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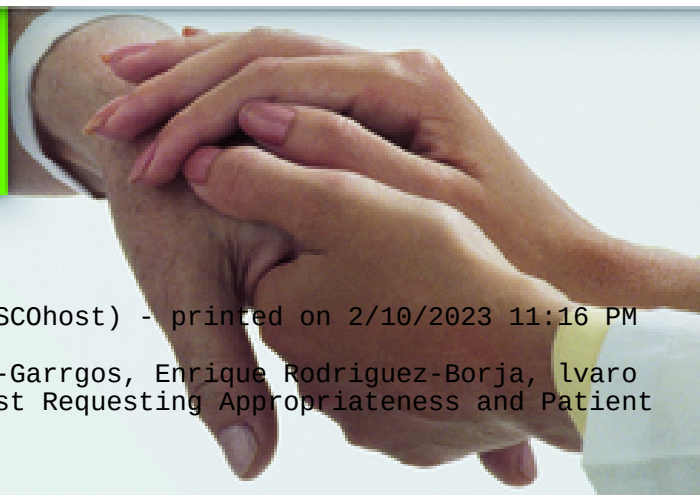
LABORATORY TEST REQUESTING APPROPRIATENESS AND PATIENT SAFETY

PATIENT SAFETY



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Preface

Sciences in Clinical Laboratory have taken a dramatic turn in recent years. The laboratory has moved from being a supplier of laboratory data to a provider of clinical information crucial for the diagnosis and monitoring of most diseases. Today, the Clinical Laboratory is a pillar in clinical decision-making.

Indeed, clinical data from the Clinical Laboratory is the most frequently involved in clinical decision-making and patient management. The time has come for us pathologists to leave the Laboratory walls "to get the most" of every laboratory tests request, working together with clinicians.

Two facts have clearly changed the way we should work and think; first, our role in those 70% of clinical decisions; second, the fact that errors in the request of laboratory tests are the most common among laboratory errors.

Regarding the former, the appropriate selection of laboratory tests has become one of the main goals for clinicians and medical societies, and one of the main daily tasks of the laboratory staff; not only to achieve the most efficient diagnosis and/or treatment monitoring, but also to enhance patient safety.

The main goal of this book is to raise awareness of the importance of this topic. What are the negative consequences of a potential under- or over- request of laboratory tests? How can we achieve an appropriate request? What are the advantages for patients and society?

I believe this is a unique book, and I hope you will enjoy reading the book as much as we did writing it. I also desire that reading this book will encourage you to embark in this fascinating journey of improvement of laboratory tests requests, towards the goal of a better decision making and improved patient safety.

María Salinas
October 2016

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María Salinas

1 Introduction: clinical laboratory contribution to patient safety

The global medical process is a chain of different medical multidisciplinary procedures. Success of global patient safety will depend on the safety of consecutive medical processes that intervene in this complex system.

Laboratory data are an essential part of healthcare. Indeed, it is used in 70% of clinical decisions [1]. However, as a global medical process, clinical laboratory is also a multiphase procedure, called "brain-to-brain loop" or "total testing process" (TTP) [2]. It begins when the ordering physician figures out the appropriate tests to be requested, according to relevant medical history and physical examination, and ends when he thinks, again, how to interpret the test results.

The first step is crucial. Inappropriate laboratory test requesting is extremely frequent. Although over-requesting is widely studied, the prevalence of under-requesting has been less considered. What they have in common is that both can produce devastating damage to the patient. Proper laboratory utilization contributes to patient safety. The consequences of under-requesting are clear – we are missing a diagnosis. Nevertheless, inappropriate over-requesting does not only result in excessive laboratory expenditures. It also has other adverse effects. The consequences of false-positive results due to over-requesting will not only generate additional costs from the unnecessary diagnostic procedures, patient referees, and treatments, but also patient anxiety. In addition, inappropriate over-requesting may have contributed to the considerable increase in volume of laboratory tests over the last years. This overload causes the laboratory to be commoditized, making it very difficult to pay necessary attention to appropriately requested tests and deliver meaningful clinical laboratory information instead of simply laboratory data [3]. In fact, there is a real danger for the laboratory to become a data-dispensing machine instead of a modern organization issuing personalized, individualized information. Finally, unnecessary laboratory test results can hide or mask clinically important laboratory information – test results that are necessary to clinical decision making [4].

In all, there is general consensus that the inadequacy of test requesting must be corrected through strategies and monitored over time through indicators to assure the optimal laboratory contribution to clinical decision making and patient safety.

The action of getting an appropriate test request refers to applying everything that is right and appropriate, taking into account its own peculiar characteristics.

Each laboratory test is a diagnostic tool by itself. It has some unique features. Furthermore, its behavior changes in every setting, according to the different contexts. In fact, it has different uses and characteristics, when used as a diagnostic, monitoring, or prevention tool, and even in each disease, with its inherent individualities

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such as sensitivity and specificity. Moreover, a test may show very different results, depending on the cutoff point decided as suitable for dichotomizing the population into healthy or sick, or even depending on disease prevalence. Hence, the intervention of laboratory professionals, with their expertise in laboratory tests and their participation, in this critical step of the TTP is crucial.

Smellie defined "inappropriate test" as a test that "could reasonably be avoided at no significant detriment to a patient's care" [5: p. 586] and adaptation, modulation, or demand management when using a health resource to maximize their utility [6].

When talking of appropriating laboratory test demand, it is important to differentiate the term "restricting demand", which is associated with strategies that lead to a lower test demand and that consequently has an important economic connotation, from the term "modulation or management", which is used to ensure that proper request is done.

Traditionally, the term "inappropriate request" refers to test over-requesting [7]. However, currently, it is also considered as inadequate requesting due to under-requesting [8, 9]. In this context, getting a proper demand does not only refer to a decrease in unnecessary over-demand, but also to an increase in requests for appropriate tests. The correction of test over-request will decrease laboratory expenditures. However, when establishing strategies to solve test under-request, we are also increasing laboratory expenditures, but it is when greater savings can be achieved, which should always to be checked through a continuous monitoring of the strategy through process indicators, but especially through patient outcome results.

Consequently, an appropriate test request is not always synonymous with savings in the laboratory. In this context, the use of outcome indicators that are mainly related to improvement of patient diagnosis or quality of life or merely cost savings to assess the benefit to the patient or the overall healthcare system is crucial.

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Maite López-Garrigós

2 Inappropriateness in laboratory test requesting in the literature

The objective of this chapter is not to produce an exhaustive review of the literature because excellent reviews [narrative [1–7] and systematic [8–10]] already exist on the matter. The main objective is to show the increasing interest in the literature for the appropriate use of laboratory tests. Proof of this interest is the growing number of results that are obtained when a search is carried out through PubMed using the keywords "appropriateness" and "clinical laboratory" (Fig. 2.1).

Reduction in healthcare budgets has led to pressure to reduce healthcare costs. Laboratories are one of the main targets for cost containment [11]. The number of diagnostic tests ordered is growing, and many of these tests seem to be unnecessary according to established, evidence-based guidelines. The number of unnecessary tests in the clinical laboratory ranges from 5% to 95% of the total number of laboratory tests [8]. On more than one occasion, the terms "inappropriateness" and "overutilization" are used synonymously; however, the available evidence suggests that underutilization is more frequent than overutilization (44.8% versus 20.6%, respectively). This result was obtained despite there being only one-fifth the number of studies on underutilization as on overutilization in this review [9]. The same fact is also observed in another previous review [8]. This

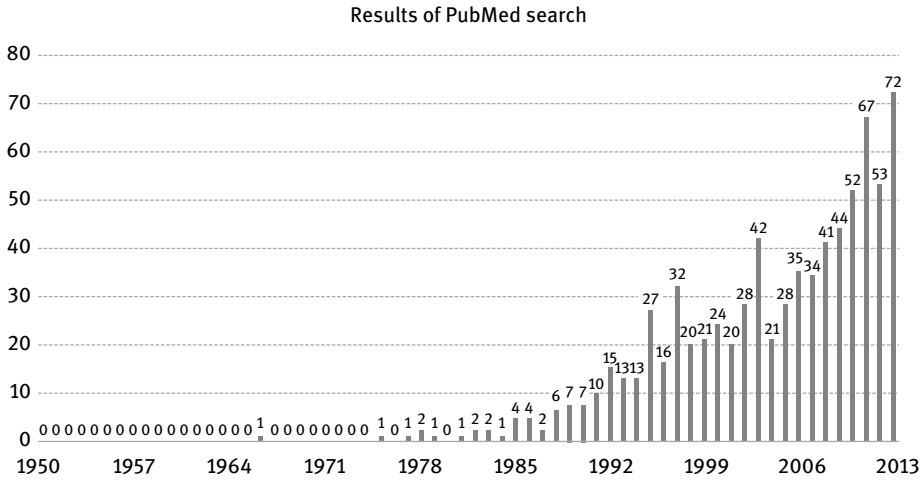

Fig. 2.1: Number of results per year in PubMed using "appropriateness" and "clinical laboratory" as a keywords. Source: Medline; August 2014

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imbalance in representation could be due to great importance being given to the overutilization of laboratory tests historically.

The volume of laboratory testing would not be a concern if increased growth were coupled with effective laboratory utilization and improved patient outcomes. Observations indicate that increased testing does not correlate positively with improved care, which is the real problem. Appropriateness is a complex concept, and managing it requires an understanding of which different factors are relevant.

2.1 Laboratory process-test request

The total testing process (TTP) is based on the "brain-to-brain loop" concept described by Lundberg [12, 13] (Fig. 2.2).

As shown in Fig. 2.2, this process begins with the clinical question in the mind of the doctor and ends with the interpretation of the result and the decision making by the same doctor. Connecting these two actions, we found six steps: collection, identification (at several stages), transportation, separation (or preparation), analysis, and reporting. Traditionally, these activities have been integrated in three perfectly differentiated phases (pre-analytical, analytical, and post-analytical phases). Some authors have introduced the phases pre-pre- and post-post-analytical for test ordering, interpretation of the result, and clinical decision making to differentiate these phases of the classical pre-analytical phase (sample collection and transport) and of the post-analytical phase (report of the results) [14, 15].

Recent studies suggest that the highest incidence of laboratory-related errors occurs in these phases (pre-pre and post-post) [14–19]. Although the laboratory has direct control only over some steps, it is responsible for the entire process, and any error in the sequence is considered a laboratory error.

In the last decades, with increased automation in manual processes occurring in laboratories, a reduction in the number of laboratory errors has been observed. However, this finding is mainly focused on the "intra-laboratory" phases, especially in the analytical phase [20]. Otherwise, in the pre-pre and post-post-analytical phases, they have not made many efforts to reduce the number of errors in ordering appropriate diagnostic tests or to improve the interpretation of laboratory tests [21].

Laboratory data are involved in 75%–90% of clinical decisions about diagnosis, treatment, or prevention; they are critical to the clinical decision-making process [22]. These data provided by clinical laboratories directly impact the treatment received by patients, making it a priority for the laboratory to promote and encourage investigations into laboratory medicine errors and into procedures for improving patient safety [23] to reduce their error rates and promote an excellent level of quality.

Carraro et al. [24] reported large variations in estimates of inappropriate laboratory use (4.5%–95%). Additionally, other authors indicate that almost two thirds of laboratory tests commonly ordered in an academic internal medicine department could

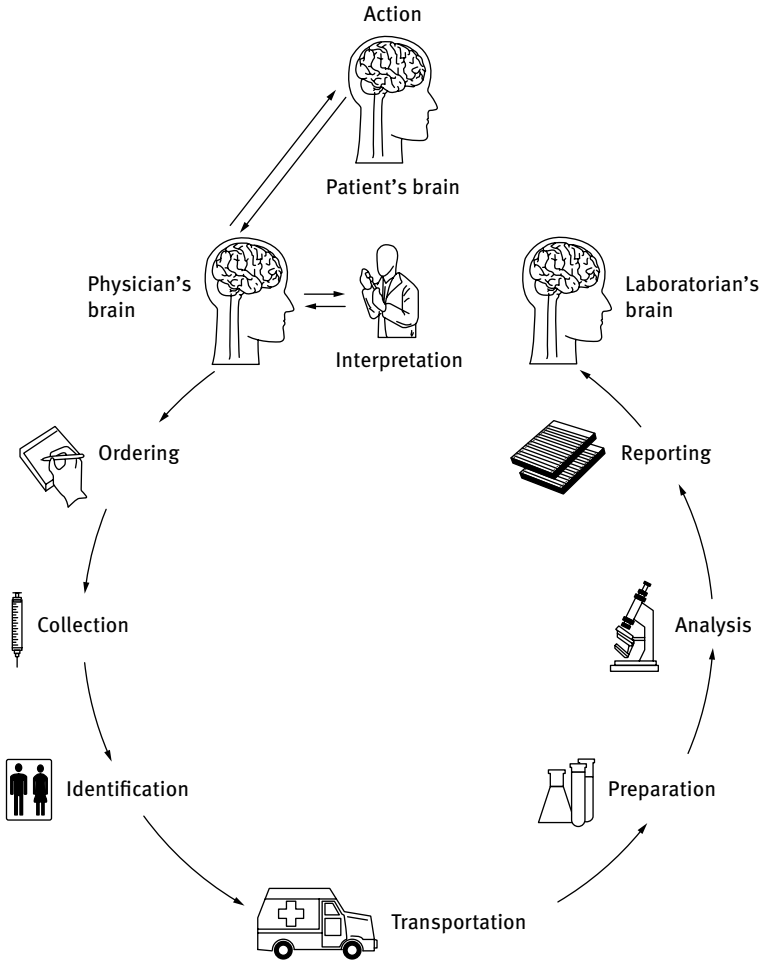

Fig. 2.2: Brain-to-brain loop: total testing process. With permission from Plebani M, Laposata M, Lundberg GD. The brain-to-brain loop concept for laboratory testing 40 years after its introduction. Am J Clin Pathol. 2011;136:829–33

have been avoided because those data did not contribute toward the management of patients [25].

In this scenario, it has been suggested that between 25% and 40% [26, 27] of all laboratory tests sent to the laboratory are questionable and between 16% and 30% [26, 27] can be regarded as inappropriate retesting.

The causes of inappropriate requests are multiple, and among them, the following have been indicated: indiscriminate use of non-agreed-upon, routine laboratory test profiles; tests that provide similar clinical information; lack of awareness of recommended repeat testing intervals; uncertainty in the patient diagnosis or in the test

indication; lack or ignorance of guidelines and of the appropriate use of new markers; and lack of awareness of the cost of testing. Although the cost of a test may be individually low, the request of numerous non-indicated tests eventually can generate high costs. However, sometimes, the laboratory gives the impression that testing is easy and inexpensive. It is very curious that this happens in an era in which evidence-based medicine prevails [28].

2.2 Definition of inappropriate requests

Another challenge concerns the question of defining "appropriate laboratory test ordering".

Fryer et al. [29: p. 63], in an excellent review regarding demand management for laboratory tests, categorize, define, and quantitate the inappropriate request:

> *A request (implying what is ordered by the requestor) that is made outside some form of agreed guidance (including those requested too late).*

This definition implies reference to some agreed guidance, and this itself can create challenges. In some cases, there is great variability in the timing of some tests, both among laboratories and between requestors, even in identical clinical scenarios [30].

Causes of inappropriate requesting include wrong patient, wrong test, wrong time, and wrong process [27].

Although in some cases the inappropriateness is clear (e.g. prostate-specific antigen determination in women), in other cases, recommendations or guidelines (evidence-based) can be needed, such as in diabetes mellitus for which the National Institute for Care and Excellence (NICE) provides guidance on testing intervals [31, 32].

Another way to establish if the test is pertinent or not is to arrive at consensus with the requestor based on literature reviews, on the sensitivity and specificity of tests, on the cost of investigations, on the recommended repeat testing interval, etc. [33].

Nevertheless, in many of the more common situations, the laboratory does not have sufficient clinical information to determine whether a diagnostic test is or is not appropriate. Therefore, the main cause of the inappropriate request is the lack of requestor-laboratory communication. This not only causes inappropriateness; unnecessary laboratory test results can hide or mask the clinically important laboratory information, i.e. those test results that are necessary for clinical decision making. Appropriate laboratory testing is a key factor to ensure patient safety.

2.3 Causes of inappropriate test requests

Whiting et al. [34] performed a search to identify qualitative studies in the area of diagnosis and to consider the reasons and context for laboratory test ordering.

The authors identified five key interrelated factor groupings that influence a doctor's decision to order a test for a particular patient: diagnostic factors, therapeutic and prognostic factors, patient-related factors, doctor-related factors, and policy and organization-related factors. Each one of the factors can affect the test request.

Therefore, the causes of inappropriateness (Fig. 2.3) can be attributed to the following factors [29]:

- The laboratory
- The requestor
- The patient
- The system

2.3.1 Laboratory

There are many reasons for inappropriateness, and there are a number of factors that contribute to the generation of an inappropriate demand [35]:

- Introducing new tests without evidence that proves their efficacy and effectiveness.
- Not eliminating poor or useless tests from the laboratory repertoire.
- Providing poor turnaround of test results.
- Request forms that include large numbers of tests and profiles (this policy has resulted in overutilization).
- Laboratories performing tests that were not requested (such as by reflex testing).
- In most healthcare systems, laboratories are run more as an industry than a medical specialty.
- The laboratory giving the impression that testing is easy.

The repetition of laboratory tests contributes to the excessive and inefficient use of the clinical laboratory; however, this situation is easily avoidable [36].

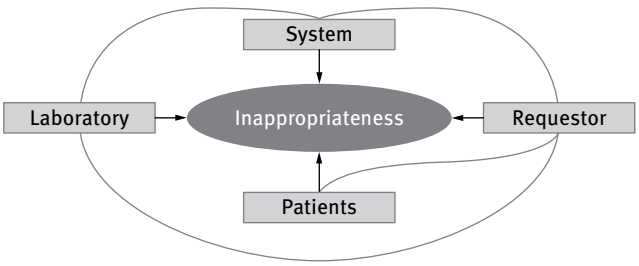

Fig. 2.3: Causes of inappropriate test requests

Test repetitions can occur for several reasons: the previous result is unknown [37–39], the physician is unaware that the test has already been requested, or routine request habits exist at the margin of clinical reasoning [40].

Test repetitions are widespread and costly [41]. In a study on the prevalence and burden associated with the repetition of the eight most frequently requested tests, Van Walraven concluded that repetitions could represent 30% of the total monthly demand. Today, even the standard practice of repeating a critical result seems unnecessary because similar results are always produced, which only delays physician notification of the result and increases laboratory costs.

2.3.2 Requesting physician

When we discuss inefficiency, all eyes are often on the requesting physician. As we will see, although the requesting physician might be responsible for the inefficiency, he/she is not the only actor involved in the process.

Certain interventions or medical decisions are currently more dependent on diagnostic tests than clinical skills.

If a requesting physician knows the basic concepts of testing (sensitivity, specificity, receiver operator characteristic curves, predictive values, biological variability, etc.), he/she can significantly reduce inefficient test requests as well as errors in the interpretation of test results. Although it is easier to attribute ignorance to the requesting physician, the laboratory can and should contribute to the avoidance of this problem by providing these test characteristics to requesting physicians.

The concept of biological variability is one of the keys needed to correctly request and interpret laboratory tests [42, 43]. Mastering this concept will make the requesting physician the master of additional laboratory concepts, including the timing of request tests, repetition intervals, reference intervals, and the clinical significance of the difference between two consecutive results.

Reference intervals are the most popular decision tool for the interpretation of laboratory reports [44]. However, this concept can be misinterpreted in several ways by the requesting physician. Unfortunately, reference intervals cannot be used to define exactly one value that confirms or rules out disease. Normal (or healthy) and reference intervals are not synonymous. In fact, using only the definition of the reference interval, 5% of the healthy people in the reference population (the extreme values) are excluded from the calculation of the reference interval. In addition, a result within the reference interval does not always signify that the patient is healthy, and a result outside the reference interval does not always indicate sickness.

We can only use the reference interval for comparing the patient's value with a selected "healthy" reference population. This comparison enables physicians to obtain extra information that must be evaluated together with the general condition of the patient and the characteristics of the test.

The following limitations of reference intervals should also be taken into account: the inability of many laboratories to establish their own reference values, the difficulty of obtaining reference values for specific groups (children, pregnant women, and/or the elderly) or analytes (lactic acid in cerebrospinal fluid), and the potential for calculating a reference interval from a population that significantly differs from the one the laboratory serves [45].

Requesting physicians often order redundant tests that provide identical information. Inefficient test repetition is more common with hospitalized patients [41]. Certain analytes should only be requested once during a patient's lifetime (except when laboratory error is suspected) because they never change (karyotype, genetic studies, Rh, human leukocyte antigen [HLA], etc.). To define a repetition interval, the characteristics of the test must be used, i.e. the half-life, metabolism, reference value of the change, etc. We have previously seen, for example, that the NICE guidelines for the study of diabetes mellitus types I and II [31, 32] recommend determining HbA1c levels at 2- to 6-month intervals, which is based on the mean lifespan of red blood cells (120 days).

Laboratory societies have published guidelines for defining the repetition intervals of specific laboratory tests [46]. However, a lack of knowledge remains concerning the recommended repetition intervals for the majority of laboratory tests [47]. This problem could be reduced by using clinical guidelines and reviewing requests by the laboratory.

Physicians routinely requesting groups of tests regardless of the patient's clinical situation can also influence laboratory demand. Historically, test profiles have been organ-based (liver, kidney, and thyroid profiles), providing a set of tests that offer information about the status and functioning of one particular organ. Specific disease profiles [27] are intended to simplify and standardize the common test requests necessary for the diagnosis or monitoring of a specific pathology. These profiles are established by consensus by the requesting physicians and the laboratory. However, disease profiles present more disadvantages than advantages. Although they are established with the consensus of the laboratory, they are not always based on evidence. The 2011 report of the National Pathology Benchmarking Service, which includes approximately 50 laboratories in the UK, demonstrated that up to 12 different hepatic function profiles were in use [48].

Another factor that results in request inefficiency is physicians monitoring the clinical course of a disease with a higher frequency than that which is recommended and physicians extending requests or requesting new tests due to abnormal test results without any interest in monitoring the patient.

Finally, increasingly defensive medicine is practiced today. The increase in malpractice claims against medical professionals, who, in turn, take unusual measures to avoid being sued (or for their defense, if they are sued) leads to the practice of defensive medicine, which involves practicing medicine with the intent of avoiding medical malpractice complaints [49]. This objective is achieved by performing an excessive number of diagnostic tests to rule out extraordinary situations (when there is another reasonably clear diagnosis).

2.3.3 The patient

With respect to the patient, it appears that the pressures exerted on the physician by the patient for diagnostic tests may condition the requesting doctor to order them. Thus, the patient has the inaccurate perception that "something is being done".

In fact, the current trend is toward a patient-centered healthcare model, which involves the patient and physician in joint decision making.

2.3.4 Factors inherent in the system

The pressure to reduce the mean length of a hospital stay and the rapid exchange of patients may contribute to the inefficiency of requests for laboratory tests.

In addition, new surgical techniques such as transplantation and the creation of special units can contribute to the problem.

2.4 Reducing inefficiency in the laboratory diagnostic process

Reducing inefficiency in requests for laboratory tests is desirable for several reasons, the greatest of which is the concept of cost/opportunity and achieving maximum information with fewer tests [50]. Additional motivations for reducing inefficiency include the following:

- The enormous increase in the demand for laboratory tests, which are being requested in all countries [51], and above all, the soaring variability of these requests in different populations, which cannot be explained by demographic, social, or other factors [52].
- Improvement of the clinical outcome of the patient, which also produces health economy savings in general [53] (particularly when decreasing inefficiency due to errors) by promoting the early diagnosis of certain diseases that may improve their prognosis and quality of life and lead to a decrease in costs for the health system overall.
- Decreasing the cost of an inefficiently requested test. A laboratory test itself might be inexpensive; however, if it belongs to the group of diagnostic technologies referred to as the "little ticket test", it contributes to high health expenditures because it is requested in very high quantities [54].
- Decreasing the costs associated with false-positive results. A laboratory test that is generally inexpensive can have very expensive results in the long run if a false-positive result is generated. This occurs most straightforwardly in populations with a low prevalence of the disease (positive predictive value of the low test) or, due to the statistical nature of the reference values, as Rao's paradox states, an

exponential increase in false-positive results caused by an increasing number of test requests [55]. The false-positive result also generates Ulysses syndrome [56], or "imaginary invalid syndrome" [57, 58]. Strategies focused on reducing demand, and consequently, false-positive results, will improve patient safety [59]. Reducing false-positive results not only decreases the costs of other diagnostic tests and unnecessary interventions, which are generally more expensive than those of the laboratory, but also collateral costs, such as the patient's loss of working hours and quality of life.

- Improvement in the interpretation of laboratory tests. At present, the results of tests with high diagnostic value can be obscured by those of tests that serve "appearance" purposes, thus confirming the paradox that increasing test requests can decrease the value contributed by the laboratory [60].
- Obligation of the laboratory professional. Since the introduction of the concept of the laboratory as a brain-to-brain loop [12] or TTP [61], it is the "duty" of the laboratory professional acting outside its walls to consider their role from the time the doctor requests an analysis until he/she interprets it [62].
- Improvement of the efficiency of other hospital processes. Because the laboratory is a central service that also intervenes in many medical procedures, resolving the inefficiency of laboratory test requests will collaterally enable other hospital processes to improve their inefficiency [29].
- The resources generated for the establishment of emerging tests with high diagnostic power.

2.5 Tools described in the literature for the management of the demand for laboratory tests: before, during, and after the request

The major challenge consists of managing physicians' demands for laboratory tests. Several studies have investigated this challenge, with variable degrees of success.

The currently available tools for managing laboratory demand are given below. These strategies are framed on modulating the demand prior, during, or after the test request.

2.5.1 Before

2.5.1.1 Portfolio review services

The portfolio of clinical laboratory services should be standardized; however, several factors make this situation difficult to achieve [27]. Consequently, each laboratory constantly reviews its portfolio of services to match emerging needs [63], eliminating obsolete tests and incorporating new determinations.

2.5.1.2 Educational strategies

There are numerous references in the literature to educational interventions, including both verbal and written initiatives [2, 27, 64, 65]. In information session interventions, the laboratory informs the requesting physicians about changes to the catalogue of services, obsolete tests, recommended repetition intervals, and other items related to the laboratory tests. These sessions should be prepared in conjunction with clinicians for the management of specific clinical conditions. For example, the laboratory, together with specialists in digestive medicine, can inform physicians about the latest recommendations and clinical guidelines for celiac disease. They can also share periodic bulletins with the requesting physicians. However, the literature suggests that the effectiveness of these measures is variable [5, 6]. For example, CRP requests from the emergency laboratory of the University Hospital of San Juan decreased after the implementation of a request protocol associated with diverse medical specialties (Fig. 2.4). However, after a few months, physicians' demands for CRPs increased [66]. Therefore, these strategies require exhaustive monitoring on the part of the laboratory.

2.5.1.3 Request forms

The design of the request form, either in paper or electronic format, has been used as a strategy to manage demand [5, 6, 67–70]. At present, paper request forms are being

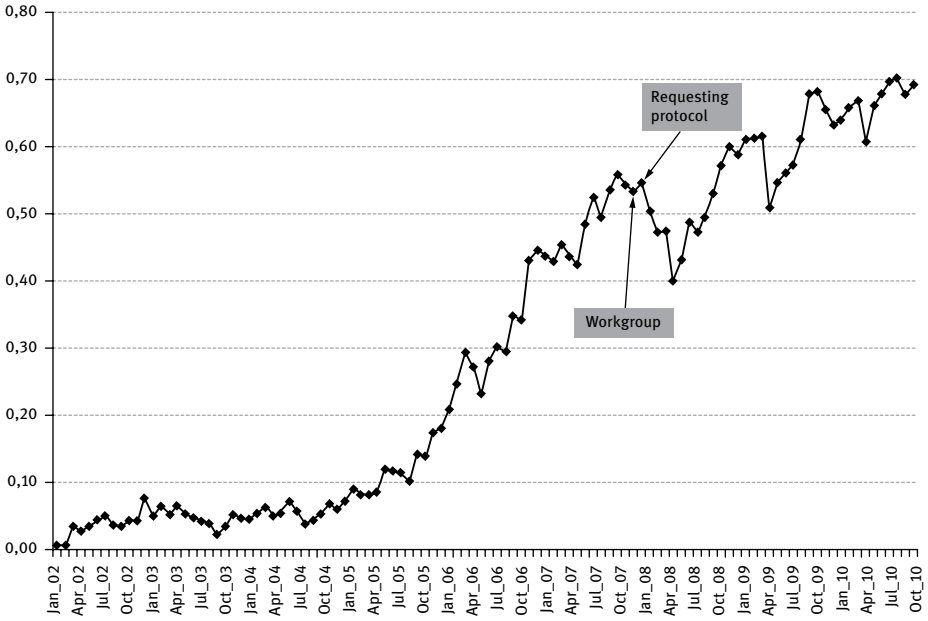

Fig. 2.4: CRP requests from the emergency laboratory of the University Hospital of San Juan before and after of educational strategies

used less frequently than electronic request forms, giving us a wide range of opportunities for managing demand.

2.5.1.4 Test profiles

Test profiles vary across different laboratories [71]. The ideal profile does not exist, and profile differences can cause confusion and affect patient safety [72]. Removing tests that provide little information from the profiles can save money, avoid physician requests for additional tests, and reduce confusion for doctors [73].

2.5.1.5 Clinical guidelines or protocols

Protocols and clinical guidelines that include a request for analytical testing should be consensual and jointly defined by the requesting physicians and laboratory professionals, following, if available, the recommendations of scientific societies and published systematic reviews [74].

2.5.2 During the request

The context for a laboratory request is basically limited to the electronic request linked to the patient's clinical history, and its implementation depends on the possibilities and capabilities of the respective information systems available at each health center [74].

Addressing the laboratory test's support of the clinical decision and ensuring proper testing are increasingly relevant tasks for the laboratory professional. The complexity of test selection is aggravated by increasingly busy physicians with less time than ever before for each appointment and patient. Software tools may be able to mitigate these challenges [75].

Useful software tools can help decrease the number of unnecessary test repetitions [76] via alert messages to the requesting physician. More complex measures have also been described for guiding the requesting physician toward the most appropriate test [77, 78].

These software tools can be informative or restrictive. Informative tools inform the requesting physician about a characteristic of the test or patient so they can reflect on whether to request it or not; these tools can show the cost of the test, generate notices of excessive request frequency, describe tests as redundant, or provide indications of diagnostic utility. Restrictive tools limit the request for the test based on, for example, recommended minimum time intervals.

Strategies that are implemented during test request formation are considered to be the most powerful [79] because they are implemented from a quantitative

perspective and require less maintenance by the laboratory. In addition, their effects are more sustained over time because they do not depend on ambient factors, such as the inevitable relaxation of the habits for requesting physicians or permanent staff changes.

2.5.3 After the request

Once a request is made, the appropriate strategies are difficult to implement without an automatic computerized solution due to the high volume of samples that are handled by laboratories today.

Clearly inappropriate tests may be rejected (such as repetitions of HLA, karyotype, etc.) after a request has been made. Clinical justification may be required for the request of certain tests with very limited indications, little scientific evidence, or high costs.

2.6 The future: where we are going

Clinical laboratories should develop strategies for managing test demand. Ideally, these strategies should include institutional or professional association support if they are to be adopted by all laboratories in a standardized form.

Laboratory professionals should resume contact with requesting physicians; only a close collaboration between the two can lead to appropriate strategies to adjust laboratory test demand.

There is a need for more research on the effectiveness of adaptation strategies, the repetition intervals of tests, and the impact of these approaches on clinical outcomes.

Today's current financial constraints have increased interest in the management of test demand, and this presents a great opportunity for jointly improving patient care and reducing costs.

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Álvaro Blasco

3 Causes and negative effects of inappropriateness in laboratory test requesting

3.1 Introduction

Laboratory medicine has huge impact on diagnosis and patient management, as 75%–90% of all diagnosis are made on the basis of laboratory tests [1]. The information provided by clinical laboratories impacts directly on the treatment and management received by patients, making it a priority for clinical laboratories to reduce their error rates and promote an excellent level of quality [2].

The last few decades have seen a significant decrease in the rates of analytical errors in clinical laboratories. Currently, laboratory errors have a reported frequency of 0.012%–0.6% of all test results [1] owing to laboratories' efforts to enhance patient safety through a range of improvements such as increased automation of manual processes, introduction of systematic internal quality control and external quality assurance program, among others.

We focus the improvements of these interventions "inside" the laboratory, especially on analytical phase [3], but we reduce the intensity of the efforts "outside" the laboratory like improve the communication, thereby making pre-pre- and post-post-analytical phases more vulnerable to laboratory errors [4].

In this sense, in the era of evidence-based medicine, it is striking that the rates of inappropriate test requesting ranging from 4% to 95% [5] is one of top five causes of pre-analytical errors [6]. Two thirds of common laboratory investigations ordered during hospitalization of patients did not influence management decisions [7].

An "inappropriate request" is a request ordered by the requestor made in the wrong patient, at the wrong time, in the wrong way, or is for the wrong test, outside some form of agreed guidance [8].

Different mechanisms for laboratory-related diagnostic errors have been defined [9]:

- Inappropriate test is ordered.
- Appropriate test is not ordered.
- Appropriate test result is not properly utilized.
- Appropriate test result utilization is delayed.
- Appropriate test result is wrong.

It seems that these errors are outside the control of laboratory because an "expert" requests the test and the laboratory have unquestioning faith in the order. Analyzing the causes of inappropriate request and measuring the rates of errors, we would change our mind.

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The main causes of the inappropriate request are ineffective clinical-laboratory communication with an improperly feedback and unawareness of test characteristics that do not allow correct interpretation.

It demands a proactive laboratory attitude working together in multidisciplinary team to reduce this vulnerability in patient safety. The laboratory is a key partner in assuring patient safety.

In this chapter, we analyze in detail the causes of the inappropriate request to realize the implication of the laboratory medicine and to serve as a prelude for the discussion, in the next chapters of the book, of the interventions to solve the root causes of conflict.

3.2 Causes of inappropriateness in laboratory test requesting

The reasons for inappropriate request by clinical, include clinician's unawareness about the test, communication between clinical and laboratory, and other causes [10–12].

3.2.1 Clinician's unawareness about the test

3.2.1.1 Test concept: characteristics and use

Sensitivity and specificity: It is assumed that tests are not always perfect. It could cause false-negative or false-positive results. But if physicians know some basic test concepts [sensitivity, specificity, receiver operator characteristic (ROC) curves], the ratios of and inadequate test interpretation and request would improve.

Sensitivity and specificity are internal characteristics of a test. Sensitivity is the percentage of individuals with disease who have a positive test result, and specificity is the percentage of individuals without disease who have a negative test result.

It is important to know that sensitivity and specificity are influenced by many factors:

- Disease stage: severe stage is easier diagnostic and improves the sensitivity.
- Clinical variables or demographic variables with together are known as "illness spectrum bias" [13], e.g. women suspected to have coronary heart disease do not behave like men in the stress test.
- Illness prevalence. Most times, illness is neither black nor white. Also, tests are not always perfect; thus, the probability of misclassification of subjects with values close to the cutoff value (decision threshold) is higher [14]. Generally, when prevalence increases, sensitivity increases as well, but specificity decreases.
- Measurement process characteristics: precision, inaccuracy
- Population characteristics.

For any given test, there is always a trade-off between sensitivity and specificity, such that choosing a cutoff value for a particular test that maximizes sensitivity occurs at the expense of specificity [15].

In some cases, it may be desirable to use a laboratory test with high sensitivity while sacrificing "some" specificity or vice versa. Generally, if the risk associated with failure to diagnose a particular disease is high (e.g. acquired immunodeficiency syndrome), false-negatives are unacceptable and only a laboratory test with high sensitivity is acceptable. Meanwhile, if a disease is potentially fatal and no therapy, other than supportive care, is available (e.g. cystic fibrosis), false-positives would be unacceptable [15].

ROC curves provide a useful tool in assessing the diagnostic accuracy of a laboratory test because it shows the relation between sensitivity and specificity and provides information on test performance at all decision thresholds [16].

A diagnosis based on only one test is rare. Normally, physicians request more than one test. Requesting many tests affects the interpretation and number of false results.

There are two criteria for requesting a set of test: serial requests or simultaneous requests (all at once).

Serial requests cause an increase in global specificity (more than each individual specificity test) and a reduction in global sensitivity (less than each individual sensitivity test). It is the criteria of an expert requestor.

Simultaneous requests produce the contrary effect: reduction of global specificity and increase of global sensitivity. It is the criteria of an inexperienced requestor, which is generally afraid of a false-negative result and requests many tests, looking for increased sensitivity, thus causing many inadequate test requests and increasing the number of false-positive results.

Consequently, one of the general rules of laboratory test utilization is: "Too many good tests are the same as one bad test" [17].

Predictive values: However, sensitivity and specificity do not have a direct use in clinical practice. We need to define positive and negative predictive value to answer the question: What is the probability of a patient having a positive (or negative) test result if this patient has (or has not) disease X?

Positive predictive value (PPV) is the percentage of individuals with a positive test result who truly have the disease, and negative predictive value (NPV) is the percentage of individuals with a negative test result who do not have the disease.

Both depend on the prevalence of disease. If there is an increase of the prevalence of disease, PPV increases and NPV decreases, and vice versa.

Physicians who perform excellent history taking and physical examination could appropriately select patients on whom the test should be performed, increasing the predictive value of laboratory tests. Consequently, one of the general rules of laboratory test utilization is: "Laboratory testing is for sick people" [17].

Likelihood ratio and Bayes theorem: The more challenging question facing clinicians, however, is: What is the probability of this patient having disease X if the test result is positive (or negative)? [18].

Likelihood ratio is as a way of quantifying how much a given test result changes the probability of disease in your patient. More exactly, it is the factor by which the odds of disease either increase or decrease as a result of your test.

Combining suspected diagnosis by examination (prior probability) with likelihood ratio test by Bayes theorem (probability theory), we could obtain posterior probability to answer the question.

Physicians suspect a diagnosis (prior probability) and request the test, obtaining subsequently a result that increases or decreases substantially them suspects (posterior probability). Consequently, one of the general rules of laboratory test utilization is: "If you ask a stupid question, you get a stupid answer" [17].

In this sense, the "treatment threshold probability" generally says [19: p. 1110]:

- If the prior probability of disease is very low (the no-treat-test threshold), then even if the test is positive (or high), the post-test probability will still be low (the treatment threshold), and you would not treat the patient, so no test is requested.
- If the prior probability is very high (the test-treat threshold), then even if the test is negative (or low), the post-test probability will be above the treatment threshold, and you would treat the patient despite the negative test result.
- If the prior probability is not very low or high, the test may be indicated, because it at least has the potential to affect management.

However, it is not so easy because we also have to contemplate the consequences of the decisions, especially the costs:

- How bad is it to treat someone who does not have the disease?
- How bad is it to fail to treat someone who has the disease?
- What is the cost (cost of time, money, health) of the test?

3.2.1.2 Biological variation

Life is not a static condition. There are many physiological changes inherent to growth, aging, pregnancy, menopause, and other normal circumstances that occurs daily, weekly, or over the years. As a reflection of these changes, many of the quantities measured in laboratory medicine change over the span of life.

The biological variations of the human body components examined in laboratory medicine (analytes) are of three types: variation over the span of life, predictable cyclical variation that can be daily, monthly, or seasonal in nature, and random variation.

Each person's setting point may be different from another's, and the overall variation resulting from this difference is known as between-subject or interindividual biological variation [20].

Knowledge of the concept of biological variation is one of the keys to a properly request and interpretation of laboratory test. With this knowledge, the requestors will understand other laboratories concepts: when to request the test, repeat testing intervals, reference intervals, or evaluating the clinical significance of changes.

3.2.1.3 Reference intervals

The reference interval principle is the value interval of an analyte of a group of healthy people chosen using stated selection criteria. It is important to know that it is based on selected people with the criteria considered by the authors of the study.

It is usual to take the central 95% of a reference population [21] with some exceptions: the 99th percentile of a healthy population for cardiac specific troponins [22], the glucose concentration associated with risk of the development of diabetes and macrovascular diseases [23] or therapeutic intervals for therapeutic drug monitoring.

Because of biological variation, the population-based reference values may need to be stratified in the majority of the analytes into subgroups according to age, sex, race, or other demographic variables [24].

Reference intervals are the most common decision support tool used for interpretation of numerical pathology reports [25]. However, this concept is misinterpreted many times by the requestor of the test.

We cannot use this concept to define exactly the value to determine illness. Normal interval (or healthy interval) and reference interval are not synonyms. In fact, 5% of healthy people of the reference population of the study, the extreme values, are taken off in the calculation of reference interval.

A result inside the reference range does not always mean the patient is healthy; similarly, a result outside the reference range does not always mean patient has a disease. Sometimes, the clinician does not understand it.

We can only use the reference interval to compare the value of the patient with a reference and selected population that is considered as "healthy". This comparison lets the clinicians obtain extra information that have to be considered along with the general status of the patient or the characteristics of the test.

Other limitations should also be taken into consideration: the impossibility of some laboratories to made their own reference values, the difficulty in obtaining reference values in some groups (children, pregnant, elderly) or in some analytes (lactic acid in the cerebrospinal fluid), or the adoption of reference interval made in a population very different from the population assisted by the laboratory [26].

Because of the reference interval limitations, other concepts have been developed to assist in clinicians in decisions such as decision limits, likelihood ratios, or reference change value (RCV), but the information obtained should also be interpreted along with the clinical status of patient, characteristics of the test, and other causes of variability [26].

3.2.1.4 Repeat testing intervals

Repeat testing interval is one of the main causes of inappropriate laboratory test requesting. For instance, inappropriate requesting of glycated hemoglobin (HbA1c) is widespread, and in some cases, 21.3% of the request are unnecessary [27].

Inadequate repetition was more common in hospitalized patients, varied extensively among tests, and was concentrated in a limited number of people [28]. Even the practice of repeating a critical test appears unnecessary, as it yields similar results, delays the notification of the treating clinician, and increases laboratory running costs [29].

Some analytes should only be requested once in patient's life (except if the clinicians suspect a laboratory mistake) because they never change like karyotype, blood type, mutation analysis, polymorphisms analysis, some antibodies (Rh), or human leukocyte antigen typing.

To define the repeat test interval, analytical data (such as analyte half-life, metabolism, or RCV) can be utilized. It is known, for example, that erythrocytes have a lifetime of 120 days, so the UK National Institute for Care and Excellence guidance for types I and II diabetes mellitus recommends HbA1c testing at 2- to 6-month intervals [30, 31].

Some laboratories societies published guidance to define recommended retest intervals for some analytes: 1 day for liver function test, 21 days for tumor markers, 28 days for ferritin, 28 days for thyroid function test, 28 days for lipid profile, etc. [32].

However, there is a lack of awareness of recommended repeat testing intervals in the majority of the analytes [33].

In addition, while this approach may appear straightforward, differences arise between primary and secondary care as routine tests performed in primary care can be simplistically divided into those used for monitoring or diagnosis, whereas, in the acute phase, the minimum retest interval is dependent on the clinical state of the patient in addition to previous results [8].

Nevertheless, this problem could be reduced with the use of guidance, making the requestor aware of it and the review of the request by the laboratory.

3.2.1.5 Critical difference between consecutive laboratory test results

Physicians frequently order the same test at multiple time points during the course of the patients' management. They are faced with the challenge of interpretation when the magnitude of change in values of an analyte is significant enough to affect medical decision making.

It is necessary to know the possible causes of the change: disease process, biological variation, imprecision of the measure, or random error.

Fortunately, most assays for a wide variety of analytes have excellent precision, <5% to 10% coefficient of variation (CV), such that the influence of biological variation in the difference between consecutive test is normally higher than the imprecision of the test.

Knowing the precision of the measure CV and the biological variation CV, we could calculate the RCV. If the difference between consecutive laboratory test results is not included in the RCV, the main cause of the difference is the disease process, but we also discard random error [34].

3.2.1.6 Specialist request

High rates of unnecessary laboratory tests have been recorded in pediatric [35], surgical [36], and even emergency departments [37], as well as in intensive care units. The reasons could be the urgency of the request, the difficulties in the management of the patient, defensive behavior, and fear or uncertainty.

In addition the lack of knowledge or the lack of specializationis a cause of an inappropriat request. In this sense, the resident do more mistakes requesting than experiment specialist or attending doctor do more mistakes than specialist [38].

3.2.1.7 Appropriate collection

Incorrect sample collection represents one of the most widespread reasons for request rejection [39]: 1.5% of samples were rejected, and 5% of these had results with critical values [40].

The quality standards for sample collection (sample container, patient's pre-analytical conditions) should be defined and available in a local guide or laboratory book for the phlebotomist.

3.2.2 Communication between clinical and laboratory departments

3.2.2.1 Request form

Request form design: The design of the request form has long been a potential target for demand management strategies [41–44].

There are many details that influence the increase in inadequate demand of the test: the request form with tick boxes generate a higher demand of test compared with the request form where the test should be written; tests that are written on the top of the paper are more demanding; color marks in the request form could generate more demand; writing the name of the test could generate errors.

However, these issues have largely been superseded by the issues arising from the implementation of electronic test requesting, which is addressed in more detail later.

Nomenclature: Central to the process of optimal selection test is the physician's ability to correctly decipher laboratory test nomenclature as seen on an order entry screen or requisition, so that she can correctly order the best possible test [45].

It is not always easy because there are different ways to call the same test: synonymous, abbreviation, colloquial name, biochemistry name.

For example, some of the nomenclature options for vitamin D are vitamin D2, vitamin D3, 25-OH vitamin D2, 25-OH vitamin D3, 25-OH vitamin D, 25 hydroxy vitamin D2, 25 hydroxy vitamin D3, 25 hydroxy vitamin D, 1,25(OH)2 vitamin D2, 1,25(OH)2 vitamin D3, 1,25(OH)2 vitamin D, 1,25 dihydroxy vitamin D2, 1,25 dihydroxy vitamin D3, 1,25 dihydroxy vitamin D, vitamin D 25 hydroxy D2, vitamin D 25 hydroxy D3, vitamin D 1,25 dihydroxy, calcifdiol, calcidiol, and cholecalciferol.

3.2.2.2 Methods to request

Profiles: Historically, these have been organ-based profiles such as the liver, kidney, and thyroid, which provide a set of tests that offer information about the state or functioning of the organ system, harmonizing these different profiles. There are also disease-specific profiles [8].

The objective of the profiles is to establish an easy and uniform way to request the common tests necessary to diagnose/following a pathology agreed between clinicians and the medical laboratory.

On a balance, the profiles have more disadvantages than advantages. They are made with the consensus of the laboratory and clinicians of a few centers and are not always based on current medicine evidence; they have limitations to request some tests and not others; they are too general in some cases; and there are huge differences between laboratories.

The 2011 report from the National Pathology Benchmarking Service, which included approximately 50 UK laboratories, demonstrated that 12 different "liver function test" profiles were used [46].

Use of profiles to request generate overutilization and underutilization of the laboratory test.

Protocols and guidelines: The guidelines are procedures by which to determine a course of request test, based on the current medicine evidence, and made by a group of experts (scientific societies, national consensus, scientific institution).

Theoretically, the guidelines are an optimal method to obtain an adequate request. However, there are some suggestions that the effectiveness of clinical guidelines in influencing clinical practice depends on the way in which the guidelines are implemented [47].

To ensure a long-term sustained effect, the support of the directors and supervisors to implement the change, the adaptation of the guideline into the center, the continual review of the guidelines, and the continual education of the requestor are necessary [48].

Without careful planning, monitoring, and reinforcement, the general impression is that long-term effectiveness is somewhat limited [49] and result in an increase rather than a decrease in inappropriate requesting [50].

3.2.2.3 Reflexive test

Creating protocols for the sequential addition of tests based on earlier results improves diagnostic accuracy and reduces diagnostic delays and patient inconvenience while reducing test volume [51].

Reflexive tests offer the opportunity to select desired tests and ensure that, first, important tests are not omitted, and second, by offering a default set of investigations, it potentially reduces the likelihood of inappropriate tests being added [8].

The improvement in diagnostic accuracy is linked to the threshold criteria and varies with the clinical scenario; thus, simple algorithms can easily become more and more complex [52] and could generate, in some cases, inadequate tests.

3.2.2.4 Laboratory report

Lab report format: There are some aspects that are difficult to understand in laboratory reports and generate future inadequate request.

Some of these aspects are lack of reference intervals, inadequate information in laboratory report, previous results that are not easily available, absence of interpretive comments, absence of marks calling attention to critical values [53].

Inadequate educational feedback: Good communication between clinicians and laboratory is critical to patient safety. Unfortunately, when communication breaks down, patients are at risk [54].

There is a lot of knowledge in the laboratory that it is not communicated. Clinical laboratory consultants must add value to the results [55] and give feedback to the physicians to assure a correct interpretation of the test and to reduce the inadequate request [56, 57].
Criteria for providing interpretive comments are necessary [58] when

- a decision on treatment is indicated by the results in combination with the clinical details provided;
- a result is unexpected;
- a specific question has been posed, but it is not obvious whether the results provide the answer;
- a clinician has requested a test with which he/she is not likely to be familiar.

3.2.2.5 Test result not available

Test result delayed: Timely and accurate communication of results is central to ensuring that appropriate action is taken, especially with critical values, a value that represents a pathophysiological state that is life-threatening unless something is done promptly [59].

A delayed test result supposes a risk for the patient, and also it's a cause of unnecessary request.

A delayed test tends to cause that clinician's request again the same test, because of the urgency, believing that the result will be brought forward.

Difficulty in accessing test result: The inability to access previous results, limitations of laboratory and/or hospital, logistical restrictions (usually information technology) on ability to develop selective requesting, or faulty data gathering result in an increase in inadequate test request [60].

3.2.2.6 Lack of follow-up of test results

The lack of follow-up of test results is defined as having a test result noted as pending at discharge in the inpatient medical record but is not acknowledged in the outpatient chart.

Failure to follow up test results increases the risk of missed or delayed diagnoses and causes inadequate request. This may produce suboptimal clinical outcomes [38] with potential medicolegal implications [61, 62].

The extent of failure to follow up ranged from 1.0% [63] to 22.9% of inpatients [64] and from 20.04% [65] to 61.9% [38] when reported per test type, and some of the tests have never even been seen [66].

Some causes of lack of follow-up of test results are the following: many members are involved in ordering tests; forgetting a requested test; unaware that a test had been ordered; handoff from the inpatient physician to the outpatient physician; poor computer data system [38].

In hospitals where multiple team members are involved in ordering tests, systems must be in place to ensure that the persons responsible for test follow-up are aware of all tests that have been ordered and have results pending at discharge [38].

3.2.2.7 Misleading result

In the face of misleading results, physicians prefer to repeat a test, order more tests, refer to a specialist, or review practice guideline instead of asking a laboratory professional [54, 67].

3.2.2.8 Inadequate time to request the test

There are many causes of a wrong time request: circadian rhythm, inadequate work organization, and clinician requestor.

Circadian rhythm: Following the concept of biological variation, many analytes have predictable cyclical variation because their regulation are affected by outside influences such as light-dark (cortisol, thyroid-stimulating hormone, or renin), day of the month (follicle-stimulating hormone, luteinizing hormone, progesterone), season of the year (vitamin D), or metabolism (glucose, insulin, peptide C). This is what is known as circadian rhythm. The concentration variation of some of these analytes, which are dictated by regular time intervals, is perfectly known.

It is necessary to know the proper time to collect the sample in order to obtain the maximum information of the test and interpret them correctly. The appropriate time to investigate a cycle must be defined by the laboratory, following their generated reference values [68].

In addition, the absence of predicted rhythms may indicate the presence of a disease. For example, Cushing disease, the 24-h cortisol secretory pattern is characterized by a lack of normal circadian variation [69].

Inadequate work organization: Inadequate test ordering is statistically significantly higher on weekdays compared with weekends even though the patient population remains constant [70]. Ordering frequencies on Monday and Friday were shown to be statistically significantly higher than on other days.

This finding is postulated to be due to inadequate organization. Clinicians request a number of tests on Fridays, many of them unnecessary, because the workforce is decreased to a minimum on weekends; thus, clinicians adopt a defensive behavior in order not to fall short of requesting.

On Mondays, they have to make up for lost time and request more test than necessary.

Moment of the request: It is interesting to note that almost two thirds of the investigations ordered beyond the first 24 hours of hospitalization did not seem to have contributed to diagnosis, whereas only approximately one fourth of tests ordered on the first day in the hospital seemed to be redundant [7]. The percentage of tests ordered beyond the first day, for which inadequate rationale was provided, is striking and can be explained in the context of reports on laboratory overuse from emergency departments [37].

A similar situation occurs in tests requested at night or "out-of hours". Some laboratories implemented a scheme whereby out-of-hour requests were processed only following a discussion between the requesting consultant and consultant-level laboratory staff [71, 72].

3.2.3 Others

3.2.3.1 Patient features

Certain patient characteristics could pose difficulty in doing appropriate medical exploration, creating bias in inadequate request: age (children and elderly), consciousness, uncooperative, deceptiveness, prolonged hospitalization, unfavorable outcome (defined as death or lack of diagnosis), and rare clinical case [7].

In addition, a patient of a particular stereotype is sometimes assumed to have a diagnosis common in that type, leading to incorrect test request and diagnosis [73].

3.2.3.2 Appropriate person

The phlebotomist should ask the patient (or the assistance of ward nurse, legal guardian, parent, or accompanying person) to state the full name and compare the obtained information with the information on the request form to avoiding doing the test to the wrong person.

3.2.3.3 Clinician's unawareness of the cost of examinations

Sometimes, the medical laboratory gives the impression that testing is easy and inexpensive. Disseminating information of the cost or volume information to users of laboratory services [74, 75] could generate awareness of adequate test request and would encourage physicians to concentrate on the quality of their investigations, but it is unlikely that this information alone will be the key driver [76].

3.2.3.4 Inadequate test catalogue

Inadequate test catalogue refers to unavailable tests and lack of consensus on removal of outdated tests [8].

3.2.3.5 Difficult to collect the sample

A test that involves a difficult to collect sample (e.g. arterial blood or cerebrospinal fluid) usually have fewer inadequate request.

3.2.3.6 Some more

- Patient or peer/supervisor pressure
- "Fashion" test: new publication or the last congress
- Eagerness to publish
- Defensive behavior, uncertainty, or fear of litigation

3.3 Negative effects of inappropriateness in laboratory test requesting

In the era of evidence-based medicine, the causes of inappropriateness test requesting are striking.

Following the "Swiss cheese theory" [77], it is difficult not only to know the direct consequence of an error in the laboratory test request, but also to estimate the risk for the patient.

Inappropriateness test requesting violates the safety of the patient and causes unnecessary patient discomfort, unnecessary blood draws and other sample-collection procedures [78], entails the risk of generating false-positive results [79], incorrect diagnoses, increased costs [80], and adverse outcomes due to unwarranted additional intervention [81], thus overloading the diagnostic services, wasting valuable healthcare resources, and leading to other inefficiencies in healthcare delivery, undermining the quality of health services.

Summarizing, we could quote Epner and Astion [9: p. 7], "The impact is the same: delayed diagnosis, delayed or inappropriate treatment, increased costs and patient harm".

We need to build a collective awareness of the importance of this responsibility and must put together clinical teams to solve the root causes of the problem.

Thus, improvements in appropriateness of requesting should be reflected in (a) savings in the wider health economy, (b) improved clinical outcomes, (c) better patient quality of life (from reduction in unnecessary phlebotomy episodes and improved clinical outcomes), and (d) wider societal benefits such as fewer lost working day [8, 82].

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4 Strategies to correct inappropriateness in laboratory test requesting

4.1 Introduction

Population growth, aging population, community expectation and exigencies regarding healthcare, and expansion of chronic diseases are putting pressure in health resources. The present background causes difficulties to all the process actors. Medical providers have a short time to ensure correct anamnesis and screening related to test selection. In addition, some medical providers are insufficiently training, the cost of their requests is barely known or without financial management goals, and some are prone to practice defensive medicine [1, 2].

Patients, meanwhile, are increasingly demanding additional tests based mostly on what they read on the Internet.

Technology automation has allowed the laboratory scientist to process a huge number of samples and generate a great amount of results with short turnaround time. Although this has occasionally led to a passive attitude, transforming their role into a biological product receiver and data issuer rather than a medical professional who is trained to give the optimum test screenings and accurate diagnosis [3].

Despite the increasing availability of laboratory tests and the massive capacity to analyze multiple biological magnitudes, a big amount of data generated does not necessarily lead to patient clinical benefit.

It is hard to determine the number of inadequate test orders. Published estimations are very different. In a recent meta-analysis of published studies related to inappropriate utilization between 1997 and 2012, 20.6% of overuse (95% CI, 16.2%–24.9%) and 44.8% (95% CI, 33.8%–55.8%) of underuse have been estimated [4]. Carter report on NHS laboratory services (pathology services) estimates that, in the UK, 25% of the ordered tests were unnecessary [5]. If we consider the low in vitro diagnosis (IVD) expenses in the UK (Fig. 4.1), it might be assumed that there is a larger number of avoidable tests in other developed countries. To give an example, US expenses are five times proportionally higher than those of the UK [6]. A great variety in costs is evident among USA and developed European countries in terms of the IVD per capita related to gross domestic product and total healthcare expenditure (Tab. 4.1). In addition, big differences are shown even within the same country regions [4, 7–15].

Currently, efficient test-ordering management represents a professional challenge and will remain so on the future. For countries with universal national health system based on social solidarity, it also means an ethical commitment.

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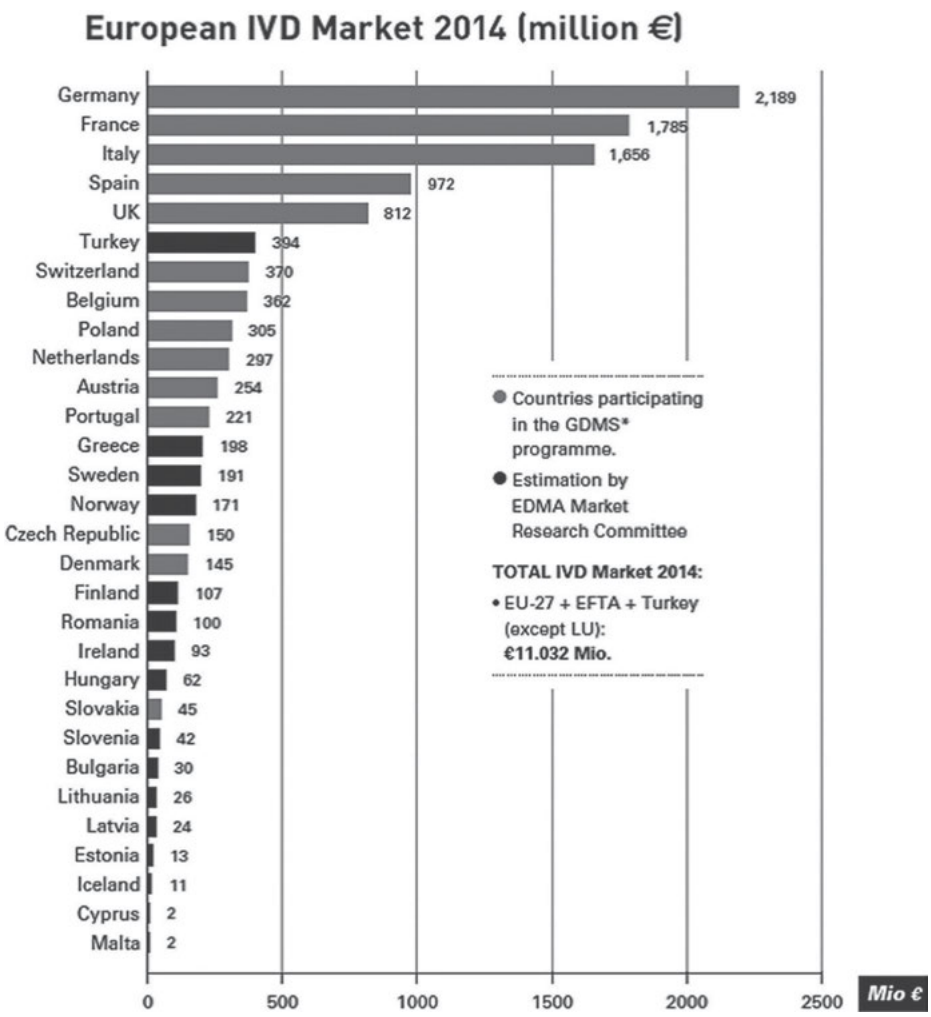

Fig. 4.1: IVD Expenditure in Europe. European IVD market statistics 2014, page 4. MedTech Reports. http://www.medtecheurope.org/ index.php/node/703

4.2 Types of strategy to correct inappropriateness in laboratory tests

Plenty of experiences on strategies to correct inappropriate laboratory testing utilization have been promulgated. The majority is geared toward individual actions, but there are also institutional initiatives, such as the Quality Use of Pathology Program (QUPP), which is led by the Department of Health and Ageing of Australia. In particular, they have focused on performing undergraduate and pre-vocational education and also on general practitioners' vocational training [3]. QUPP also supports

2014 Market Statistics

Countries	Population	GDP	GDP / capita	THE	THE / capita	THE as % GDP	IVD mkt.2014	IVD mkt.2013*	IVD mkt. growth rate 13-14	IVD mkt. / THE	IVD mkt. / capita
	Thousands	Mio €	€	Mio €	€	%	Mio €	Mio €	%	%	€
	Source Eurostat 2013	Source WHO 2013					Source EDMA				
Germany	80.767	2.737.600	33.895	309.272	3.829	11,3%	2.189	2.190	-0,1%	0,7%	27,1
France	65.835	2.059.852	31.288	240.214	3.649	11,6%	1.785	1.786	-0,1%	0,7%	27,1
UK	64.351	1.919.265	29.825	174.993	2.719	9,1%	812	796	2,0%	0,5%	12,6
Italy	60.782	1.560.024	25.666	141.820	2.333	9,0%	1.656	1.667	-0,7%	1,2%	27,2
Spain	46.512	1.022.988	21.994	90.834	1.953	8,9%	972	990	-1,8%	1,1%	20,9
Netherlands	16.829	602.658	35.811	77.654	4.614	12,9%	297	309	-3,9%	0,4%	17,6
Greece	10.903	182.054	16.698	17.881	1.640	9,8%	198	212	-6,6%	1,1%	18,2
Portugal	10.427	165.690	15.890	16.087	1.543	9,7%	221	217	1,8%	1,4%	21,2
Belgium	11.203	382.692	34.160	42.808	3.821	11,1%	362	356	1,7%	0,8%	32,3
Sweden	9.644	423.446	43.908	41.118	4.264	9,7%	191	185	3,2%	0,5%	19,8
Austria	8.506	313.067	36.805	34.544	4.061	11,3%	254	249	2,0%	0,7%	29,9
Denmark	5.617	248.815	44.297	26.432	4.706	10,6%	145	144	0,3%	0,5%	25,7
Finland	5.451	193.443	35.488	18.182	3.336	9,4%	107	105	1,9%	0,6%	19,6
Ireland	4.605	164.050	35.624	14.636	3.178	8,9%	93	95	-2,1%	0,6%	20,2
Luxembourg	549	45.478	81.749	3.228	5.880	7,1%	-	-	-	-	-
EU-15	**401.961**	**12.021.122**	**29.905**	**1.249.704**	**3.109**	**10,4%**	**9.282**	**9.301**	**-0,2%**	**0,7%**	**23,1**
Poland	38.017	393.724	10.357	26.234	690	6,6%	305	285	7,0%	1,2%	8,0
Romania	19.947	140.551	7.046	7.504	376	5,3%	100	93	7,5%	1,3%	5,0
Czech Rep	10.512	151.467	14.409	10.972	1.044	7,2%	150	143	4,9%	1,4%	14,3
Hungary	9.877	98.865	10.010	7.959	806	8,5%	62	61	1,6%	0,8%	6,3
Bulgaria	7.245	39.823	5.497	3.037	419	7,6%	30	32	-6,3%	1,0%	4,1
Slovakia	5.415	72.134	13.321	5.925	1.094	8,2%	45	44	2,3%	0,8%	8,3
Lithuania	2.943	34.521	11.730	2.153	732	6,2%	26	27	-3,7%	1,2%	8,8
Latvia	2.001	23.226	11.607	1.328	664	5,7%	24	23	4,3%	1,8%	12,0
Slovenia	2.061	37.246	18.072	3.231	1.568	8,8%	42	40	5,0%	1,2%	20,4
Estonia	1.315	18.613	14.154	1.065	810	5,7%	13	14	-4,3%	1,3%	10,2
Cyprus	858	16.504	19.235	1.227	1.430	7,4%	2	2	0,0%	0,2%	2,3
Malta	425	7.263	17.089	634	1.492	8,7%	2	2	0,0%	0,3%	4,7
New MS	100.616	1.033.937	10.276	71.269	708	6,9%	801	769	4,6%	1,1%	8,0
EU-27 (EU-15 + new MS)	**502.597**	**13.055.060**	**25.975**	**1.320.973**	**2.628**	**10,3%**	**10.083**	**10.025**	**0,6%**	**0,8%**	**20,1**
Switzerland	8.139	497.582	61.136	57.054	7.010	11,4%	370	345	7,2%	0,6%	45,5
Norway	5.107	357.153	69.934	34.190	6.695	9,5%	171	168	1,8%	0,5%	33,5
Iceland	325	11.075	34.077	1.003	3.086	9,0%	11	11	0,0%	1,1%	33,8
EFTA	13.571	865.810	63.799	92.247	6.797	4,2%	552	524	5,3%	0,6%	40,7
TOTAL (EU-27 + EFTA)	**516.168**	**13.920.870**	**26.970**	**1.413.220**	**2.738**	**10,1%**	**10.635**	**10.549**	**0,8%**	**0,8%**	**20,6**
Turkey	76.667	541.866	7.068	30.291	395	5,6%	394	370	6,5%	1,3%	5,1
TOTAL (EU-27 + EFTA + Turkey)	**592.835**	**14.462.736**	**24.396**	**1.443.511**	**2434,929**	**10,0%**	**11.029**	**10.919**	**1,0%**	**0,8%**	**18,6**

• The data regarding population, GDP and healthcare expenditure are from the World Health Organisation (WHO).

Tab. 4.1: IVD expenditure respect to the total health and the gross gomestic product (GDP) of the countries of Europe. European IVD market statistics 2014, page 3. MedTech Reports. http:// www.medtecheurope.org/ index.php/node/703

LabTests Online development and maintenance, a web resource offering professionals and users updated and reliable information about laboratory tests and how to use them properly [3, 9].

The Spanish Association of Medical Biopathology (Asociación Española de Biopatología Médica) started in 2013 as a project with the main aim of reducing unnecessary health measures such as those that are non-efficient, with limited effectiveness or no effectiveness at all, non-cost-effective, or non-priority. The secondary objectives were to avoid iatrogenic conditions associated with this kind of actions, decreasing clinical practice variability, promoting quality commitment among healthcare professionals, and raising awareness of the right use of health resources. The project tries to

reproduce others such as the Choosing Wisely in the USA or the National Institute for Health and Care Excellence plan in the UK and operates within the Spanish Network of Health Technologies Evaluation Agencies (Red Española de Agencias de Evaluación de Tecnologías Sanitarias) activities framework [16].

Health system demand management could be defined as the treatment of a health resource utilization to maximize its value [17].

Although financial demand management can be thought of as a constraint to fulfill through the existing resources, in the context of the right clinical practice, it is understood as the actions for laboratory optimum use [17].

The strategies' ideal goal is to correct the inappropriateness in laboratory test requesting by doing the right test on the right person at the right time. Strategies have been classified depending on their type (Tab. 4.1), laboratory process step (Tab. 4.2), and performing tool used (Tab. 4.3) [9, 17–25].

The most important strategy type suggested are the following (Tab. 4.1).

Tab. 4.1: Broad approaches to demand management

Category of approach	Examples
Education, audit and feedback	Education programs, guideline dissemination, pre- and post-analytical feedback on test appropriateness, feedback on test predictive value, and feedback on test costs
Rules and agreements aimed at restricting test requests	Re-engineering and implementation of clinical guidelines or pathways, implementation of minimum retest interval schedules, and linking requesting authority to clinical staff seniority – the "traffic-lights" approach
Re-design of the request form to provide guidance to requesters	Providing a list of approved tests that requesters can circle, tick, or order, listing test costs to send a price signal, aligning request forms with modified clinical practice guidelines for test ordering, and unbundling or banning the use of test panels on request forms
Computerized physician order entry (CPOE) systems	Includes real-time decision support
Reimbursement and funding models	Budget holding by the laboratory, budget holding by the requester, diagnosis-related group- or activity-based funding, and budget holding by the regulator

Taken from the *Encouraging Quality Pathology Ordering in Australia's Public Hospitals* [3].

4.2.1 Strategies based on education, audit, and feedback

These strategies rely on setting laboratory utilization agreements with the health services based upon scientific evidence. These agreements performed by the most expert

clinicians of each area promote, through local guidelines or recommendations, efficient laboratory use, both clinically and economically. Feedback on test predictive value will be an asset on these agreements within each disease in any considered clinical situation. Obsolete ones will be removed from the catalogue; it will be also determined whether they are redundancies between them, which ones have higher sensitivity for a particular disease and also detect possible complications that may arise, and finally, those that can also make a valuable contribution to treatment control. Feedback on test cost will also be given to help users identify among the low, middle, expensive, or extremely costly tests, since there is a general perception that laboratory tests are very cheap compared with other screening tests as image technologies.

To evaluate the effectiveness of the strategies, we use either simple or more complex procedures. The most complex ones involve clinical effectiveness (as diagnosis improvement regarding sensitivity to detect or confirm the presence of a disease and specificity to refute other pathologies requiring differential diagnosis), early diagnosis/discharge, rapid response to starting treatment, and the effects on the patient (e.g. early antibiotic administration). Markers are hard to determine, and their direct connection with laboratory reports might not be easily noticed, although intelligent use of the electronic medical record may help in evaluating the effectiveness in medical practices.

It is easier to determine test quantity and cost-effectiveness by comparing pre- and post-intervention feedback. The total or average cost ordering for each scope of action or care policy area [emergency department (ED), inpatients, outpatient care, general practitioner, critical care units, day hospitals, randomized clinical trials, etc.] could be controlled if the Laboratory Information System (LIS) configuration allows it. Even the audit could establish a tracing per requester.

From the laboratory services sustainability and care process point of view, the strategies to be implemented are direct consequences of the economic impact generated by the high-cost tests overuse. In addition, maintaining Pareto's principle [26], (for many events, roughly 80% of the effects come from 20% of the causes), we should take action in those tests that represent the large proportion of the expense. In the same perspective, benchmarking with other laboratories is also an interesting tool to relatively fix the test laboratory utilization ratio related to its population coverage and the use relation between related tests (cardiac markers, thyroid function tests, liver or kidney function test, sepsis markers, etc.) [14].

Educational strategies contribute to a necessary and effective strategy but not enough in itself since its effect will decrease over time.

4.2.2 Rules and agreements aimed at vetting test requests

Regarding rules and agreements aimed at restricting test request, minimum retest intervals are only effective as long as the LIS alerts test-ordering inappropriateness not respecting the agreed interval.

The more effective agreements related to this subject are those involving laboratory diagnostic algorithms. Algorithms start making tests more sensitive, acting as screening tests and, from the obtained outcomes, new and more specific tests are sequentially made, taking advantage of the patient sample availability lasting even for some days. As a result, laboratory works with maximum efficiency since it has the capacity to discard pathology when screening tests are not altered. A frequent example of this particular strategy follows:

ALT serum activity is set to detect or discard hepatic disorder. Any other liver disease-related screening is unnecessary if the activity is found in the age- and sex-specific reference range since the sensitivity of the selected screening test allows discarding. When the test is altered, new tests can be performed using the sample available to get oriented to a hepatic or bile parenchymal process, such as aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase activity, total bilirubin concentration, and also conjugated bilirubin if the previous one is too high. Complete blood count (CBC), serum albumin concentration, prothrombin time, activated partial thromboplastin time, and clotting time will help determine the degree of liver injury. Etiologic studies will first show a possible hepatotropic virus infection, with hepatitis A, B, and C viruses being the most frequent. Therefore, if the cause is not evident from different antigen or viral antibody tests, low-frequency liver disease tests such as autoantibodies antinuclear (ANA), anti-smooth muscle (ASMA), antimitochondrial (AMA), anti-liver kidney microsomal type 1 (LKM), antiliver cytosolic antigen type 1 (LC1), and/or anti-soluble liver antigen (SLA) will be needed.

As result, the laboratory contributes to an efficient management of the patient in a unique process care, being able to determine if organic alteration exists, its etiology and severity.

The Spanish Association of Medical Biopathology (Asociación Española de Biopatología Médica), in its *Recomendaciones de No Hacer* [16] (*Do Not Do Recomendations*), includes the following examples of things that should not be done:

- Do not generate serum tumor markers as population-based screening (except at-risk groups defined for each type of tumor) (Recommendation from the European Group on Tumor Markers [28].
- Do not order HbA1c more than twice a year in diabetic patients with good clinical and metabolic outcome [29].
- Do not make thyroid screening test in inpatients. The following should be tested only on an outpatient basis: thyroid-stimulating hormone (TSH), free thyroxine (FT4), and others such as free triiodothyronine (FT3), antithyroperoxidase antibodies (anti-TPO), and anti-TSH receptor antibodies if needed [30]
- Do not re-evaluate ANA for periods of less than 3 months [31].
- Do not repeat lipid profile determination for periods of less than 2 years in diabetic patients with low-risk dyslipidemia and cardiovascular disease [34].

- Do not order HbA1c screening test for diabetes mellitus type 2 [35].
- Do not order protein electrophoresis determination in adults younger than 50 years without no clinical signs of monoclonal gammopathy or use electrophoresis to study isolated serum proteins [36, 37].
- Do not order BNP or NT-proBNP for diagnosis other than for differential diagnosis of acute dyspnea in ED and chronic or acute heart failure evaluation [38].
- Do not order D-dimer test in patients at high-risk for pulmonary thromboembolism or deep vein thrombosis [39].
- Do not order karyotyping in peripheral blood as first option in patients with mental disabilities or mental retardation, autism spectrum disorders, or congenital anomalies [40–42].
- Do not order preoperative laboratory tests in patients without pre-existing indications [43–45].

Test-ordering selective authorization depending on requester category or experience, medical specialization, or assistance level (ED, critical care units, inpatients, outpatients, or primary healthcare) is an intervention that helps, for example, in not overusing STAT (short turnaround time) tests. In addition to not being required in decision making, excessive test ordering leads to an emergency laboratory services saturation. Consequently, this can cause delays on extremely urgent tests. Apart from reaching rapid diagnosis, ED physicians must decide the care level a patient requires aside from giving a rapid diagnosis. Besides, they have to make a decision whether to discharge a patient with or without treatment, deciding whether to keep the patient under observation for a few hours, hospitalize, or admit in a critical care unit. Once test ordering has been cautiously managed and pretest probability, being determined from anamnesis and physical examination, is high to confirm a diagnosis, or on the contrary, too low to rule out it, then the patient management system is improved. Meanwhile, when test ordering is inappropriate due to a lack of time or provider experience, then the non-specificity of most laboratory tests can cause unexpected results and out-of-range values will be a constraint for patient management, even when these values are not considered pathological but because they are not present in 95% of the reference population. Minimum retesting intervals will be different for those critical care units compared with other care units since changes in critical patients take place in shorter periods. Hence, retesting intervals could be fixed for inpatients and outpatients.

Frequently, before patient discharge, an assorted test requesting is needed even though the period of hospitalization is short, especially in patients who underwent surgery. However, agreed retesting intervals must be justified based on their clinical usefulness for each scope of action, testing of half-life, and their importance in making informed decisions [46].

4.2.3 Re-design of the request formularies

Re-design of request formularies has been a useful intervention in avoiding overuse of inadequately ordered tests. The use of paper-based forms where almost any test from the catalogue is available leads to overutilization. Occasionally, those forms are substituted for basic test panels or profiles. Additional tests might be ordered through catalogue consultation. Even though this strategy is quite effective to prevent overuse, it could be unwieldy in the event of high provider workload. Besides, it neither guarantees an appropriate test use nor promotes correct test utilization.

Formulary re-design strategies based on previous agreements with medical providers should be include the use of clinical (or "disease-specific") profiles/panels and/or diagnosis/monitoring profiles. This way, physicians can specify the patient's clinical presentation and then the laboratory performs agreed tests sequentially. Offering a default test selection allied with local best-practice guidelines and/or national guidelines will contribute to improved patient safety and management with less degree of confusion especially for junior doctors (Fig. 4.3).

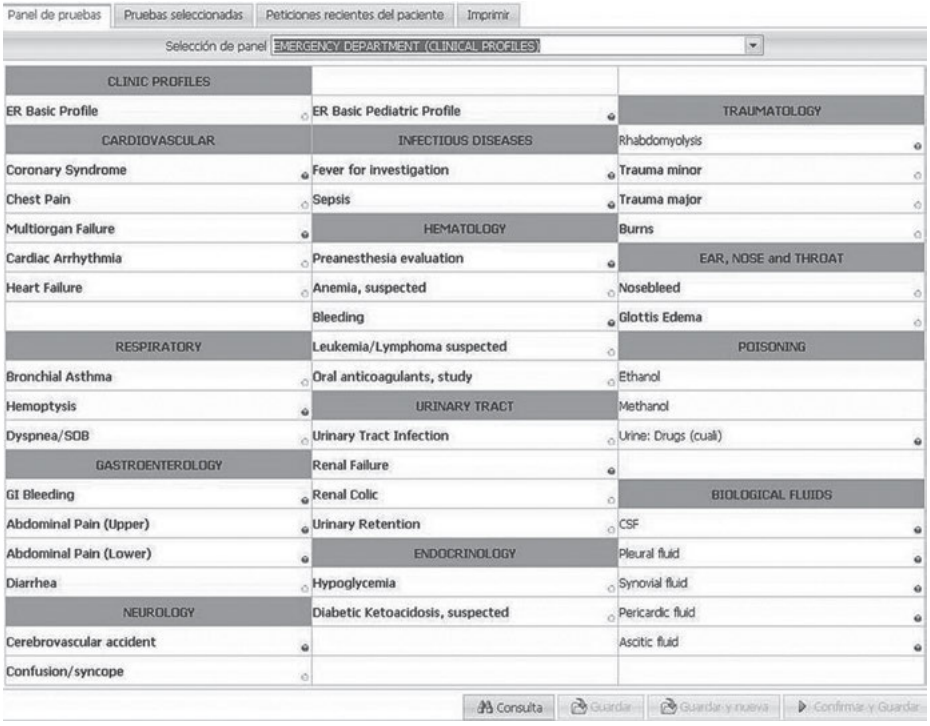

Fig. 4.3: Electronic request form based on clinical presentations for ED (Laboratory of Biochemistry and Clinical Pathology, Hospital Clínico Universitario de Valencia, Spain)

4.2.4 Computer physician order entry

The potential of CPOE systems in terms of test management will be fully described in next chapters. Some of the interventions that could be implemented in these systems include permanent educative strategies, customized formularies, easy available search functions, clinical decision supporting rules, display costs/fees, etc. All of them provide a better integration of the laboratory into global healthcare processes and promote a real-time collaboration between laboratories and physicians.

4.3 Strategies to correct inappropriateness in laboratory test requesting and phase of intervention

We consider two particularly relevant documents related to this subject: the project proposal of the management strategy classification according to phase of intervention, made by members of the Clinical Laboratory Management Commission from the Spanish Society of Clinical Chemistry and Molecular Pathology (2013) [20] and the paper of Dr. Danielle Freedman (from the National Academy of Clinical Biochemistry, UK) published in eIFCC in January 2015, "Towards better test utilization – strategies to improve physician ordering and their impact on patient outcomes" [9].

According to intervention levels, strategies can be categorized as pre-requesting, during requesting, and post-requesting strategies (Tab. 4.2).

Tab. 4.2: Strategies depending on the intervention level

Pre-requesting phase	
Education	Guidelines Test formulary design Education programs Regular newsletters
Pathways and clinical guidelines	Consensus Scientific evidence Systematic reviews Clinical societies' recommendations
Ordering patterns	By pathology or clinical situation Diagnostics profiles Monitoring profiles Algorithms
Ordering forms	Scope of action access Level of care access Requester qualification access Electronic order

Tab. 4.2 (continued)

During requesting phase	
Laboratory	Test costs Ordering costs Manage retest frequency Clinical use information Ordering requirements Catalogue easily available
Post-requesting phase	
Post-laboratory	To guarantee sample collection, transport, and sample pre-treatment Refusing due to inappropriate ordering Holding test until justification Reflex testing, Complementary testing Stratify response time Feedback on analytical demand Benchmarking Cost related to each care unit or physician Interpretative reports

4.3.1 Pre-requesting phase interventions

4.3.1.1 Education

On a survey carried out on 117 medical interns from Cape Town hospitals, 23% of 61 responses admitted not having enough confidence to interpret test results. They highlighted the need to perform their training and suggested access to online guidelines. Owing to the fact that medical interns are responsible of the largest number of test ordering in hospitals, the author recommends reinforcing undergraduate education. Consequently, this will lead on improvement in appropriate use in laboratory requesting and therefore cost reduction.

Similar results were obtained in a comparable analysis where first and second year medical interns working at the Sheffield (UK) Teaching Hospitals Trust were surveyed. A total of 82 surveys were completed, approximately half of the total, with merely 18% having confidence in their test-requesting capacity and less so in their interpretation ability. Respondents advised on their need to receive specialized training in their last year before graduation and during first year. Training preferences resulted in workshops (44%), presentations (31%), online guidelines (17%), and other methods (8%) [45].

From a total of 1,768 GPs from the USA, 14.7% admitted uncertainty related to requesting process and 8.3% regarding results interpretation. Taking into account that laboratory test ordering is requested on 31.4% of the patients, then it

can be concluded that uncertainty is a great challenge for GPs. Thus, they ask for test-ordering guidelines through information technology such as electronic ordering, but these systems are not fully available. Also, they suggest interpretative comments coming from laboratory professionals and better channels of communication between laboratory and medical services [73].

Test catalogue/guidelines must contain detailed, updated, and documented information referring to test clinical use and preferably with double access: from test to clinical use and from clinical use to test, as has been designed by Labtestonline (https://labtestsonline.org/), which can be accessed by professionals and users.

Some experiences based on re-design test ordering have been reported. The Emersons' experience [52] in the USA includes mandatory requirements and intralaboratory analytical algorithms for thyroid function, anemia, and urine screening test, and this has led to a significant decline in test ordering.

4.3.1.2 Pathways and clinical guidelines

Strategies based upon justified recommendations of test utilization as the ones we use in our health department have a limited effect over time if they are not consolidated in the own requesting form (Tab. 4.3).

Tab. 4.3: Recommendations on the use of laboratory tests for GPs (Laboratory of Biochemistry and Clinical Pathology, Hospital Clínico Universitario de Valencia, Spain)

DEPARTAMENT DE SALUT DE VALÈNCIA CLÍNIC-LA MALVA-ROSA	**Hospital Clínico Universitario Laboratory** **Recommendations on the use of diagnostic tests**	**February 2010**
Subclinical Hypothyroidism: Recommendations for interpretation		
When FT4 within range between 0.93 and 1.7 ng/dL **If TSH: What to do?**		
– 4.3–7.0 µU/mL: Order a new test request in one year – 7.1–10.0 µU/mL: Order a new test request in six months – > 10.0 µU/mL: Treat		
Autoimmune thyroiditis: Antibodies – Thryroperoxidase (TPO) Antibodies, serum: Aiding in the diagnosis of thyroid autoimmune disorders with TSH and FT4 – DO NOT USE thyroglobulin antibody, serum: It's not useful for thyroiditis diagnosis and besides it has a high false-positive rate		
Diabetes: Use of glycated hemoglobin (HbA1c) – DO NOT USE for diabetes screening – USE only for diabetic control and diagnostic confirmation – Order at 2- to 6-monthly intervals in patients with unstable diabetes – In those with stable diabetic control on unchanging therapy, intervals of 6–12 months are recommended.		

Tab. 4.3: (continued)

Serum Tumor Markers – DO NOT USE tumor markers for screening/diagnosis purposes. – USE only for diagnostic confirmation and monitoring
Vitamin B12 and folate – USE only for investigation of macrocytic anemia and neurologic defects associated with vitamin b12 deficit.
Iron metabolism: Fe (iron), transferrin, and ferritin – USE only for investigation of microcytic anemia – USE only FERRITIN together with CBC for monitoring purposes
Lipids – Order only a maximum of two annual controls in dyslipidemic patients.

Using these recommendations repeatedly and taking into account a feedback system that allows to compare intervention effects, Thomas et al. [53] have achieved a mild decrease in required tests volume, but other related interventions have accomplished a more relevant impact [74].

A better degree of effectiveness can be achieved when recommendations become local clinic guidelines made cooperatively by the laboratory and medical services. This is the case of intervention in primary care. They removed after agreement, several unnecessary tests from their hepatic function, ferric metabolism, rheumatic disease, and celiac disease profiles [75]. Schulenburg-Bran et al. [54] in the UK decreased 32% of tumor marker use in general surgery departments after compromising in terms of clinical use, minimum retesting intervals, and selective ordering. Similar results were obtained in the USA by Tapper et al. [55] on ceruloplasmin management.

However, other studies have shown the existence of underuse for some laboratory tests, leading to underdiagnosed celiac disease [76, 77], familial hypercholesterolemia [78], primary hyperparathyroidism [68], diabetes type II [67], and other chronic diseases in the elderly [79].

4.3.1.3 Clinical profiles

Moving toward “disease-”, “symptom-”, or “question-specific” profiles could be very effective if they are based on medical evidence. This clinical profiles can be divided into diagnostic or monitoring profiles improving their precision. The first ones are generally more sensitive because they include more tests for screening purposes [51]. Both types might be implemented as algorithms [27].

4.3.1.4 Request format

Request format could facilitate a more rigorous and selective laboratory demand. Systems should offer different request forms based on medical specialties, scopes of actions, and/or group of doctors that share an specific area of knowledge [51].

4.3.2 During requesting interventions

Supported by the LIS, several agreed-upon clinical decision rules could be performed involving retesting minimum intervals, vetting tests, or special requirements needed. Furthermore, request forms should display economic information like test or request costs [63]. The benefits of electronic request systems to ensure compliance through "online" assistance are currently being studied by several authors, and they will be reviewed in the next chapters [60, 62, 80].

4.3.3 Post-requesting interventions

4.3.3.1 To guarantee sample collection, transport, and sample pre-treatment

The accuracy of patient's exploration by the laboratory (in vitro examination of their biological samples) requires a careful process involving sample extraction, transport, and pre-analytical treatment.

A pre-analytical quality program is compulsory to ensure unequivocal patient identification, use of correct tubes and containers, sample traceability, and best pre-analytical procedures. This program must be well documented and periodically evaluated through key performance indicators with the purpose of implementing corrective actions. As an example, we present the program implemented in a healthcare area that covers 370,000 inhabitants, in which the laboratory receives samples of more than 1,800 patients daily. The area has 31 phlebotomy centers that are evaluated at intervals.

The main strategy consisted of implementation of a quality program fully integrated into our LIS. During phlebotomy, LIS displays information regarding patient ID and types of tubes and containers needed including pictures through computer. Additionally, phlebotomists can register any pre-analytical incident real time. Samples are labeled and dispatched to the laboratory following special transport procedures. Any additional incident related to sample ID, volume, hemolysis, or merely a non-received sample or tube are registered in the LIS. If those incidents endanger complete analysis, administrative assistants from the laboratory contact the phlebotomy centers and/or patients as soon as possible to make a new appointment for the pending sample. In this manner, the patients' results are complete and available for providers when necessary.

Four times a year, a confidential electronic report is e-mailed to every phlebotomy or venipuncture center supervisor. This report collects all incidence rates for a trimester and compares the information with the incidence rate of the entire area (total median) and with the target value established by the laboratory (Fig. 4.4).

Additional data such as total requests dispatched, samples reclaimed and recovered, percentage of requests without any incidence, and an updated ranking are included in these reports.

The recovery samples initiative recovered more than 60% of the samples from 2013 (Fig. 4.5).

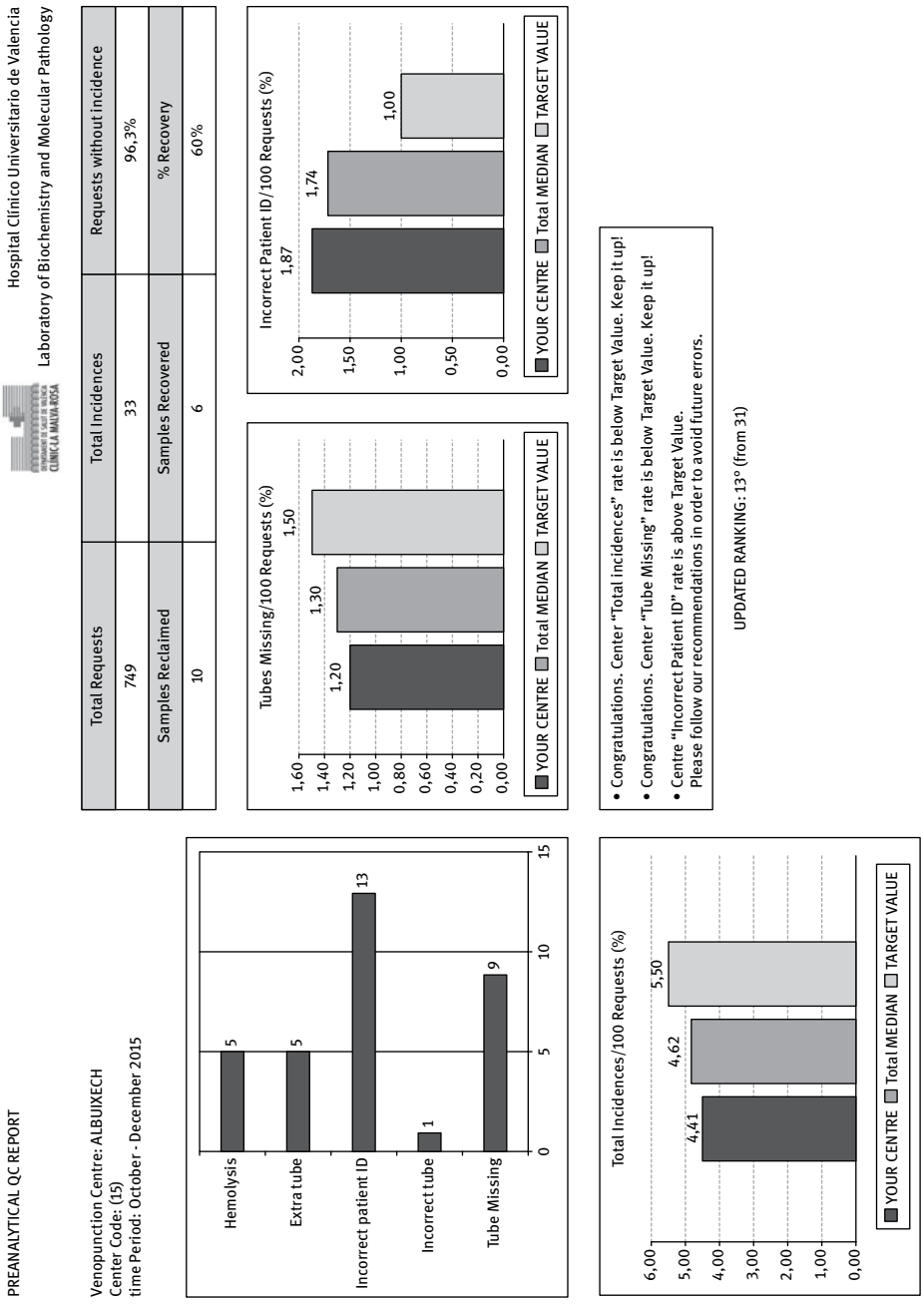

Fig. 4.4: Quarterly report for venipuncture centers

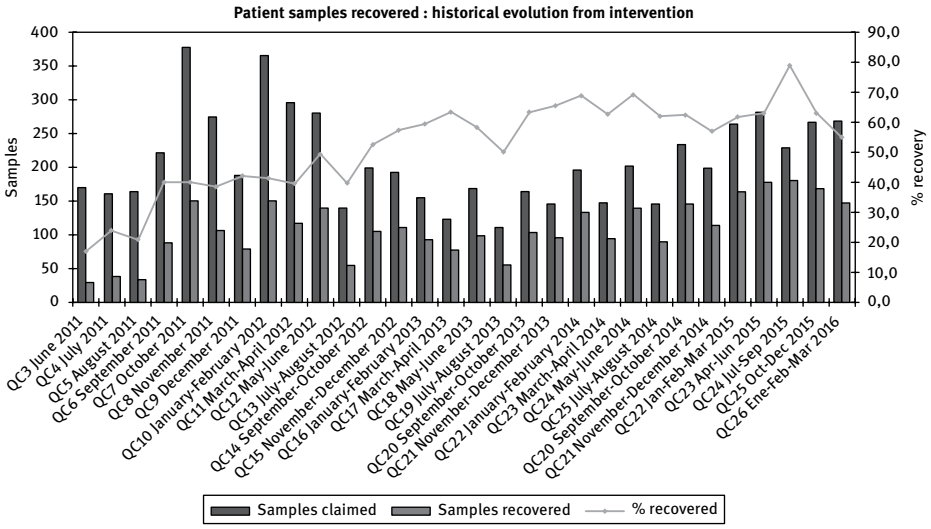

Fig. 4.5: Patient samples recovered after new appointment: historical evolution

The pre-analytical quality program decreased the number of total incidents from 14% to <5%. Those that directly affected patient care (samples not received, ID, IT incidences, and spare tubes) decreased as well from 7.5% to <2% (Fig. 4.6).

4.3.3.2 Vetting due to inappropriate request

Although avoiding inappropriate test requesting through educative strategies is preferable, effectiveness could be insufficient and may require further control. The strategy of Salinas et al. [64] of not performing uric acid tests in asymptomatic patients avoided unnecessary hyperuricemia treatments [64]. Meanwhile, Dickerson et al. [65] obtained a decrease of 58% in 1,25-dihydroxyvitamin D tests, by substituting the test for 25-dihydroxyvitamin D in some cases and reporting this change to providers. Similar results were obtained by Salinas et al. [75] with these vitamins.

4.3.3.3 Reflexive tests/complementary tests

Tests generated automatically in the laboratory based on previous results (that work as screening) are called reflexive tests. For example, free prostate-specific antigen is generated when the total prostate-specific antigen concentration is higher than the age reference value or free T4 (FT4) when TSH is elevated or suppressed in thyroid disease screening. 25-Dihydroxyvitamin D can be generated when true hypocalcemia is detected or when bone alkaline phosphatase is

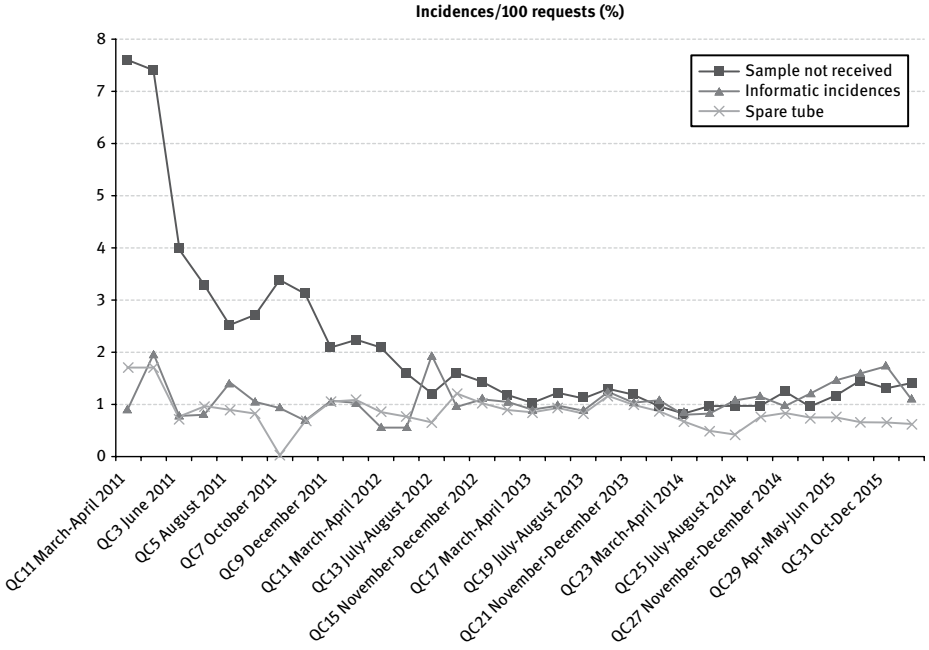

Fig. 4.6: Evolution for pre-analytical incidences affecting patient care

augmented. Parathyroid hormone can be incorporated in case of unexpected hypercalcemia. Hereditary hemochromatosis studies could be allowed if the transferrin saturation rate is high [66].

Other complementary interventions may reveal diseases at their subclinical phases. Early detection could avoid occurrence of complications. This is the case of primary hyperparathyroidism detection through serum calcium systematic analysis in asymptomatic primary care patients [67] or through the incorporation of HbA1c in fasting patients with hyperglycemia and without a previous result of glycated hemoglobin [68].

4.3.3.4 Stratifying turnaround times

Even if the test, time, and patient are appropriate, it will be of little use if turnaround times (TATs) are inadequate. Stratification of laboratory TATs should fit healthcare necessities. According to priority, we suggest urgent requests as those coming from the ED or inpatients, critical care units, day-hospital requests, routine inpatient requests, and finally outpatients.

4.3.3.5 Feedback of test cost information

Providing costing information to physicians produced short-term reductions in requesting activity, but not all interventions are sustained over time. However, some

authors have found evidence that the introduction of laboratory budget holding combined with changes in the laboratory request form could produce significant savings. Reductions in variability of requesting costs when reduced could be taken as a surrogate indicator of improvement in quality [53].

4.3.3.6 Benchmarking

Strategies based on benchmarking, which have obtained good results in external analytical quality programs, account for excellent resources when it comes to demand management decision making. The use of rates like number of particular tests per year and per 1,000 people and ratios between related tests that may be redundant could be used as reliable indicators. These indicators should be only compared with similar healthcare settings like the ED or primary care. Such initiatives will prioritize tests where we must act a first preference. The REDCONLAB program in Spain (benchmarking on demand management) is followed by more than 100 laboratories in the country voluntarily [14].

4.3.3.7 Explanatory comments

The great volume of requests that our laboratories receive everyday and the limited information available, until recently, regarding clinical situation and/or patient treatment have traditionally hindered the entry of interpretative comments related to laboratory tests.

Recently, despite the fact that laboratory demand increases year after year, the LIS has develop into a powerful tool that enables a more efficient clinical validation, but, above all, gradual computerization of medical records allowing laboratory professionals to consult real time on all the information related to our patients has opened the possibility for an improvement in laboratory reports through implementation of explanatory comments.

Even though these tools promote a better results understanding, their effectivity regarding patient clinical course relies on an excellent relationship between laboratory and clinical providers, which should build on agreed clinical guidelines.

These comments should be cautious, giving valuable advice for each particular case rather than standard text and avoiding obvious and/or repetitious findings. Comments could be different based on provider's professional qualification or scope of action (e.g. medical specialist versus general practitioner).

Comments will be necessary in the face of:

- Unexpected results, when they suggest several possible diagnostic alternatives (not only the expected)
- Under the suspicion of an analytical interference (e.g. due to an specific drug or treatment)
- When laboratory decides to add new tests to look for a specific diagnosis
- When some tests are cancelled due to inappropriateness

They are relevant constituents of a good explanatory comment [71, 72, 81]:
- Presence of an anomalous result and its severity
- Clinical implications suggested by results
- Following/monitoring proposals related to results

There is evidence of interpretative comments in the majority of laboratories in the UK through a survey questionnaire made by Kilpatrick and Freedman in 2011 that included 196 laboratories [70]. Kilpatrick [69] showed that explanatory comments regarding thyroid function have been beneficial in patients monitoring.

There is also evidence that institutions need to devise strategies to fulfill the learning needs of new graduates in the area of chemical pathology and clinical biochemistry [47]. Despite biochemistry being a major part of the research and knowledge base of diverse medical specialties, reports indicate that there has been a significant reduction in the time available to teach it. This lack of information has a great impact not only in ordering skills but also in results interpretation. In a teaching hospital, implementation of explanatory comments might be an excellent contribution when it comes teaching new specialists.

4.4 Laboratory medicine

Laboratory professionals must be committed in playing an active role at each stage of the famous and totally alive "brain-to-brain" loop process, as was formulated by Lundberg [82]. For many years, laboratories have focused in performance improvement through analytical quality, reaching a high degree of standardization and harmonization between methods and results as testified by external quality control programs.

The recent implementation of pre- and post-analytical quality programs has noticeably improved quality related to phlebotomy, patient identification, transport, and samples pre-treatment operations, on the one hand, and quality allied with reports information (reference values based on age, sex, and biological cycles), turnaround times, and critical and alert values report, on the other hand.

Incorporating new tests must follow a phase-based process similar to incorporating new drugs, which involves determining its analytical validity, efficiency, and effectiveness (Fig. 4.7):

In addition to its normal activities as biological properties in vitro examination consultant (Tab. 4.4), the laboratory must focus on avoiding diagnostic errors related to inappropriate demand management (Tab. 4.5).

Taken from Epner et al., "When diagnostic testing leads to harm: a new outcomes-based approach for laboratory medicine" [23].

Intervention strategies should consider each clinical setting in the patient pathway (Tab. 4.6).

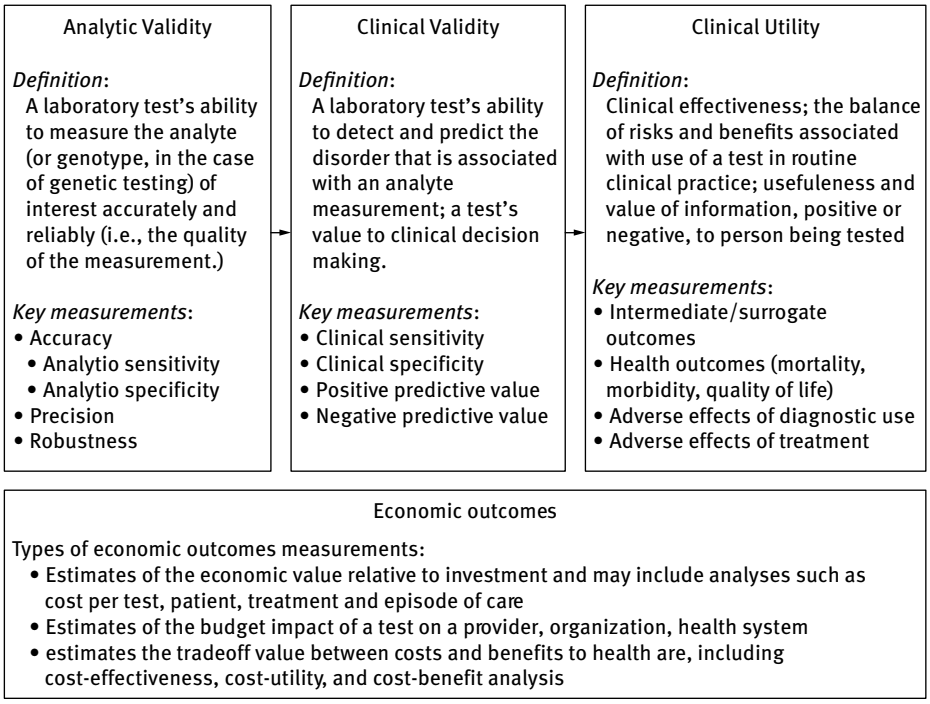

Fig. 4.7: New test's validity algorithm. Taken from the Lewin Group, *The Value of Laboratory Screening and Diagnostic Tests for Prevention and Health Care Improvement* [83]

Tab. 4.4: Professional usual laboratory activities

– Laboratory test utilization
– Profiles, protocols, and laboratory guidelines
– Elaborating clinical practice guidelines
– Specialists training outwalls and inwalls
– Referral protocols between primary care and specialized healthcare
– Pre-analytical, analytical, and post-analytical quality guarantee
– Methods and instruments assessment
– Research programs

Tab. 4.5: Diagnostic error cause classification related to laboratory test ordering

– Inappropriate test ordering
– Appropriate test not requested
– Appropriate test result is missed, misunderstood or not applied
– An appropriate test has been delayed or missed and it is no longer available when needed
– Appropriate test result is inaccurate

Tab. 4.6: Uses of diagnostic tests in the patient pathway

– Disease screening
– Risk stratification
– Diagnosis
– Treatment selection
– Monitoring
– Secondary effects prediction
– Early diagnosis of adverse events
– Prognosis

Taken from Hallworth et al., "Current evidence and future perspectives on the effective practice of patient-centered laboratory medicine" [49].

4.5 Epilogue

We must consider the clinical laboratory as essential in healthcare in terms of diagnosis and as absolutely necessary in decision making. The clinical laboratory integrates all the medical pathophysiological basic disciplines, and the clinicians have the obligation and responsibility to generate information to preserve population health.

Do not consider care specialty as an auxiliary diagnostic service but as a medical diagnosis service: laboratory medicine, that is, as a consultation where the laboratory clinician is part of the diagnostic chain performing all logistics, organization, metrologies, economics, and report-issuing activities under the inclusive approach of improving patient health [16].

The basis of success and excellence lie in knowledge. Therefore, we should defend responsible and generous involvement within the future specialists training.

More than discussing about inappropriate test requesting, we should talk about inadequate management from laboratories not having a right design on their diagnosis contribution approach and disease monitoring. There are not inappropriate tests requesting, but laboratories treating requesting as work orders rather than clinical consultations. Laboratories must be fully integrated on the care process to do what has to be done for the benefit of patient health [16].

Right test ordering management leads not only to cost reduction but also to high clinical profitability and efficiency in care process. In addition, it prevents unnecessary inconvenience and worries to patients.

Thus far, demand management has involved different types of strategies as educational, general agreement of specialists implicated, developing new laboratory formularies, cost feedback, specialist stratification or provider qualification, and others based on the utilization of the LIS.

Clinical laboratories have started to incorporate intelligent electronic ordering systems, which help thousands of doctors requesting our services everyday in terms

of guidance and proposals and by accepting or refusing laboratory requests while the patient is still present. Let us take advantage of this great technological opportunity for the benefit of patient health and taxpayer money.

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5 Practical pathway to design, establish, and monitor over time test requesting appropriateness strategies: indicators to detect the inappropriateness and to monitor after interventions

5.1 Introduction

When one thinks of the possibility of a new strategy to correct inappropriateness in laboratory test requesting, it is crucial to find a simple approach to detect inappropriate request for laboratory tests and choose the correct test and population to establish the strategy; to opt toward a simple automated design based on information technologies; and to monitor after intervention establishment, through process and outcome indicators customized according to the type and stage of strategy. Through those indicators, it is easy to see at a glance how the strategy is running over time. Moreover, the measurement of outcome indicators is essential in knowing how the clinical laboratory is enhancing its contribution in terms of patient outcome and economic savings, i.e. achieving the best contribution in the diagnosis, monitoring, and prevention of disease at the lowest cost. It is the laboratory professional who must lead each of the phases of the strategy, as the professional that has the knowledge and experience in laboratory tests.

5.2 The plan-do-check-act cycle as a basis in the design of strategies to correct inappropriateness in laboratory test requesting

The proper tool to be used for any organization strategy is the plan-do-check-act cycle (PDCA cycle). This is often referred to as the Deming cycle or the Deming wheel, after its promoter, W. Edwards Deming. It is also sometimes called the Shewhart cycle.

Deming, best known as a pioneer of quality management approach and for introducing statistical process control techniques, used them with great success. He assumed that a key source of production quality lies in having clearly defined, repeatable processes.

The four phases in the PDCA cycle involve:

- Plan: identifying and analyzing the problem.
- Do: developing and testing a potential solution.

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– Check: measuring how effective the test solution was, and analyzing whether it could be improved in any way.
– Act: implementing the improved solution fully.

5.3 Indicators that intervene in strategies to correct inappropriateness in laboratory test requesting

5.3.1 Indicators in clinical laboratory: general considerations

Clinical laboratory professionals have been pioneers in quality subjects. Proficiency testing, external quality assurance, and peer testing programs have been designed, implemented, and performed in clinical laboratories for years.

The tool to measure is the key performance indicators (KPIs) [1], and thus, we should pay careful attention to them. Continuous measuring of laboratory total testing process through KPIs is the daily task of every clinical laboratory.

It is certain that we cannot manage what we cannot measure. But what is certain is that we cannot manage if we do not measure properly.

There are four main considerations related to KPIs that should be remembered when using them in daily practice.

First, it is fundamental to measure KPIs whose correction will result in tangible organization improvement.

Second, measure automatically collected and/or calculated indicators. Manual collection can result in the loss of registers, which is not likely to occur when data are collected in an automated manner, i.e. with warehouse programs from laboratory information system (LIS) [2]. In fact, it has been shown that laboratories more focused on detecting and correcting errors may have higher error rates than others that do not pay much attention to it [3].

Third, if we are designing KPIs, we must clearly define what we want to measure. As technology develops, we can better define that. For instance, currently, we can measure hemolysis using the hemolytic index, a much more convenient indicator than the manual color serum visualization [4].

The main objectives of using indicators are either to study results over time or to compare one's results with other organizations. For the former, the use of absolute numbers usually render observation of evolution over time rather difficult. For the latter, absolute numbers will not aid in comparisons. A relationship has to be established by comparing a result with another, setting the numerator as the value that we want to measure and the denominator as the value we want to relate to. If it is important to define the numerator clearly, it is also crucial to initially determine the denominator so that the indicator really measures what we want to and keeps valid over time to grant comparison of intra- or inter-organization results. The choice of the denominator must be adequate. Let us illustrate this through an

example: two laboratories want to measure coagulated samples in cell blood count (CBC) samples, and they calculate the number of CBC not processed due to sample coagulation. For both, the sample was coagulated in 10 occasions, in one month. Are both laboratories making mistakes with the same frequency? Do they have the same expertise in phlebotomy procedures? To determine the answer, we need to know other data such as how many requests were received by each laboratory in the same period. Curiously enough, both got 10,000 requests, resulting in 0.1% coagulated samples. Interestingly, if we continue to investigate, the request form for the first laboratory covers only chemistry and hematology. For the other one, the request form also includes microbiology. Many requests are only for microbiology tests, which results in 9,800 CBC samples for the first laboratory and 8,000 in the second; thus, it can be concluded that the first laboratory is doing better with phlebotomies (0.102% versus 0.125%). Using the number of requests as a denominator, especially when comparing the performance of different organizations, may be very dangerous. It is also problematic when comparing one's results over time since a better CBC coagulation sample indicator in 1 month can only reveal an increased number of requests without a CBC demand.

Finally, if we are designing KPIs, validating the indicator before establishing it as a tool to improve the organization processes is important. Everyone in the organization should trust in indicator results. Indicator results should be available and trusted by every member in the organization, since everyone contributes to achieve the indicator target. When an indicator is badly constructed, the laboratory professional is the first to detect it since they perceive that their efforts are not related to indicator improvement over time. Thus, we reaffirm that it is absolutely necessary to validate the indicator before establishing it as a tool to improve the organization processes [5, 6]. If not, the workers will most likely begin to distrust the indicators and disbelieve the whole laboratory management system [7, 8].

Efforts should be accomplished to measure correctly through harmonization of pre-analytical quality indicators [9]. It is certain that without measuring, we cannot manage, but it is equally certain that when measuring incorrectly, we can manage but we can also manage incorrectly, driving the organization to unsecure and dangerous directions.

5.3.2 Indicators to detect test inappropriateness and to monitor after the establishment of the different interventions

Table 5.1 shows the main indicators to be applied in strategies to correct inappropriateness in laboratory test requesting.

Indicators are classified as either process and outcome. Process indicators are used to detect test inappropriateness and/or assess progress through regular monitoring after strategy implementation. Outcome indicators are used to measure the

Tab. 5.1: Different indicators used to detect test inappropriateness and monitor after the establishment of the different interventions

Type	Name	Design	
		Numerator	**Denominator**
Process: to detect inappropriateness and/or to check if the strategy is working properly	Per inhabitants/admissions	Test request	1,000 residents/ admissions
	Absolute number of tests added, eliminated or not measured but reported.	Tests added, eliminated, or not measured but reported	
	Per highly requested test	Test request	Request of a highly demanded test
	Per related test	Test request	Request of a related test
Outcome: to evaluate the benefits of the strategy	Diagnosis	Cases detected	
	Costs	Euros saved	
	Cost per case detected	Euros saved	Cases detected

benefit of the strategies in terms of economical savings or patient benefit in diagnosis, treatment, prevention of diseases, or even quality of life.

5.3.2.1 Process indicators

In strategies to correct inappropriateness in laboratory test requesting, process indicators are used to detect and monitor after strategy implementation.

Taking into account the previous recommendations for indicator design and process indicators to detect test inappropriateness, the proper election of the denominator is crucial. Test requests per 1,000 inhabitants in a primary care setting [10, 11] or per 1,000 patient admissions in an emergency department (ED) [12, 13] are very easy to construct. In the first, test-utilization rates are calculated by standardization with the population attended by each laboratory and are very useful in public healthcare models. The second type can be used in any healthcare model. Both indicators are used to, in an indirect way, detect test inappropriateness when comparing to other areas.

However, the second type of process appropriateness indicator, ratios of related tests requests, is very useful in detecting test inappropriateness in any setting, but it can also be used to monitor after strategy implementation. Some even have a goal to reach [14]. In this type of indicators, the test whose demand should be corrected figures as the numerator. When we do not have at our disposal a "ratios of related

tests request" indicator to monitor after strategy implementation, monitoring through indicators that relates test demand per a highly requested test is advisable [15].

5.3.2.2 Outcome indicators

In strategies to correct inappropriateness in laboratory test requesting, outcome indicators are used to measure the benefits that strategy implementation has in the patient or healthcare organizations.

To date, there are few laboratory studies that focus on the benefit that laboratory improvements cause in the patient.

In strategies to correct inappropriateness in laboratory test requesting, monitoring through outcome indicators is a crucial step. Determining the number of new patient diagnosis, the cost of each new case detected [16, 17], and/or money saved because of the strategy [18] is an imperative step. The first step is to decide whether to continue or not through the strategy, and the second step is to measure the strategy benefits over time.

5.4 A step-by-step description of strategies to correct inappropriateness in laboratory test requesting

Table 5.2 shows a practical step-by-step strategy pathway.

Tab. 5.2: Summary of the different steps of the proposed approach to identify and correct a potential inappropriateness in the use of laboratory tests

Identify laboratory test inappropriateness
– Studies on tests utilization differences between geographical areas
– Retrospective study of the number of requests in the LIS patient database
– Comparison to guidelines or disease prevalence
– Systematic review of the tests that generate greater economic cost
Selection of test and target population for strategy implementation
– Population: generates the most improvement in patient outcome
– Test: risk evaluation of test over- or under-request
– Strategy: easy, automatic, and simple
Generation of the idea
– Should rely on automatic processes, based on the LIS
Pre-design of the strategy
– In consensus with requesting physicians, after LIS retrospective simulation
Final design
– Write the procedure: strategic initiative, objectives, indicators, and goals

Tab. 5.2 (continued)

Strategy establishment – Specified period
Monitoring through process indicators
Evaluation through outcome indicators
Final decision regarding to continue/stop strategy

5.4.1 Identify laboratory test inappropriateness

The first step is to identify laboratory test inappropriateness. There are several ways to do it. Traditionally, it has been done through the revision of patient medical records through implicit and explicit criteria. Usually, this is analyzed in prospective studies that take many years before having any answers, and it is rather costly; thus, for more practical methods are needed.

In countries with public healthcare systems, there are indirect ways to investigate inappropriateness of tests that generate the greatest economic cost. As an example, Spain is divided into 17 autonomous communities (CCAA). Every Spanish citizen possesses an individual health care card, which lets access to public health services as a healthcare user throughout the National Health System. The health system in every CCAA is divided into health departments (HDs). Each HD covers a geographic area and its population. It is composed of several primary care centers and usually has a unique hospital. The laboratory located at the hospital attends the needs of every HD inhabitant. As an example, a test that generates a great economic cost is vitamin D 25-OH. In Osakidetza, in northern Spain, from 2011 to 2013, the request for vitamin D 25-OH test has doubled, reaching an annual expense of more than €600,000. As a consequence, the measurement of vitamin D 25-OH is placed among the 10 standard laboratory parameters that cost most in this CCAA. This fact has led to instructions for the measurement of vitamin D 25-OH [19], designed through interdepartmental consensus [20].

A second indirect method to identify laboratory test inappropriateness is through studies on test utilization differences between geographical areas. These researches study the variability of laboratory test request as a measure of how spread out or closely clustered a set of data regarding demand in different geographical areas is. Through those studies, detecting test over- and under-request is also possible, and an example of which is the REDCONLAB studies.

The first study was performed in Valencia community in 2009 with only eight participants. In the first national REDCONLAB study in 2010, a call for data was posted on the REDCONLAB website; in the second year, via e-mail (2012). In the 2014 study, the questionnaire was also addressed to the participants of previous studies of the

REDCONLAB group that recommended other laboratories to join the current edition, and a LinkedIn group was also created (https://www.linkedin.com/in/REDCONLAB-grupo-a5663bb7). Spanish laboratories willing to participate in the study were invited to fill out an enrollment form and submit their results online. In the three consecutive studies, production statistics (number of tests requested by general practitioners) were obtained. Every patient seen in any primary care center of any of these institutions, regardless of the reason for consultation, sex, or age, was included in the studies. Each participating laboratory was required to be able to obtain patient data from local databases and to provide organizational data. In the three editions of the REDCONLAB study, 38, 76, and 110 laboratories at different hospitals from diverse regions across Spain consecutively participated.

After collecting data, two types of appropriateness indicators were calculated: test requests per 1,000 inhabitants or ratios of related tests requests. Both appropriateness indicators, as shown in Table 5.1, belong to the category of process indicators. With these data, a frequency histogram and a box plot for each of the indicators were drawn to conform a pre-pre-analytical quality control report that was sent to each participating laboratory indicating their individual results compared to those of others. Each report had a sheet for every test ordered per 1,000 inhabitants and also for ratios per related test requests (Figure 5.1).

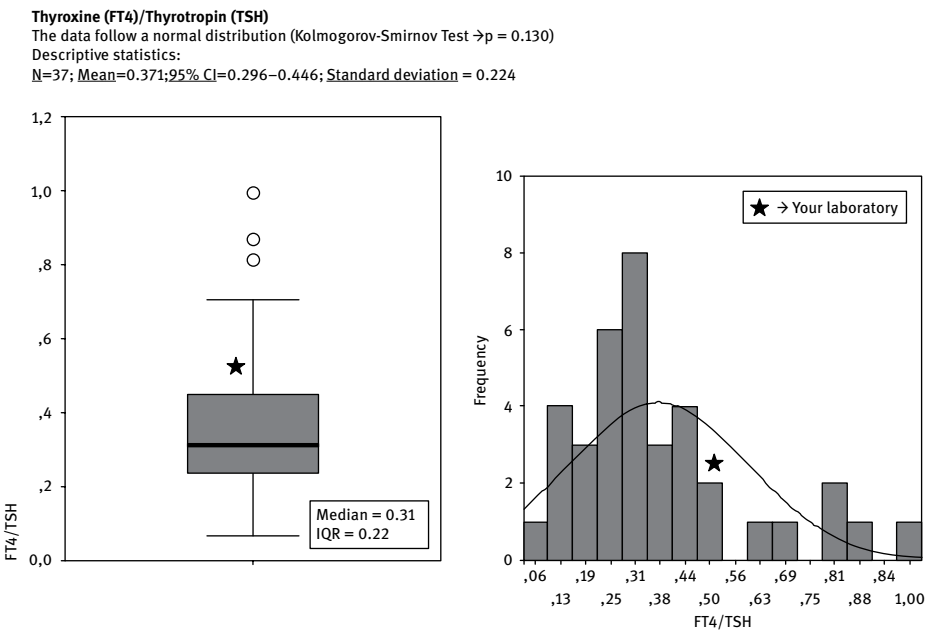

Fig. 5.1: One of the report sheets sent to every laboratory that participated in the study

In the first National REDCONLAB study, a big variability was observed [11]. Two years later, a great variability especially in less requested tests [21] and potential over- [22, 23] and under-requesting [24] were again observed.

In every REDCONLAB study, ED requests were also compared. Two types of appropriateness indicators were calculated: test requests per 1,000 ED admissions or ratios of related tests requests. Both appropriateness indicators, as shown in Table 5.1, belong to the category of process indicators. A high variability was also observed in the ED setting [12, 13].

A third indirect method to detect test inappropriateness is through comparison with guidelines or disease prevalence. Through this type of study, an over-request has been detected in tumor marker request in Italy. Gion et al. [25] developed a model matching the rate of utilization of tumor marker tests with prevalence data as an indirect indicator of laboratory tests inappropriateness. This model is useful when the availability of clear guidelines regarding clinical use of the test and epidemiological data on the disease. This epidemiological-based model does not offer a direct measure of appropriateness – it only shows areas of over-request that might related to inappropriate use, making a deeper study necessary to confirm the inappropriateness or establish interventions to reduce over-request. Also, an epidemiological model was used in the second National REDCONLAB study to identify glycated hemoglobin (HbA1c) underrequest. To investigate whether HbA1c was appropriately requested to manage patients with diabetes mellitus (DM), that research compared the theoretically ideal number of HbA1c requests that should have been ordered to the number of real HbA1c requests in a population of 20 million inhabitants in Spain. The former was calculated according to disease prevalence in Spain (6.9%) [26] and to the current guideline recommendations regarding glucose monitoring (HbA1c test at least two times a year) and testing for DM in asymptomatic patients (HbA1c every 3 years in patients older than 45 years) [27]. A total of 2,439,729 HbA1c requests would have been necessary to appropriately manage the existing patients with DM. A total of 2,384,408 tests would have been needed to diagnose new patients, according to the current guidelines. Considering the real number of tests performed, a total of 3,280,183 additional tests would have been necessary for both purposes. Not a single HD of the 76 participants reached those theoretical figures.

5.4.2 Selection of the test and target population

The second step of our approach, strategies to correct inappropriateness in laboratory test requesting, is the selection of the test and target population for strategy implementation. To make this important decision, we also must take into account, right from the start, the potential ease in future strategy design: an easy, automatic, and simple strategy.

Through the realization of the previous step, detection of test inappropriateness in many laboratory tests is possible. The key is to have the knowledge and the

experience to make the right decision regarding which test to choose to achieve its proper demand. It is mandatory to begin with tests whose demand could be tailored through easy, automatic, and simple strategies. If the only way to diminish 25-OH vitamin D demand is by manual checking of every patient to determine if the test request relates to the clinical question or diagnosis or suspected diagnosis, a lot of human resources are necessary. However, to get a better demand for folic acid test in primary care is easier, using a computer algorithm taking into account hemoglobin and mean corpuscular volume values. It does not happen to vitamin B12 test, which must be requested in additional clinical contexts in primary care patients.

It is also crucial to choose the target population to whom the strategy should be established. Our experience is to begin in primary care or ED, where little effort bring improvement to many patients.

Finally, evaluating the simplicity, risk, and financial consequences of every test in every potential strategy is necessary. It is necessary to classify laboratory tests regarding its strategy simplicity and evaluate the risk and savings generated.

Figure 5.2 shows in color the three degrees or levels that these three conditions are to be evaluated.

Fig. 5.2: Classification of test over-request adverse effects and savings

The simplest strategy will have a green color, and the strategy for the correction of the tests that are economically expensive or would generate adverse effects if not established will have a red color.

As an example, in Figure 5.3, we can observe aspartate aminotransferase, γ-glutamyl transpeptidase (GGT), urate, folate, urea, transferrin, gliadin IgA, and antithyroglobulin antibodies classified through these items. As we can see, urate and GGT are cheap, but can lead to great damage in a patient if over-requested. On the contrary, folate could generate great savings if its demand is corrected, but no adverse effects if over-requested.

5.4.3 Generation of the idea

The third step of our approach is the generation of the idea. A crucial condition, also stipulated in the previous step, is that the strategy should rely on automatic processes,

TEST	Simplicity strategy	Adverse effect	Saving
AST			
GGT			
Urate			
Folate			
Urea			
Transferrin			
Gliadin antibodies			
Tiroglobulin antibodies			

AST: aspartate aminotrasferase
GGT: gammaglutamil transpeptidase

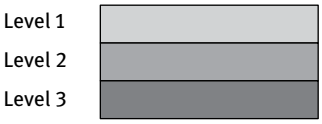

Fig. 5.3: Example of tests classified through "simplicity, risks, and savings"

based on the LIS. Once designed through interdepartmental consensus, if established based on information technologies, they will be continuous over time, without additional efforts needed [18].

5.4.4 Pre-design of the strategy

The fourth step is the pre-design of the strategy. Doing this step in consensus with requesting physicians is crucial. It is also important to have a simple comprehensible pre-design as well as to arrive at the meeting with "virtual strategy results" achieved by a LIS retrospective simulation of potential results of strategy implementation. The benefits that the patient and healthcare organization are going to achieve with the strategy implementation should be explained in detail.

5.4.5 Strategy final design

The fifth step is the strategy final design. In this step, the procedure must be written down in our standard operating procedure and comprises the strategy initiative, objectives, indicators, and goals.

5.4.6 Strategy establishment

The strategy always must be established for a specified period. A specified period is very important to ensure strategy monitoring, which is the core of any strategy. As Deming stated [28], a key source of production quality lies in having clearly defined, repeatable processes. A specified period of time to monitor, evaluate, and decide whether to continue, stop, or re-design the strategy for better results is necessary.

It is in this step of strategies to correct inappropriateness in laboratory test requesting when the evaluation through process and outcome indicators is most important.

5.4.7 Monitoring through process indicators

Process indicators (Table 5.1) show how the strategy is working overtime, in terms of test measurement diminution or increase, depending on whether we are solving test over- or under-requesting [18]. Monitoring is always advisable through the use of indicators that measure ratio of the request of related tests. There are a lot of examples in bibliography as free thyroxin/thyrotropin or aspartate aminotransferase/alanine aminotransferase. This type of indicator has an additional advantage. Some have a target to be reached. When we do not have at our disposal this type of indicators, we must monitor the number of requests of the test we are correcting the inappropriateness related to a highly requested test. An example is the ratio of uric acid to glucose request in primary care when solving uric acid over-request [15].

5.4.8 Evaluation through outcome indicators

We are always saying "laboratory data intervene in 70% of clinical decisions"; however, are we measuring this intervention in terms of patient improvement? It is the main point of any strategy design. From the beginning, and also through consensus, it is necessary to decide what are we going to measure to know the improvements achieved in patients and healthcare organizations. This requirement is especially important when the strategy is established to correct tests under-request because we are increasing expenses and it is imperative to know if we are detecting occult diseases [16] and the cost per case detected. These strategies are very useful in detecting occult diseases such as hyperparathyroidism and diabetes, the number of diabetic [17] or primary care hyperparathyroidism patients detected [16], and the cost per detected case. Also, when diminishing uric acid demand, a concomitant decrease in the prescription of allopurinol, and a reduction in the laboratory and overall health system economic costs occurs [15, 18].

5.4.9 Final decision whether to continue or stop the strategy

Through the evaluation of outcome indicators, we could make the right decision whether to continue or to stop strategy in terms of improvement in patient and healthcare organization.

I hope reading of this chapter will encourage the readers to be part of this fascinating journey of improving the request of laboratory tests for a better decision-making and patient safety. It has been very gratifying for us. It is a never ending expedition; we daily design and establish new strategies, following our step by step procedure [29] with the purpose of achieving the most efficient approach focusing on enhancing patient safety.

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Enrique Rodriguez-Borja

6 Potential of computer physician order entry (CPOE) to improve patient safety related to laboratory test requesting

6.1 What is a computer physician order entry (CPOE) system?

A computerized physician (or provider) order entry (CPOE) system is a software application that allows clinicians to enter orders directly into a computer [1]. Although the first CPOE systems were initially implemented on drug prescribing to minimize medication errors, currently, CPOE systems are seen as a useful tool for improving the appropriateness of laboratory test requesting. For this reason, they are also known as electronic test requesting systems.

The recent introduction of CPOE systems is widely perceived to be an important building block for establishing electronic medical records. As we will see in this chapter, CPOE systems not only automate the clinical ordering process but also incorporate several features such as decision support mechanisms, built-in alerts, and rule-based prompts, which provide the potential to improve the quality of healthcare and final patient outcomes [2].

However, based on how it is designed and implemented, CPOE can be a pure blessing or a fatal curse. In the worst-case scenario, we can face an electronic test requesting system in which almost any test from the full catalogue, from the most common to the most esoteric, is easily available to all practitioners, or a computer application where the minimum interval-based retesting recommendations are starkly absent [3].

An effective CPOE system must incorporate design strategies and clinical decision support systems to optimize practitioner's test-ordering behavior. Otherwise, they would not be different from the old paper-based systems and not only would be unable to find any advantage, but we will also experience unexpected drawbacks.

In the following pages, we will describe the ingredients to obtain a recipe for success, instead of a recipe for laboratory misutilization. Readers should keep in mind most of the suggestions next time they want to implement a new CPOE system or update or improve their current one. From all the technology in our laboratories at the present time (pre-analytical devices, automated analyzers, storage facilities, etc.), the most developed system should be our CPOE due to its importance and influence at any level: pre-analytical, analytical, and post-analytical.

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6.2 CPOE interventions

There are two particular strengths of CPOE systems that distinguish from other types of interventions related to test appropriateness like clinical guidelines development, education strategies, or reimbursement and funding models.

First, they include real-time decision support. All the available strategies work together efficiently when clinicians are entering orders. The laboratorian's brain can interact in the ordering process, reformulating the brain-to-brain loop concept for laboratory medicine introduced by Lundberg [4] 40 years ago (Fig. 6.1).

Second, CPOE interventions (if they are well designed) are sustained over time with little effort. Unlike most of the educative strategies (when the intervention finishes, testing behavior reverts to preintervention levels), CPOE interventions do not require continuous feedback and they keep a constant level of adherence and effectiveness due to their automatic/algorithmic nature.

We can classify CPOE interventions into to two major groups depending on how they work:

– Design strategies: They are mostly based on CPOE design or architecture. Their actions can affect to laboratory formularies (or request forms) and test/profiles basically. They are easy to implement depending on CPOE capabilities and they normally tend to act passively.

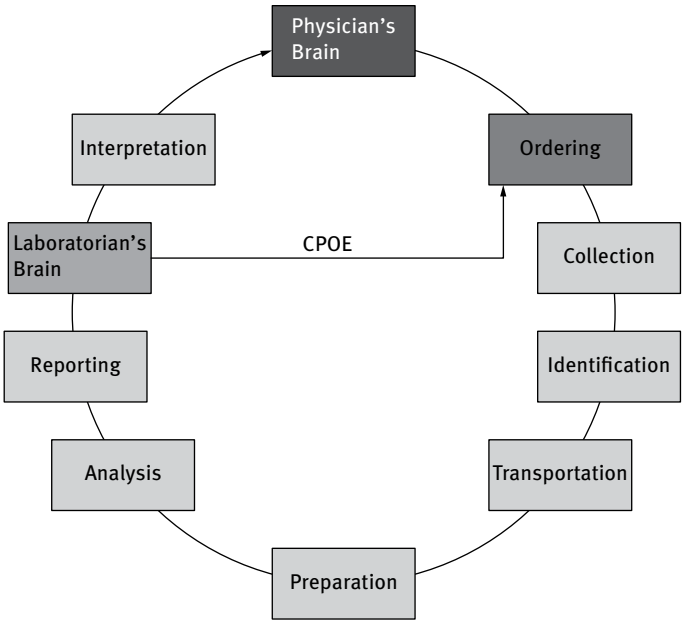

Fig. 6.1: Brain-to-brain loop concept for laboratory medicine reformulated introducing CPOE

– Clinical decision support rules (CDSRs): They actively match the characteristics of individual patients, providers/physicians, or scopes of action (e.g. emergency departments, inpatients, outpatients, general practitioners, etc.) to a computerized knowledge base and provide specific recommendations or rules [5]. They are much more evolved than design strategies and imply a certain degree of algorithmic programming using Boolean operators (e.g. AND, OR, NOT, or AND NOT).

Needless to say, all the interventions introduced in a CPOE system must be developed with full involvement of laboratory staff, physicians, and other stakeholders.

6.3 Design strategies

Interventions included in this group are shown in Tab. 6.1.

6.3.1 Re-design of the request formularies

A laboratory (test) formulary is similar to the pharmaceutical request form present in most institutions. It can include individual tests and/or profiles/panels (groups of tests). Re-design of the request form involves making changes so as to restrict requests for individual tests or groups of tests with the objective of encouraging more appropriate test use in a range of clinical settings. In general, it is closely aligned to promotion of clinical practice guidelines [1, 6–9].

From a practical viewpoint, the simplest way of reducing test demand is to remove its availability from the test request form. Results are immediate. These decisions are normally initiated by the laboratory rather than by the user and usually rely on consensus expert opinion or local protocols because of the difficulty in providing high-level evidence most of the time.

However, the success of these measures must be seen against a baseline situation. There are limits as to which tests can be removed from a formulary without potentially adversely influencing patient care. There is an increasing trend toward

Tab. 6.1: Design strategies for CPOE systems

Design strategies for CPOE systems
Re-design of the request formularies
Use of clinical (or disease-specific) profiles/panels
Customized formularies
Display costs/fees
Search functions
Research/clinical trials formularies

limiting the number of tests available as ticking boxes and expecting users to request the specific tests they wish through a search engine.

Although we will discuss later, the use of clinical profiles, "disease-specific" profiles, or "question-specific" profiles (e.g. "celiac disease diagnosis" or "diabetes mellitus monitoring"), rather than "organ-specific" profiles (e.g. "liver profile" or "kidney profile"), is a good approach to manage re-design processes.

Owing to the low marginal costs for laboratories running multichannel continuous flow analyzers, inclusion of large numbers of tests on request forms used to be commonplace. This decision could be counterproductive. We suggest other different approaches.

When we design a formulary, we have to take into account both the type of provider and the scope of action. If it is going to be a generic formulary, open to every medical specialty and available in any scope, the use of specific clinical profiles should be restricted and esoteric tests and expensive parameters (e.g. immunoassays, advanced tests) should be removed from the form. In this case, unbundling profiles into its constituent analytes and/or introducing simple and common profiles/panels very harmonized between medical specialties could be a good approach.

Laboratories must increase their efforts to engage with the test users to provide a useful formulary without making the process unwieldy. Having well-designed request forms is a key success factor prior to implementing more evolved interventions.

6.3.2 Use of clinical (or "disease-specific") profiles/panels

Allied to request form re-design is the intervention of "test profiles". Historically, these have been conventional organ-based profiles such as liver, kidney, and thyroid. However, in clinical practice, patients presenting with non-specific symptoms are investigated for a range of possible diagnoses that may include different organ systems. Besides, monitoring tests can be simplified and there is no need to measure all the tests included in a profile if the main goal is merely to detect a variation in one particular test [6, 10].

Moving toward "disease-", "symptom-", or "question-specific" profiles could be very interesting if they are customized for several medical specialties or scopes of action and if they are only available for those particular providers in customized formularies as ticking boxes. Additionally, in teaching hospitals, introduction of this type of profiles could have a relevant educative purpose.

Clinical profiles could be defined based upon a list of clinical scenarios that span most cases for each medical service or scope. These profiles should include the minimum required amount of tests to diagnose or monitor a specific disease or condition (e.g. "lupus diagnosis"/"lupus control"; "female hirsutism diagnosis"/"female hirsutism control"; "chest pain in emergency department"/"myocardial infarction monitoring"). Normally, monitoring profiles should include fewer tests than diagnosis profiles. Needless to say, reflexive tests would not be included in those profiles.

In case of outpatients or primary care requests, this is a promising opportunity for CPOE systems to offer a default test selection that can be supplemented if necessary, rather than a larger profile or profiles being selected by default. If the profiles are fully agreed with clinicians, requests for an identical clinical situation will be more robust and homogeneous, with less degree of confusion for junior doctors or doctors moving between different hospitals.

Additionally, requesting process by clinical profiles should be wieldier and faster than ticking tests one by one. This would not only improve the physician's testing behavior but it would also make users more familiar with CPOE systems in a shorter period of time, thus overcoming resistance to change. We strongly recommend that included tests should appear when the cursor hovers over a profile cell or tick box (as a pop-up box for example) in order to give extra information.

When it comes to developing these profiles, we recommend developing local best-practice guidance, allied to national guidelines. Despite its potential, clinical profile-driven requesting can result, if not implemented and managed carefully, to an increase rather than a decrease in inappropriate requesting. Unfortunately, although the concept of clinical profiles (e.g. admission profile) was described 30 years ago, little has been published on this subject.

6.3.3 Customized formularies

A robust CPOE should offer dozens of request forms based on medical specialties (e.g. oncology, endocrinology, pediatrics, etc.), scopes of actions, and/or group of doctors that share an specific area of knowledge (e.g. neuropediatricians).

These customized formularies should be only available to allowed users. CPOE should detect physician ID and specialty/subgroup and filter only the authorized request forms based on this information.

The process of design customized formularies has to imply both laboratory professionals and medical services, and it can be a didactical and rewarding dialogue between both parts. It is not only a matter of having a powerful tool to manage demand for laboratory tests but also of achieving a handy, quick, and useful setting for physicians. In a ticking box CPOE system, we first suggest classifying test/profiles into four major groups (Figs. 6.2 and 6.3).

1. Diagnostic/symptom profiles: These profiles can be deployed in the first column of a customized formulary. It should represent most of the clinical scenarios of a medical specialty in a patient's first visit and ensure important tests for diagnosis are not omitted. Moreover, by offering a default set of investigations, it potentially reduces the likelihood of inappropriate tests being added. However, implementation of such profiles needs to be monitored closely to prevent misuse and increased inappropriate profile usage (e.g. a good KPI could be ratio the of the number of diagnostic profiles to the total number of requests, with a high ratio implying an inadequate ordering behavior).

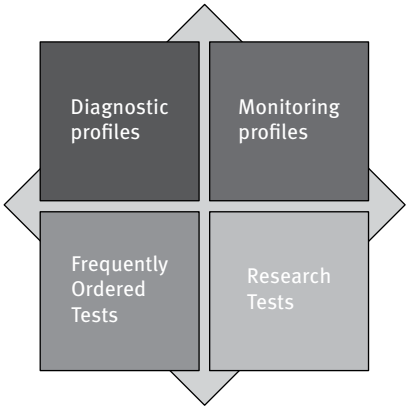

Fig. 6.2: Customized formularies: groups of tests/profiles

2. Monitoring profiles: These profiles can be disposed in the second column. We suggest matching in the same row diagnostic profiles with the related monitoring profiles in order to ease the physician's ordering process (e.g. "lupus diagnosis" and "lupus control"; "diabetes mellitus type I diagnosis" and "diabetes mellitus type I control"). If our CPOE has an evolved test restriction system, it could be interesting vetting one of them when both types of related profiles (diagnosis and monitoring) were ordered in the same request.
3. Frequently ordered tests (FOTs): In the following columns, several individual FOTs can be deployed. These tests are not included in the previous profiles but are frequently used by this particular medical specialty (e.g. hepatology form: coagulation tests should not been included in any profile but they should be easily available if necessary; endocrinology form: urine cortisol for similar reasons). Again, when setting these tests aside, we decrease the odds of being ordered massively and inappropriately. The rest of the tests from the full catalogue should be only available through a search engine. When examining the effectiveness of demand management strategies, FOTs should be carefully reviewed. If we detect an overuse (FOTs ordered are equal or almost equal to clinical profiles ordered) and we are not able to find a logical explanation, it is better to move those tests out of the customized form to the search engine.
4. Research tests: If we have developed special research protocols with a particular medical service (research tests, in house clinical trials, specific aliquoting, sample storage or treatment after analysis, etc.), it could be interesting to deploy these tests/profiles in some final ticking boxes. If we want to familiarize physicians with CPOE systems, it would be better to introduce all the elements associated with the laboratory (both healthcare and research) in their request forms.

6.3.4 Display costs/fees

Although overuse of diagnostic tests is a multifactorial problem (physicians' practice of defensive medicine, insufficient understanding of the limitations of tests, patient expectations, inability to retrieve the results of a test already performed, learned behaviors, etc.), it is also clear that most physicians do not know how much tests cost and this fact may also influence ordering behavior.

Several studies have been published showing the effects of feeding back either the cost or volume information to users of laboratory services, but only a few in a CPOE context. It seems the impact of feedback test costs is likely to depend on the requesting physician's direct responsibility for laboratory expenditure [6, 11–17].

Cost containment is not a new concern. Tierney et al. [18] in 1990 were the first to display charges at the time of test ordering in an outpatient academic clinic. They found that the number of laboratories and costs decreased, but the differences did not persist after the intervention ended. Studies published afterward have showed variable success. In fact, the most recent studies offer a modest overall financial impact just by simply displaying fees of some laboratory tests in the CPOE with no additional interventions [19, 20].

Normally, all these studies have an important limitation – the durability of the results over years is not known. It remains unknown if displaying fees of all tests would lead to a more dramatic reduction in test ordering or desensitize providers to the displayed fee information.

We should not dismiss the idea that providing cost information would encourage physicians to concentrate on test appropriateness, but it is unlikely that this intervention alone will be the key element due to its modest effect.

If we want to introduce fees in our CPOE system, we can achieve a more effective visual impact if test/profiles are classified in groups (low, medium, high, and very high) based on their cost and a visual color code is assigned for each group (in a traffic light way) instead of merely introducing an economical quantity. A similar approach could be done for the requests, categorizing them in groups based on their final cost and additionally displaying the same color code as in test/profiles (Fig. 6.3).

6.3.5 Search functions

If our CPOE system is going to rely upon clinical profiles and/or FOTs included within customized forms or specialty-restricted templates, it is obvious that the majority of our full catalogue would not be available unless we have an accessible test search engine.

The functionality of this search engine must include truncated search (typing incomplete words anywhere in the test name), use of test synonyms (and common acronyms), and search of clinical profiles (using names of conditions and/or diseases).

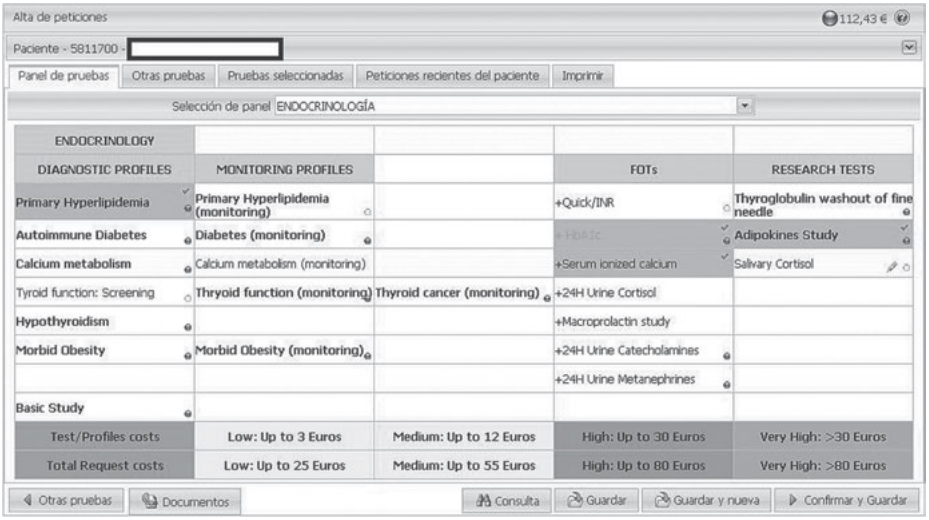

Fig. 6.3: Customized formularies/clinical profiles and display costs: endocrinology formulary (Hospital Clínico Universitario de Valencia, Spain). Request total cost in euros is shown right at the top. Each profile/test has a colored dot showing its price range

Our available ordering catalogue (used by this search engine) can be different from our full catalogue (used for consultation) in terms of inclusion of fewer tests. That is necessary if we decide that some of them can only be added within laboratory (as some reflective tests). For this purpose, it would be interesting, when defining new tests, to specify if the test just can be consulted or if it is available for both consultation and ordering through CPOE.

6.3.6 Research/clinical trials formularies

CPOE technology described previously allows us to keep apart laboratory activity related to routine healthcare from the activity linked to big research studies or randomized clinical trials (RCTs).

We can develop several formularies where we collect all official and active clinical trials in our institution. Normally, pharmacological clinical trials include several monitoring requests based upon trial's phases or treatment cycles (e.g. oncology RCTs). These cycles might be configured as clinical profiles and displayed on customized forms or templates restricted to allowed users as we described before (Fig. 6.4).

In this way, if our laboratory information system (LIS) can deal with this information, we can exploit from a statistical standpoint not only the volume but also the costs associated with this specific activity in terms of feeding back or, more importantly, getting financial incentives from RCT promoters [6, 11, 21].

Fig. 6.4: RCT formulary: lung cancer RCTs formulary (Hospital Clínico Universitario de Valencia, Spain). Request total cost in euros is shown right at the top. Each tick box represents a treatment cycle for a particular RCT

6.4 Clinical decision support rules

Clinical decision support (CDS) is defined as "the use of information and communication technologies to bring relevant knowledge to bear on the healthcare and well-being of the patient" [22: p. 8]. CDSRs in laboratory test-ordering interventions are shown in Tab. 6.2.

6.4.1 Specialty/staff-grade limitations

A further way to prevent inappropriate requesting, particularly of the specialist and esoteric tests, is to limit requesting to specific specialties and/or more senior staff. This approach, while really effective, was often difficult to police in non-CPOE contexts [6, 23–26].

The results of two Australian studies [26, 27] supported the observation that senior clinicians were likely to request fewer tests when they had a more direct involvement in planning clinical pathways and in the early stages of the patient's management. However, the general impression is that long-term effectiveness was somewhat limited due to the lack of a CPOE system.

Fortunately, electronic request systems allows us to restrict more easily and in a sustained manner any test order depending on provider grade (or ID) and/or medical specialty. However, some authors have stated that if it is not set up and policed carefully, this intervention can result in the opposite effect [6].

Some examples regarding this intervention could be:

- IgD only available for oncology and hematology services (because it is only useful as a marker of changes in the size of the clone of monoclonal IgD plasma cells) (see Fig. 6.5).
- CA15-3 in men only available for oncology services (because breast cancer managing in men is just an exclusive task of this specialty).
- β-Amyloid and tau peptides in CSF only available for neurology services (because Alzheimer disease is managed by this specialty).
- Glomerular basement membrane antibodies IgG only available for pediatrics, internal medicine, pneumology, and nephrology services (because it is only useful for evaluating patients with rapid-onset renal failure or pulmonary hemorrhage, as an aid in the diagnosis of Goodpasture syndrome).

Tab. 6.2: Clinical decision rules for CPOE systems

CDSRs for CPOE systems
Specialty/staff-grade limitations
Minimum retest intervals
Asking for additional information: questions
Suggestions/corrections

Fig. 6.5: CDSR for IgD (Hospital Clínico Universitario de Valencia, Spain). IgD is cancelled if it is not ordered by an oncologist or hematologist

6.4.2 Minimum retest intervals

This strategy aims at repeat requests for tests within a time frame that is considered too short for detection of a meaningful change in clinical status. The time interval, usually based on analyte half-lives and reference change value, can be established from clinical protocols or published guidelines and consensus statements [1, 28–30]. Electronic requesting has a major advantage over other laboratory interventions: it prevents requests at source prior to phlebotomy, avoiding inconvenience for patients.

In a CPOE context, requests are monitored to identify repeat requests that fall within the minimum retest interval. Commonly, computer-generated notifications and feedback are provided to clinicians using pop-up alerts if repeat requests are made within the retest interval, inviting cancellation of the repeated test. Clinicians can override the time limit accompanying a reasonable explanation in the electronic request that should be reviewed afterward in the laboratory. This is also known as "soft-stop" clinical decision support rules. Soft-stops have to be accompanied by a "send-and-hold" system [3] within the laboratory to check if the override has been correctly justified. We will discuss about this functionality later.

For some tests, like genetic tests (results are invariable) or when the evidence strongly supports cancellation (e.g. inpatients' lipid profile within 10 days), CPOE should reject the test automatically without exception. We could consider this way a "hard-stop" CDSR. Even a hard-stop seems to be more effective (and they are); for some patients, it could be an inappropriate approach due to a possible harmful clinical impact.

Some evolved CPOE systems can even cancel a test if there is a pending result (due to a long turnaround time, like genetic tests), but the sample was received in the laboratory in the past. In fact, some systems allow to cancel test if there is a previous order, but for the future test.

Even though laboratories admit to using their LIS to identify such requests, and studies advocate this as an approach to demand management, there is a lack of published data on recommended minimum retest intervals or their effectiveness. An exception is the National Minimum Re-testing Interval Project prepared for the Clinical Practice Group of the Association for Clinical Biochemistry and Laboratory Medicine UK in 2014 [31]. This document covers minimum intervals before retesting for common tests in clinical biochemistry, therapeutic drug monitoring, hematology, and immunology in specified clinical situations, supported by an evidence base.

Most of the recent studies about this subject are restricted to a specific scope of application. It is obvious that differences arise between primary and secondary care. In the acute phase, minimum retest intervals are very dependent on the clinical state of the patient in addition to previous information or results [6, 32–35].

Recently, Moyer et al. [36] have showed good results implementing CDSRs for serum ionized calcium, magnesium, and N-terminal pro-brain natriuretic peptide (NT-proBNP) in intensive care unit patients through a soft-stop system. They also

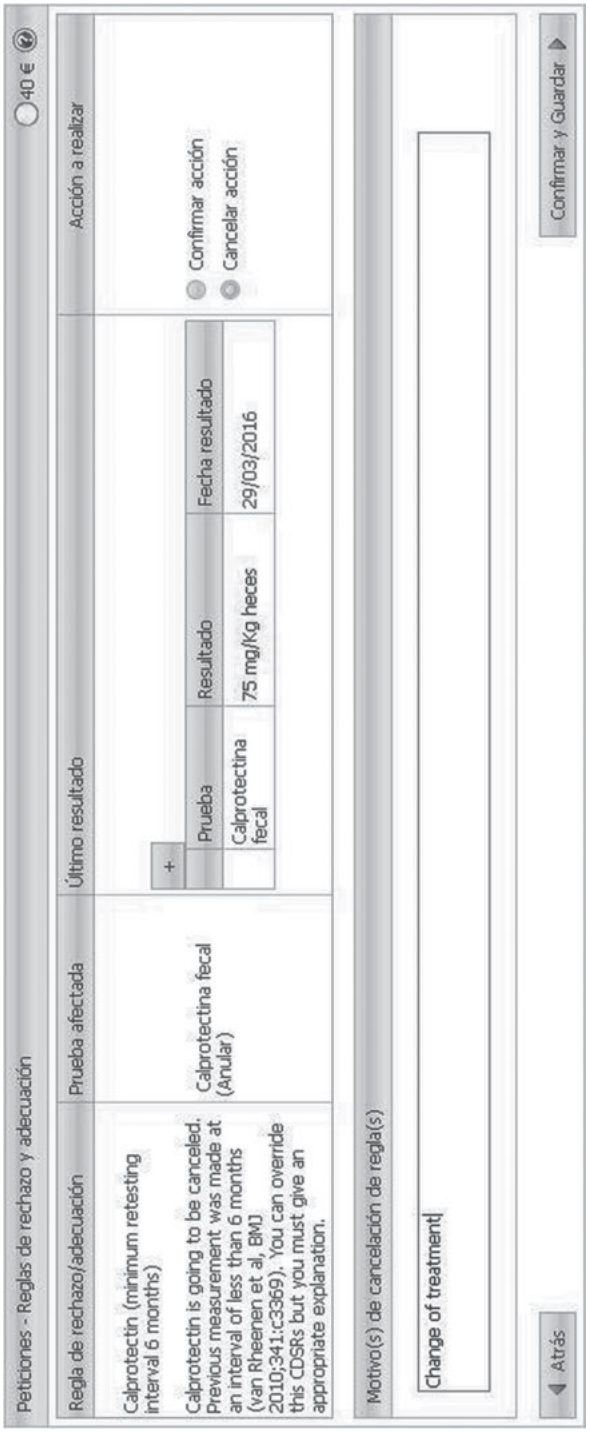

Fig. 6.6: CDSR (soft-stop) for calprotectin (Hospital Clínico Universitario de Valencia, Spain). Providers have to explain the reason for overriding the rule if they want to finish the order, and laboratory will review their explanation afterward ("send and hold")

found a significant decrease in pop-up alert volumes during the first 3 months of the intervention, which suggests that providers changed their test-ordering patterns to avoid interacting with the CDSR pop-up alert box. Be reminded that inundating our providers with tons of pop-up boxes could be counterproductive whether they underuse some tests to get rid of pop-ups or, even worse, they just consider CPOE system a disruption because of the many alerts.

Decreasing the frequency of testing does not result in improved quality of care if patients are experiencing adverse effects as a result of this decrease in testing. To ensure this is not the case, after implementing CDSRs, we have to be aware of any change in the incidence of related conditions or any feedback from clinicians with concerns that this approach has harmed patients.

Nevertheless, this strategy makes up a promising area and one that could certainly reduce the tendency to repeat unnecessary tests. Some examples regarding this intervention could be:

- HbA1c testing [31] at 2- to 6-monthly intervals in patients with unstable diabetes, with a measurement made at an interval of fewer than 3 months being used as an indicator of direction of change rather than as a new steady state.
  - In those with stable diabetic control on unchanging therapy, intervals of 6–12 months are recommended.
- Fecal calprotectin: minimum retesting interval 6 months [31] (Fig. 6.6).
- Fecal elastase: minimum retesting interval 6 months [31].
- NT-proBNP: serial or repeat measurements during hospitalization are of questionable clinical utility and not recommended. Measurement once at admission (to confirm diagnosis of heart failure if unclear) and once before discharge [36].

6.4.3 Asking for additional information: questions

CPOE systems can trigger several questions related to specific test that provider have to answer compulsorily. The aim of this intervention is double. On the one hand, laboratory wants additional information regarding the patient or condition to know if the test is appropriate or not (or just because it is necessary for test validation purposes). Normally, this information is not easily available through medical records. On the other hand, indirectly, providers will change their test-ordering behavior to avoid interacting with the questions when the test is not necessary.

This strategy must be accompanied by a "send-and-hold" system. A "send-and-hold" is an automated functionality that allows providers to make their test orders by answering some questions, but puts on hold those tests until laboratory professionals review the reasons given and decide if they are appropriate or not [3] (Fig. 6.7).

When it comes to designing questions, we suggest, instead a free text field, proposing multiple-choice questions (if it is possible) [36]. In multiple-choice questions, respondents are asked to select the answer out of the allowed choices from a list.

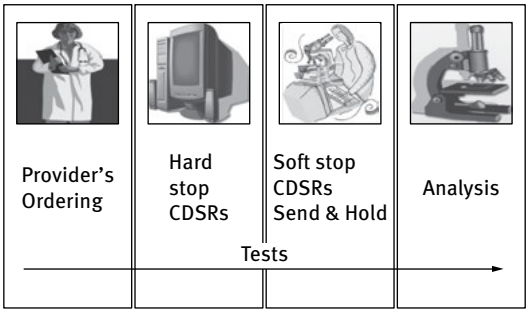

Fig. 6.7: CDSR: scheme

There are several advantages to multiple-choice questions even if they are a "yes/no" question. They are easier to answer, require less time to administer, and they are wieldier to review. Besides, captured information will be systematized if we want to treat it statistically. Additionally, for some questions regarding test adequacy, it could be an indirect educational intervention sustained in time [37].

For example, if ordering providers are asked to specify an indication for repeat NT-proBNP measurement in intensive care units and the only allowed indications are "major intervention", "change in therapy", "rule-out heart failure", and "hospital discharge monitoring", it will be better if this information is entered through a multiple-choice question rather than a free text field. Always showing an options list will reinforce the main message to new providers: "these are the four only allowed indications for this test".

Finally, if our CPOE allows for the possibility, some of the questions could be reformulated as a file uploading. A good example is the signed informed consent, compulsory in most of the genetic tests, other diagnostic tests unavailable in medical history (imaging tests), or a brief summary of the patient's medical record if the test is going to be outsourced to an external laboratory and this information is essential, etc.

To recap, "send-and-hold" systems imply a new dimension for laboratory professionals, not only in their design and planning but in a new daily task in laboratory work process to manage test demand.

Some examples regarding this intervention could be:

- Genetic tests: "informed consent" (attached document), "genes of interest", "relevant clinical data", etc.
- Prenatal screening: "nucal translucency", "ultrasound data", etc.
- Monitoring drugs: "weight", "height", "doses", "frequency", "other concomitant drugs", etc.
- Vitamins: "reason for the request", "relevant symptoms", "suspected diagnosis", etc. (Fig. 6.8).
- D-dimer: "Wells score".
- Troponins: "symptoms time onset"

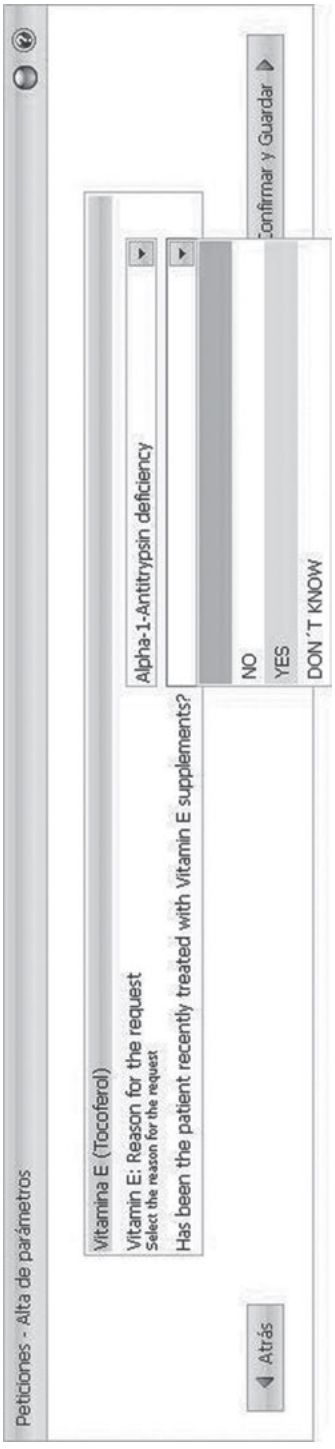

Fig. 6.8: CDSR for vitamin E (Hospital Clínico Universitario de Valencia, Spain). An example of a multiple-choice combo question

6.4.4 Suggestions/corrections

In this chapter, we have explained some strategies through CPOE to avoid test overuse, assuming that the CPOE system can only cancel tests, not correct or add tests. The emphasis of laboratory utilization programs should never be exclusively on reducing the number of tests. Again, it is imperative to consider clinical outcomes and the changes to patient management.

Zhi et al. [38] found the mean rate of under-utilization of testing in their systematic review to be 44.8%, more than twice the rate of over-utilization. Missed tests may have a significant impact on patient outcome.

CPOE systems can suggest or correct ordered tests through CDSRs based on the potential of their results database. For all these, suggestions/corrections override by provider should be allowed after giving a justified reason or answering some questions as in "soft-stop" rules. We do not recommend "hard-stop" rules in this case due to its inappropriateness.

Fu et al. [39] showed that a lower frequency of HbA1c monitoring is significantly associated with poorer glycemic control. If we detect an underused test that should be measured more regularly for a specific patient, a basic CDSR could propose its measurement. The same for a misused test ordered improperly due to confusion (normally related to the test name). The only requirement for implement this strategy is that CPOE has to be able to trigger the rule where the test subject to control has not been ordered.

Suggestions can just give additional information on best practice around testing at the same time of requesting or provide requestors with information regarding test prerequisites to be met in with the purpose of interpreting future results. Again, the frequency of this additional information should be kept to the minimum required, in case of using pop-up boxes, to prevent frustration on the requestor [6].

Improvement in information technology and clinical decision support systems may reduce physician's uncertainty. Even so, utilization of electronic requesting systems as an automated educational tool remains not thoroughly studied.

Some examples regarding this intervention could be:

- Addition (HbA1c): diabetic patient without results of HbA1c in the last year.
- Addition (urea and electrolytes): urea and electrolytes not ordered in an emergency request coming from a patient with previous hypocortisolism.
- Addition (urine electrolytes): urine electrolytes in an emergency patient with euvolemic hyponatremia (SIADH suspected).
- Correction due to a possible confusion: 1,25-$(OH)_2$-vitamin D ordered instead of 25-OH-vitamin D from primary care. 1,25-$(OH)_2$-Vitamin D is restricted in patients with severe renal condition or 1-α-hydroxylase deficit. CPOE proposes a test exchange (Fig. 6.9).

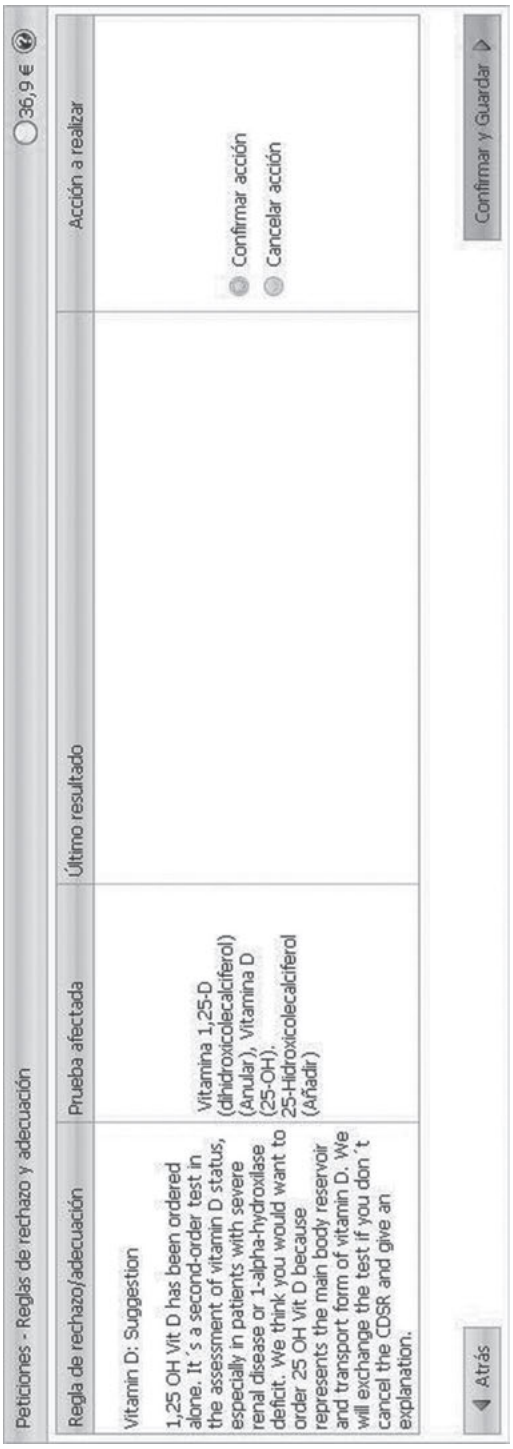

Fig. 6.9: CDSR (soft-stop) for 1,25-$(OH)_2$-vitamin D (Hospital Clínico Universitario de Valencia, Spain). An example of a correction CDSR due to a possible confusion. 1,25-Vitamin D has been ordered instead of 25-vitamin D

6.5 CPOE advantages in pre-analytical phase

Apart from all the advantages described previously, the introduction of electronic requesting can reduce the number of pre-analytical errors and improve the quality of information received with each request. Turner et al. [40] showed a marked decrease in the number of pre-analytical errors following the introduction of electronic request in primary care: pre-implementation error rates ranged up to 5.7% of orders, whereas post-implementation error rates were <0.6%. CPOE systems can avoid specific issues in this area as illegible writing, mismatch of patient ID, wrong sample container used, unlabeled samples, etc.

CPOE systems can generate printed sample labels that clearly indicates which sample tube should be used, where the sample should be sent, or, in more evolved systems, display additional information through computers to phlebotomists at the time of venipuncture (number and type of tubes, special requisites or procedures, etc.) (Fig. 6.10). Owing to electronic request flexibility, modifications can be made continuously to ensure users have the most up-to-date information. In some of these systems, phlebotomists can report electronically any incidence related with the venipuncture process real time.

By means of this functionality, CPOE systems not only improve the quality of information supplied with each request, avoiding risks related to patient safety but have the potential to reduce the repeat requests created when the original sample was non-compliant.

6.6 Conclusions

Successful management of laboratory test requesting demands that the entire laboratory team to use their knowledge to detect utilization issues and implement an strategy that will achieve more effective laboratory testing without forgetting that the target of requesting of the test and of the results should be the patient.

A systematic review of the CPOE literature made by Georgiou et al. [41] in 2006 aimed to review evidence of the impact of CPOE on hospital pathology services. They identified 19 studies that contained some form of “control group” and categorized these into three groups: studies comparing CPOE with no decision support to paper systems; CPOE with decision support to paper systems; and CPOE systems with specific pathology features compared to systems without those features. Sixteen were considered outcomes that could be specifically related to appropriateness issues such as clinical indicators, length of stay, or appropriateness of stay. The CPOE systems (both with and without CDSRs) when compared to no CPOE showed an overall trend toward reduced test cost and volume. Additionally, fewer tests and fewer inappropriate tests were performed in the decision support group. Four studies demonstrated improved compliance with testing guidelines for CPOE with CDSRs.

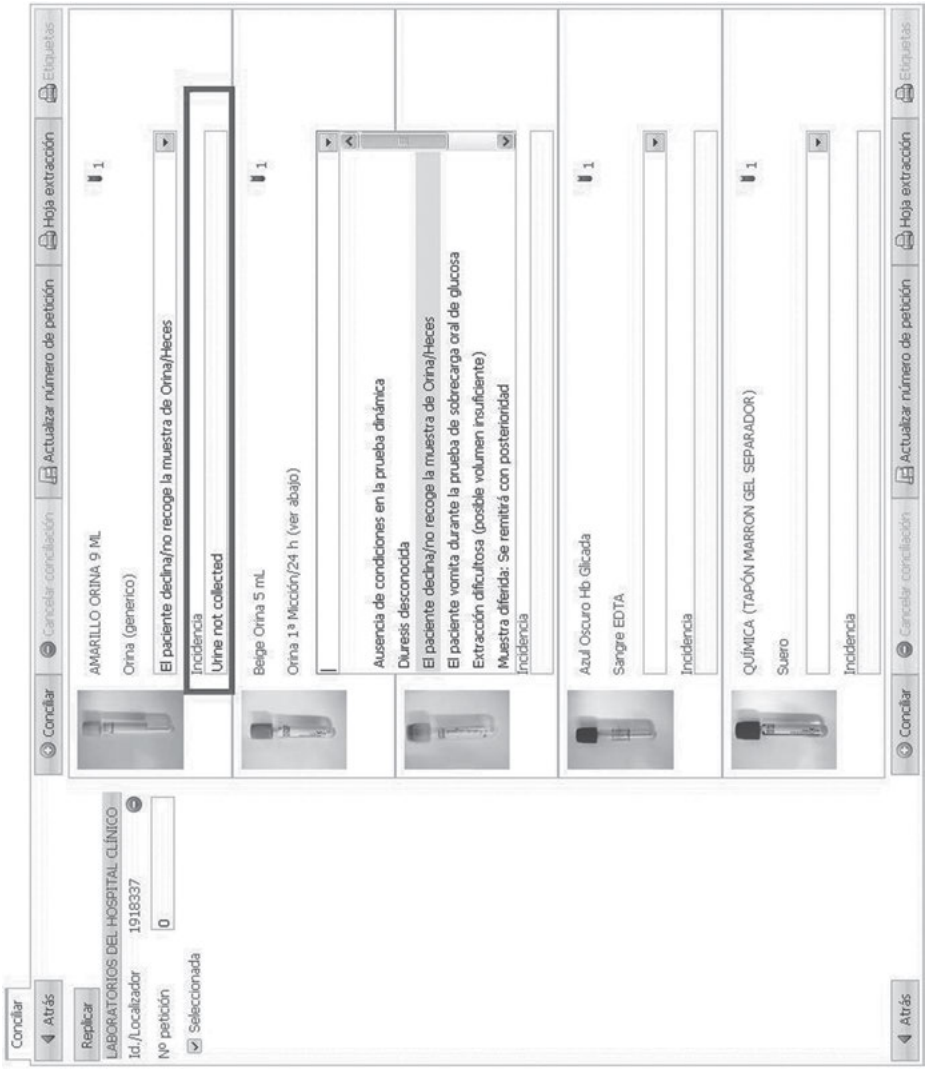

Fig. 6.10: Real-time venipuncture software with incidence report module (Hospital Clínico Universitario de Valencia, Spain)

In our particular experience, CPOE has allowed us to implement several strategies through a multifaceted approach, which appears to be most effective. We show some annotated results (data not published) in Fig. 6.11.

Several strategies were implemented longitudinally in Fig. 6.11: (1) a full re-design of the electronic emergency request form, removing expensive tests from the request form and making them available only through a search engine (May 2011); (2) costs were displayed (February 2013), but its impact was mild. Shortly after April 2013, CDSRs were developed for expensive emergency tests like NT-ProBNPs, D-dimer, and

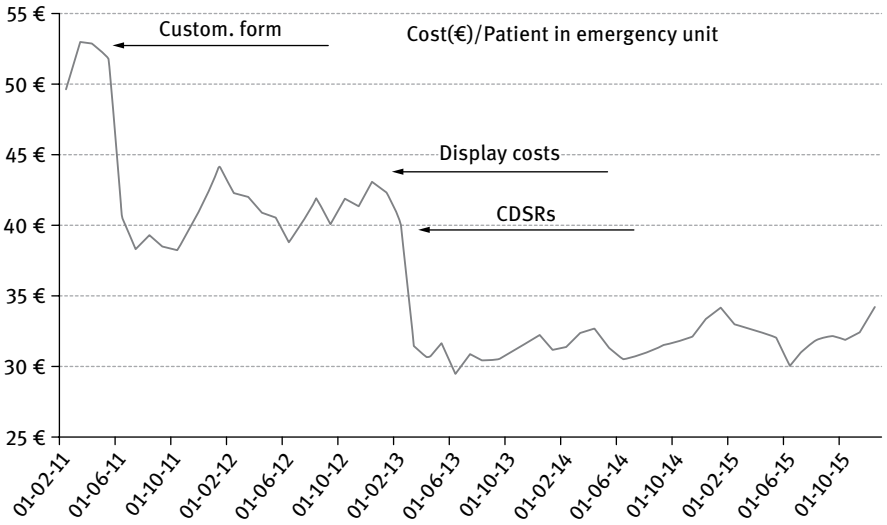

Fig. 6.11: CPOE with CDSRs in the emergency unit: cost (€)/patient in the emergency department, February 2011 to December 2015 (Hospital Clínico Universitario de Valencia, Spain)

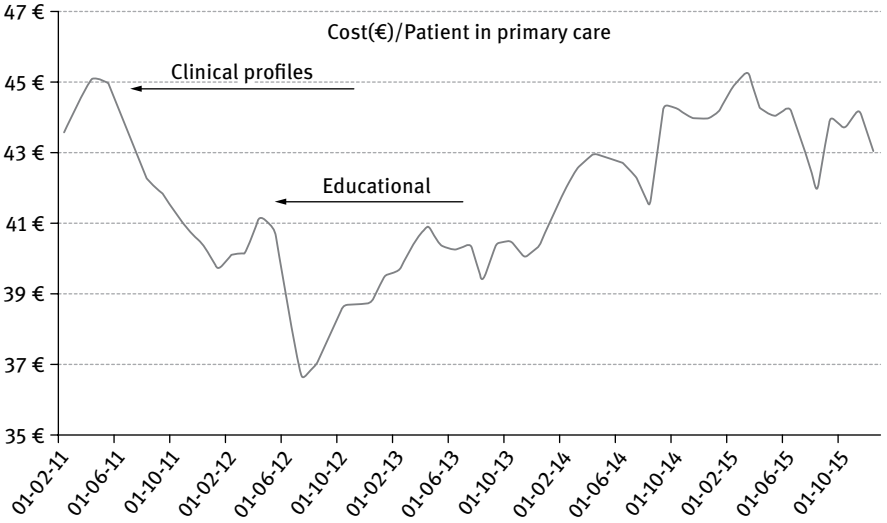

Fig. 6.12: CPOE without CDSRs in primary care: cost (€)/patient in primary care, February 2011 to December 2015 (Hospital Clínico Universitario de Valencia, Spain)

procalcitonin by means of soft- and hard-stops, achieving good results in terms of cost. It seems quality of healthcare and patient outcomes were not altered during this time period after asking our providers repeatedly.

Our CPOE system for primary care was less evolved than the previous one and did not allow us to implement CDSRs (Fig. 6.12). Only two interventions were made: (1) the development of clinical profiles (May 2011) that worked well but in a brief period of time and (2) an educational activity through face-to-face sessions with general practitioners (June 2012) with short sustainability. Even though successful schemes more commonly use a combination of approaches, it seems CDSRs are essential to obtain constant and effective results in the long term.

As yet, there is limited published evidence on the impact of CPOE systems on clinical outcomes, but it is undeniable that, while not being a panacea, CPOE will reduce diagnostic errors, thus improving the quality of requesting and therefore patient safety [42, 43].

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