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Review

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Abstract

Background: The inappropriate use of laboratory resources, due to excessive number of tests not really necessary for patient care or by failure to order the appropriate diagnostic test, may lead to wrong, missed or delayed diagnosis, thus potentially jeopardizing patient safety. It is estimated that 5–95% of tests are currently used inappropriately, depending on the appropriateness criteria, thus significantly contributing to the potential of generating medical errors, the third leading cause of death in the US.
Content: In this review, we discuss the reasons as well as the medical and financial consequences of inappropriate utilization of laboratory tests. We then provide demand management (DM) tools as a means for overcoming this issue and also discuss their benefits, challenges, limitations and requirements for successful implementation.
Summary and outlook: When based on current evidence, adapted to local conditions and developed in close collaboration with clinicians, DM is a reasonable strategy for progressing toward better management of over- and underuse of laboratory resources.

Keywords: inappropriateness of laboratory utilization; overutilization; postanalytics; preanalytics; test demand management.

Background

Laboratory medicine has become an indispensable discipline in medical care [1, 2]. Blood for laboratory testing is collected from almost every patient entering a medical facility. The analyses performed on this specimen aid clinicians in many, if not most, medical decisions, and in several instances laboratory results are the only means for making the right diagnosis, for establishing the prognosis or even for treatment decisions. Some examples are cardiac troponins for diagnosing non-ST-elevation myocardial infarction [3], hemoglobin A_{1c} (HbA$_{1c}$) for diagnosing and monitoring diabetes mellitus [4], molecular testing for identifying mutations or polymorphisms associated with monogenetic disorders [5], serology, microbiology and resistance testing for diagnosing and treating infectious diseases and the list goes on.

The available test repertoire, including a variety of diagnostic methods, has evolved massively over the past decades. Accompanying this evolution was the increasing frequency with which laboratory analyses are being ordered and thereby their potential inappropriateness, which should be defined according to the clinical context and the need to improve outcomes [6]. High throughput laboratories are processing anything up to tens of thousands of samples per day. However, it is highly questionable if every single test ordered is indeed used (or required) for the clinical decision making. In a recent study, we estimated that 60–70% of high throughput laboratory tests in clinical chemistry and coagulation are potentially inappropriate, or of minor clinical relevance [7]. Other authors reported inappropriateness ranging between 5% and 95% of tests,

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depending on the criteria used for establishing appropriateness [8–10]. Additionally, utilization of laboratory tests varies between hospitals and regions [11, 12], which cannot be wholly accounted for by population differences.

Inappropriateness does not only include the excessive use of tests not really needed for patient care, but also the failure to order the appropriate diagnostic test, a circumstance estimated to be prevalent in about 50% of laboratory orders [13, 14].

Another issue challenging medical laboratories is that not only does the volume of samples increase year after year, but also the percentage of test requests flagged as urgent rises up to >50% of all tests, depending on the type, size and location of laboratories [15], thus challenging the laboratory staff on a daily basis.

Inappropriate use of laboratory tests, and overutilization in particular, may have a significant impact on patient safety. Each ordered diagnostic test, especially those not really necessary for patient care, carries a risk such as incorrect diagnosis and treatment, unnecessary follow-up tests, incorrect test ordering which delays the actual diagnosis, increases the length of hospital stay, causes unnecessary blood loss, increases resource utilization and causes unnecessary stress for the patient [13]. On the other hand, failing to order the appropriate diagnostic tests may lead to missed or delayed diagnoses, thus contributing further to compromising patient safety. Gandhi et al. evaluated 307 such malpractice claims, and found that 181 of these caused patient harm, up to death in 55 of such cases [16]. Singh et al. estimated that diagnostic errors may occur in at least one in 20 US adults [17]. A recent OECD (Organisation for Economic Co-operation and Development) study estimated that every adult in the US will experience a diagnostic error at least once during their lifetime [18]. And overall, Makary and Daniel recently estimated that medical errors may be the third leading cause of death in the US [19].

How much does inappropriate testing cost us?

Besides potentially serious medical consequences for patients, inappropriate laboratory utilization may generate an enormous financial burden. Health care expenditures increase every year. The current health care expenditure in Europe has risen from 930 USD to 2192 USD per capita (from 6 to 8% of gross domestic product, respectively) in only 15 years (from 2000 to 2015) [20]. Although direct in vitro diagnostic expenses in Europe contribute

only approximately 0.7% (0.4–1.4%) to total health care spending [21], the consequences of wrong, missed or delayed diagnosis, prolonged hospital stay, unnecessary follow-up tests, adverse events and so forth may significantly contribute to the large waste of financial resources. Slawomirski et al. calculated that 15% of hospital expenditure and activity in OECD countries may be attributed to treating quality of care failures. They refer to missed or delayed diagnosis as one of the five most burdensome reasons for these adverse events, contributing to annual costs in England, equivalent to 2000 general practitioners or 3500 hospital nurses [18].

What are the reasons for inappropriate testing?

It is obvious that such a progression of inappropriate use of diagnostic resources is unsustainable. When trying to overcome this issue, the reasons for over- und underuse of laboratory tests should be identified. The most obvious reason may be the advancement in technology, assay repertoire and improved turn-around time (TAT), thus making test ordering and receiving results very easy, quick and comfortable. As availability is creating demand, an electronic order-entry (OE) system may lead to increased test ordering, especially when using the so-called laboratory ordering profiles/panels [7].

Another major factor is the practice of defensive medicine, based on the threat of malpractice liability. Studdert et al. surveyed over 800 US physicians in six specialties at high risk of litigation. Nearly all (93%) reported practicing defensive testing including ordering tests in terms of "assurance behavior" [22]. This is in line with other studies, which also concluded that ordering unnecessary tests is the most common form of defensive medicine [23, 24].

Clinicians and/or nurses are often unaware of the consequences of over-utilization, or they lack an understanding of the diagnostic value of a test [13]. This might be because in most medical curricula, distinct modules in laboratory medicine are missing. Laposata reported that the number of hours spent teaching medical students about the appropriate selection of laboratory tests and the correct interpretation of the test results in the US is only limited to 10 h over the entire 4-year curriculum [25]. Moreover, the real costs of laboratory tests are often ignored or overlooked when ordering tests [24]. Some other reasons for inappropriate testing include patient pressure or practical motives, such as spending as little time on ordering tests as possible [24].

How do we identify inappropriate use of laboratory testing?

Overuse (tests not needed but ordered)

When asked, every laboratory specialist and most ordering physicians will most probably be able to identify superfluous tests or orders for general or specific medical conditions. In a previous study we surveyed clinicians and nurses with the aim of acknowledging what they felt was the leading reason for excessive testing [7]. Laboratory ordering profiles and tests being obsolete because of another analysis result on the same laboratory report were two of the main reasons. Therefore, to identify tests of minor clinical significance, the following questions should be asked before any laboratory order:

– Does the result contribute to diagnosis, prognosis or treatment?
– Is it of medical value and does the result impact patient care?
– Are there other results in the same laboratory order that might be sufficient?
– Are there previous results that would make my order superfluous?
– Is my laboratory order in line with respective re-testing intervals?
– Is the significance of tests clearly acknowledged by clinicians?
– Are these tests in accordance with the current guidelines and recommendations?

Another question that should be asked, but often is very hard to answer in the acute setting, is what the particular test yields in relation to what it costs, i.e. is it cost-effective [26]. However, this question can be asked retrospectively, and results can be the basis for adapting ordering behavior in the future. Han et al., for example, identified five laboratory tests which ranked in the top 13 of the most frequently ordered, yet were least likely to be abnormal or influence patient management [27]. By implementing a financial incentive program for trainees, they could achieve a 47% reduction of selected tests, thus saving 75,000$ of direct costs per year.

Underuse (tests needed but not ordered)

To identify orders, which lack appropriate tests for the individual clinical setting, clinicians would need to know the respective diagnostic guidelines and laboratory

professionals would need to know a specific indication for such order. As both are not always the case, these analyses are mostly retrospective, as in the article published by Gandhi et al. [16]. The authors reviewed 307 closed malpractice orders in which patients alleged a missed or delayed diagnosis in the ambulatory setting, and found that an appropriate diagnostic test was not ordered in 55% of these cases. Results from these evaluations can be used in most of the tools described in the following sections of this article.

Tests needed and ordered but interpreted incorrectly

Although the right test may be ordered for the right patient at the right time and for the right reason [28], there is still a chance that it may be misinterpreted. Diagnostic stewardship should hence acknowledge the advice offered by clinical laboratories in improving test request and result interpretation [29].

When specific clinical indication accompanies the order, laboratory professionals may provide a significant contribution to the clinical decision making. In analogy with over- and underuse of laboratory tests, the assessment as to whether ordered tests were accurately interpreted and correctly used for medical care is only possible retrospectively. In the above-mentioned analysis published by Gandhi et al., 37% of the malpractice claims were based on an incorrect interpretation of a diagnostic test [16].

Albeit this analysis may be of little help, identification of inappropriate use of laboratory testing needs to be carried out locally, in each health care setting.

How can we overcome inappropriate utilization of laboratory resources?

There are several ways of improving laboratory test demand. These strategies may entail educational interventions of citizens, physicians, nursing staff, phlebotomists, carriers, etc. or limiting the tests offered by applying ordering algorithms or expert systems, thus assisting the selection of appropriate tests for specific clinical conditions. Moreover, the implementation of the so-called re-testing intervals or other gate-keeping strategies may be valuable, all of which can be summarized as demand management (DM) schemes. Some of these strategies are discussed below.

DM is sometimes misunderstood, especially by the financial department of hospitals, which tends to consider such strategies as a way of reducing laboratory tests, including the relative costs. This, however, would be called "demand control", whereas DM focuses on ensuring appropriate requesting and may subsequently lead to either increased or decreased testing, depending on the chosen pathway [30, 31].

In the pursuit of conquering inappropriate or excessive utilization of laboratory resources, we should consider that not all the following mentioned strategies may be suitable for each health care setting and for every medical condition. Therefore, implementing one or more of these options has to be carried out locally and always in close collaboration with clinicians.

1. Laboratory diagnostic algorithms

Laboratory diagnostic algorithms (LDA) are probably the most clinical and sophisticated tools for challenging the appropriate use of diagnostic testing.

LDAs, also referred to as reflexive testing algorithms, are pathways based on clinical symptoms, a suspected diagnosis or a laboratory finding (e.g. anemia or isolated prolonged activated partial thromboplastin time). Using LDAs, clinicians order a laboratory diagnostic workup of the respective clinical setting rather than single tests. Thereby, clinicians and the patient may benefit from the vast expertise of laboratory professionals. Laboratory reports, compared to those of other diagnostic specialties like pathology or radiology, mostly consist of plain outcomes of requested analyses, rather than their interpretation, thus leaving clinicians with the task of interpreting these results. By including the clinical aspect in the order when using this DM strategy, laboratory professionals may be able to select the right reflex tests and to interpret results in combination with clinical signs and symptoms, based on current evidence and guidelines. Clinicians, therefore, will receive a narrative interpretation of their order including reflex testing, which would enable to make diagnoses and treat the patients more efficiently. Hence, implementing LDAs has benefits not only for the patient and the clinician, but also for laboratory professionals, as their expertise in selection and interpretation of laboratory tests can be harnessed and subsequently their presence within any health care setting increases [32].

Human resources in laboratories are usually calculated by estimating the workload for providing results of the tests ordered by clinicians. Therefore, in order to cover the additional work of reflex testing and interpretation,

these tasks have to be as automated as possible, which may be achieved by using the so-called computerized clinical decision support systems [33]. The large time needed for screening the current literature and guidelines may be supported by machine learning systems. Machine learning is a form of artificial intelligence that uses data to learn by itself. In the first instance, a user must teach it with a set of inputs (laboratory data) and the relative outcomes. A validation phase then occurs to verify whether or not teaching has been effective. Thereafter, the computer learns as it acquires increasingly more information. This strategy has the potential to look at a set of results, thus predicting which follow-up tests are more likely to be abnormal [34].

The straightforwardness of most LDAs is simultaneously their biggest weakness. For a pathway to be beneficial, clear symptoms and patients with ideally a single disease would be needed, as well as few follow-up "branches" as possible, and clear "yes-or-no" decisions. Therefore, this intriguing concept is of limited usefulness for patients with complex diseases or non-specific symptoms, or even when using tests with possible gray zones [32]. Additionally, the lack of suitable IT tools is often a major limiting factor.

2. Educational interventions

Often the reason for inappropriate laboratory utilization may be due to a lack of knowledge of:
–   clinical significance of the test,
–   appropriate test selection for the respective clinical setting,
–   the severity of delayed or missed diagnosis,
–   the consequences of ordering tests not needed for patient care or
–   the cost of a particular test.

The responsibility for this knowledge gap should not sit solely with the clinician, as it is a clear laboratory responsibility to inform clinicians and nurses not only about the test repertoire, but also about preanalytical sources of errors, thus including inappropriate use of laboratory tests. There are several means to disseminate the information. Thakkar et al., for example, used educational flyers for teaching clinicians and nurses to collect blood and order laboratory tests only when test results would change patient care [35]. On these flyers, they raised awareness on downsides of unnecessary phlebotomies. Within 2 months, they observed a decrease in the volume of requests for complete blood counts, basic metabolic panels and coagulation

tests. Wertheim et al. took it a little further by encouraging nurses and residents (i) to use ordering guidelines, based on current evidence and agreed on, (ii) to avoid automatically writing recurring daily orders for laboratory tests and (iii) to include a new section entitled "Labs needed for tomorrow" in their daily progress note [36]. This intervention led to a modest but significant (9%) reduction of laboratory use.

Another way of educating clinicians and nurses is to display the financial consequences of laboratory ordering, as done by Fang et al., who showed the cost and the TAT of each individual test at the time of ordering in their local OE system. This information alone led to a 26% reduction of orders per patient per day, projecting a mean annual saving of $330,439 within their 613-bed tertiary care facility [37]. Miyakis et al. reviewed the usefulness of laboratory investigations over a 6-month period, including costs, and informed the medical staff about their test-ordering behavior [38]. Subsequently, they reassessed lab test ordering in the following 6 months, and observed a significant decrease in avoidable tests per patient per day. This effect of educational intervention, however, gradually waned during the following semester, meaning that repeated audits and education seem essential to maintain good quality in laboratory use.

Additionally, there are several online platforms aimed to enhance education on the appropriateness in laboratory testing. These include the Choosing wisely project [39], the Lab Tests Online project [40], which is already available in 13 different languages, or the Australian Quality Use of Pathology Program [41] and many others.

3. Gate-keeping strategies

These strategies are often preserved as dictation from the laboratory, to impose on clinicians which tests are cancelled from their order due to inappropriateness, thereby implying a lack of knowledge on how to order tests. Therefore, gate-keeping strategies have to be developed and implemented in very close collaboration and in accordance with clinicians. Unlike LDAs or educational interventions, gate-keeping strategies are usually active once the medical staff has placed a laboratory order. There are several strategies to decide as to whether the individual order is appropriate or needs to be rejected. A reasonable approach may be the so-called minimum re-testing intervals, i.e. a time limit within no additional testing of the same parameter in the same patient is clinically justified and hence allowed. An alternative option entails limiting tests to certain wards, e.g. allowing interleukin-6 testing

only in neonates for diagnosing neonatal sepsis. In the following sections, some examples are discussed.

3a. Re-testing intervals

Repeat testing is very common, accounts for a significant part of overall test utilization and is quite expensive [42]. Re-testing intervals are easy to be developed within laboratory information systems (LIS) or OE systems. Re-testing intervals for genetic disorders are probably the most simple and easy to automate. For example, no additional genetic testing would be allowed in patients for whom cystic fibrosis or hemochromatosis data are already available. The same holds true for human leukocyte antigen (HLA)-B27 testing, thalassemia or hemoglobinopathies, coagulation disorders like factor V Leiden or the prothrombin gene mutation and many others. In all these cases re-testing can be annulled, replaced by a short note that results are already available.

There are also some clinical circumstances for which official guidelines on repeat testing are available. A paradigmatic case is monitoring of diabetic patients, as HbA_{1c} should only be measured every 2–6 months in patients with unstable diabetes and every 6–12 months in those with stable diabetes [43]. In patients without diabetes and normal HbA_{1c} values, testing should be repeated at a minimum of 3-year interval [4]. Similar guidelines are available for the recommended intervals of repeat testing of many other laboratory parameters [44, 45].

Another strategy was followed by Pageler et al., who limited the possibility to plan repeated hematological, clinical chemistry or coagulation testing to 24 h. This intervention led to a significant decrease in the number of tests per patient per day. Waldron et al. could also achieve a 12% decrease in C-reactive protein testing after implementing a 48-h re-testing interval, which yielded an associated saving of £3000 [46]. Lippi et al. automatically alerted clinicians on the inappropriateness of their order rather than cancelling the request [47]. In 77% of cases, the order was annulled after triggering a pop-up alert during test prescription through OE.

3b. Other gate-keeping strategies

Testing restrictions may further be based on assessing pretest probability, especially using tests characterized by a high negative predictive value. Ordering a D-dimer test in patients with suspected venous thromboembolism, for example, is only recommended when the clinic pretest

probability is low [48]. Kristoffersen et al. showed that this recommendation is frequently overlooked [49]. Another example is the 4T-score used for ruling out type 2 heparin-induced thrombocytopenia (HIT2) [50]. In a recent study we implemented this scoring system as a mandatory step before HIT2 ordering, and we could obtain a 47% reduction of HIT2 testing [51].

There are many other triggers to identify inappropriate testing even before samples are collected. Laboratories should hence identify candidate tests which are more likely to be inappropriately requested and then discuss possible gate-keeping strategies with clinicians to meet local requirements.

4. Harmonization of test panels and request form design

As mentioned earlier, laboratory request profiles (i.e. the so-called test panels) are a major source of overutilization, as these panels can be easily ordered in spite of evidence that all tests within the panel would be really needed for the individual patient [7]. This is especially true for facilities using electronic OE systems. Therefore, revising or restructuring these test panels together with clinicians is a simple and efficient strategy for reducing overutilization. Salinas et al., for example, removed aspartate aminotransferase, γ-glutamyltransferase, phosphate and uric acid from certain panels of tests, and could reduce respective orders by up to 70% [52, 53]. By unbundling an electrolyte panel, Elnenaei et al. achieved a reduction in chloride and total CO_2 testing of 67% and 75%, and an annual saving of 45,500\$ and 48,000\$, respectively [54].

Test profiles may only be useful when appropriately used. Profiles like "routine lab" should not be used, as they would most certainly contain a broad variety of tests, intended to cover most organs or symptoms. Instead, profiles should reflect single organs or symptoms like "liver" or "chest pain with/without dyspnea" [55]. Profiles or condition-specific profiles should always be established in collaboration with clinicians.

5. Review of offered tests

The portfolio of each laboratory grows over time to fit current evidence, local and/or national/international needs or guidelines. On the other hand, laboratories should screen their repertoire for obsolete tests on a regular basis [31]. For example, orders for creatine kinase-muscle/brain (MB) isoform, myoglobin and other cardiac

biomarkers used for diagnosing myocardial infarction must now be abolished, as for current guidelines [56, 57].

What are the requirements for successful implementation of the above-mentioned strategies?

Implementing changes to the use of laboratory tests is likely to be challenged, especially when these changes include restrictions. Even if new processes seem logical and unavoidable to the laboratory staff, this does not necessarily mean that clinicians and the nursing staff will think alike. To successfully implement any of the above-mentioned tools, the following recommendations may help:

– Every change made to a process affecting the number of tests, the workload of the staff or laboratory budget should be approved by the executive board of the local health care facility, the medical director, the head of department or whatever leadership is appropriate in the organization. There is nothing more frustrating than devoting huge efforts and time into a better process that is finally held up by the management. Additionally, such an approval provides a certain legal security when using these pathways.

– An absolute premise for every LDA, re-testing interval, test-panel harmonization or whatever tool of DM necessitates a foundation on current evidence. This is probably the most time-consuming part of developing a DM strategy, but (in a medical perspective) also the most important.

– The most important aspect for the real utilization of DMs is collaboration with clinicians (and the nursing staff in charge of ordering laboratory tests). This includes awareness that ordering behavior need to be changed, selection of the best strategy, screening of literature, implementation and education as well as the follow-up evaluation. As mentioned earlier, the head of involved departments (i.e. those where the chosen DM tool will be implemented) needs to approve any of these actions.

– None of the discussed DM tools will cover all medical circumstances. Applying the Pareto principle to using DM, we could expect that targeting 20% of all the causes leading the patients to the doctor will cover 80% of all patients [58]. The remaining 20% are patients with complex diseases, indifferent symptoms or simply fall out of the scope of the respective DM strategy. Therefore, whenever appropriate it should

be possible for the treating doctor to deviate from the implemented strategy. According to the Gestalt theory, the whole is not the sum of its parts, but greater than the sum of its parts. A physician's clinical judgment should not be replaced by any clinical scoring systems and/or clinical decision system [59, 60].

- Development, implementation and maintenance of any DM, thus including education of medical staff, can be very time-consuming, depending on the strategy. Therefore, human, technical as well as economic resources must be available before starting the process. Moreover, laboratory and/or clinical staff members responsible for literature search, trainings, information technology (IT) programming, etc. should be appointed beforehand.
- As you cannot improve what you do not measure, a monitoring system accompanying the chosen DM tool should be implemented. Appropriate quality indicators might be "requests per 1000 inhabitants" or "tests per request", and should be analyzed and discussed with clinicians on a regular basis [61–64].
- The implemented DM strategies need to be revised and updated on a regular basis, at least every year, always in agreement with clinicians.
- In order to track all the DM strategies in use, each strategy needs to be well documented, including
    - responsibilities,
    - the DM strategy itself,
    - references to the underlying evidence,
    - time-points when and where the DM tool was implemented,
    - how it was programmed within the LIS or the OE system,
    - version tracking, including information on which changes were made and when,
    - evidence of an evaluation of its impact after a defined time period after implementation.

Ideally, this can be done using a documentation system, with revision control.

Conclusions and outlook

When correctly implemented, DM tools can be a useful strategy for patients, clinicians, the laboratory and the hospital itself. It helps getting the right test results to the right patient at the right time more efficiently, making it possible for clinicians to focus more on his/her field of expertise and for the laboratory to better contribute to patient care, using the respective expertise in test selection and interpretation. The hospital and the health care system may benefit from reducing excessive utilization of laboratory resources.

However, attention needs to be paid when selecting the right DM strategy for a certain diagnostic process. All limitations and local situations need to be exploited, making it impossible to simply copy and paste any strategy from the literature [65]. Developing and implementing any of the discussed DM tools needs precise planning, clear communication and intense collaboration between health care professionals and other potential stakeholders (i.e. patients' organization). We encourage all laboratories to publish their DM strategies in use including the impact on laboratory use, so that fellow specialists can profit from these experiences.

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