to minor changes, nurturing learning capacity and continuous adaptation.

Overall, complex adaptive systems are similar to an organism, with self-awareness, the desire to survive, and the ability to adapt to environmental changes.

The prospect of organizations as complex adaptive systems is fundamentally different from the traditional view of organizational systems, as machines produce outputs through tightly controlled and standardized processes. Instead, complex adaptive systems are built for adaptation, flexibility, and learning (Begun & Jiang, 2020).

"Simple rules" such as underlying cultural norms and values help ensure that agents and units react to change in a timely and coordinated manner. Relatively broad guidelines or constraints are imposed on the system from the top-down management. As a result, agents and teams have substantial autonomy to respond to change. That means responses will vary from system to system, which is 'customized' to local needs.

Sensemaking, the process by which people understand their collective experience, is critical in complex adaptive systems. It is essential in times of distress and uncertainty. Guidelines such as 'use simple rules', 'set simple rules', and 'provide minimum specifications' demonstrate the futility of micromanaging unpredictable and emergent events.

The concept of simple rules was popularized in health care with the "Ten Simple Rules for the

21st Century Health Care System' promulgated by the Institute of Medicine's 'Crossing the Quality Chasm' report in 2001. Rephrased examples of the IoM's ten simple rules include 'establish the patient is the source of control', 'use evidence-based decision making', and 'consider safety as a system property'.

Organizations that are internally highly connected encompassing elements of their environment are the most adaptable to 'connect' and 'build connections', which accelerate the flow of information and share resources in times of surprise.

As a result, complexity science emphasizes communication, collaboration, and innovation, carried out expeditiously by frontline information and evidence (Begun & Jiang, 2020). Extensive communication, collaboration, and innovation need to happen quickly in response to significant surprises. Underlying conditions necessary for a quick response include pre-existing structures and cultures that encourage widespread and diverse participation on the frontlines of care.

Moreover, reports of effective responses to the Covid-19 pandemic often include formal leadership's general attitude of 'humility'. Humble leadership requires complex adaptive systems because the future is unknown, and sensemaking is a communal activity.

Overall, COVID-19 introduced an exponential threat to the theory and practice of quality.

Applying linear models to human systems, healthcare management, and quality has improved our understanding of their system structure and function. However, such models often fall short of explaining experimental results or predicting future abnormalities in complex nonlinear systems, which help dissect and analyze individual system components.

Nonlinear models may better explain how the individual components collectively act and interact to produce a dynamic system in constant flux (Moumtzoglou, 2020). They also assist in filling in some of the results which linear models do not adequately explain. Chaos theory also provides new insights into standard as well as abnormal behavior within systems. Applications of chaos, especially fractals, may detect disease in its early stages and proves valuable in managing illness. At the same time, the pursue of complexity theory provides new insights regarding the genetic encryption of the environment in the context of biological evolution, cellular automata, and modulation of protein production using biological pulse signals (Lewin, 1999).

However, as not all medicine is nonlinear, linear modeling should not be abandoned, as the use of both models is complementary and leads to a complete understanding of system behavior. We could easily consider the integration of linear and nonlinear theories in healthcare quality and management in this context. We can draw the initial conditions of chaotic behavior from the standardization of the linear theory. Moreover, we can distinguish between desirable and undesirable variation relegating statistical process control only to issues of high certainty regarding the outcome.

Finally, given the critical role complex systems play in daily life, their understanding, mathematical description, prediction, and eventually, control is one of the significant intellectual and scientific challenges of the 21st century. The advent of Network Science is a clear demonstration that science can live up to this challenge (Barabási, 2016).

Network Science is rooted in the discovery that despite the apparent diversity of complex systems, the networks' structure and evolution is driven by a standard set of fundamental laws and principles. Therefore, notwithstanding the striking differences in form, size, nature, age, and scope of real networks, most networks are driven by common organizing principles.

Management also tends to rely on the informal network, capturing who communicates with whom. Furthermore, accurate mapping of organizational networks can help identify individuals who play an essential role in bringing different departments and products together and exposing the lack of interactions

between critical units. There is also increasing evidence that employee's productivity is determined by their position in the informal organizational network (Wu et al., 2008). Therefore, numerous companies offer tools and methodologies to map out the actual structure of an organization. These companies provide a host of services, from identifying opinion leaders to reducing employee churn, optimizing knowledge and product diffusion and designing teams with the diversity, size and expertise to be the most effective for specific tasks.

In the same direction, modern healthcare has explicitly accepted and internalized the idea of a network by adopting:

- The transparency of quality.
- The infrastructure of cross-continuum connectedness.
- The renaissance of accessibility.
- The integration of ecosystem partners.

From a contrasting perspective, Statistical Process Control (SPC) is an optimization philosophy and a set of procedures for continuous improvement developed in the 1920s by the physicist Walter Shewhart (Thor et al., 2007). The SPC approach has been founded in the theory of variation. It uses the Shewhart charts, which are more commonly called 'control charts', and incorporates the concepts of:

- The analytic study, process thinking, and prevention.
- The stratification, stability and capability.
- The experimentation, data collection, and measurement.

However, under the circumstances of network science, it is noticeably obsolete.

SPC charts in the presence of autocorrelation, and data pattern, do not detect and classify the fault correctly. As a result, many researchers propose substitute methods for process monitoring. Neural networks are massively parallel computing mechanisms emulating the human brain, which are satisfactory for various applications. In recent years, they have been applied in statistical process control (SPC).

Psarakis (2011) discusses issues concerning the combination of Statistical Process Control (SPC) and neural networks as well as the use of neural networks in:

- The detection and determination of mean and variance as well as in the pattern recognition.
- The correlation of data.
- Multivariate control charts.

Moreover, Fu (2013) acknowledges that network surveillance algorithms are increasingly important due to their ability to monitor a wide variety of data. Traffic metrics count data that display a non-stationary pattern in their mean structure. In this context, she develops three tracking statistics for anomaly detection. Two of the statistics are variants of a Bartlett-type sequential probability ratio approach:

- The first statistic is based on the approximation to the integrated likelihood.
- The second is based on the concept of h-likelihood.

She also considers a tracking statistic of an exponentially weighted moving average. Finally, she argues that the two Bartlett-type probability ratio variants are preferred SPC tools for network surveillance.

CONCLUSION

The pandemic represents an opportunity to reimagine future healthcare and rethink healthcare management unbound by preconceived notions based on the following three main drivers that emerged during the pandemic. These include transformed business models, new care delivery models disrupted by ubiquitous data and technology, intelligent spaces and digitally-enabled hospitality. Although sadly, we need a catastrophe to rethink (Moumtzoglou, 2020):

- The fundamentals of healthcare quality.
- Patient safety.
- Flexibility.
- The power of technology.
- Bold decision making, and
- Innovation.

It is imperative to reexamine all facets of healthcare management, considering that applying linear models to human systems, healthcare management, and quality has improved our understanding of their system structure and function. However, such models often fall short of explaining experimental results or predicting future abnormalities in complex nonlinear systems. Nonlinear models may better explain how the individual components collectively act and interact to produce a dynamic system in constant flux (Moumtzoglou, 2020). They also assist in filling in some of the results which linear models do not adequately explain. Finally, chaos theory might provide new insights into standard as well as abnormal behavior within systems.

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About the Contributors

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