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Review

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Health literacy: a new challenge for laboratory medicine

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Abstract: Poor health literacy and inappropriate test prescribing hamper the value of laboratory medicine. The disintermediation between test producers and interpreters may happen both in Point of Care Tests, where doctor mediation is provided, but laboratory expert supervision is not, and in Direct to Consumer Testing, where no medical mediation is provided at all. In these cases, the respect for patient's autonomy must not preclude the principles of non-maleficence (as an individual concern) and justice (as a societal concern), as wrong test interpretation can generate confusion, anxiety, inappropriate social behavior, useless medical examinations and considerable cost increase. Considering how different is patient ability to understand test results (if any) and handle any physical and psychological consequence, promoting health literacy and professional laboratory mediation become crucial professional priorities. The aims of this review are 1) to describe the importance of health literacy on laboratory test interpretation, medical advice and therapeutic compliance; 2) to discuss doctor-level, patient-level and caregiver-level educational interventions in light of the four principles of the value-based framework (personal value, technical value, allocative value and societal value). Based on these premises, the authors support the need to enhance health literacy in patients, help doctors improve the communication of results and validate commercial tests under the scrutiny of scientific community.

Keywords: direct to consumer test; health literacy; health numeracy; non-maleficence; point of care test

Introduction

Poor health literacy and inappropriate test prescribing hamper the value of laboratory medicine.

The negative impact of poor health literacy was associated with a) linguistic and cultural issues in understanding key terms such as "positive" or "negative", "reactive" or "non-reactive"; b) absence of doctor intermediation in direct-to-consumer (DTC) testing, as medical supervision is crucial to clarify the relevance of certain parameters for certain patients (e.g., the same anemia can be physiological in a pregnant woman and pathological in other patients, but the use of asterisks alone as out of range markers does not help to distinguish the respective situations) [1–7].

The negative impact of inappropriate test prescribing was associated with financial mechanisms, professional routines, patient expectations and cultural factors which prioritize the volume of tests performed on the clinical value of the procedure, that is, the ability to induce a change in patient management [8–14].

According to The International Code of Medical Ethics, "Physicians play an important role in matters relating to health, health education and health literacy. In fulfilling this responsibility, physicians must be prudent in discussing new discoveries, technologies, or treatments in non-professional, public settings, including social media, and should ensure that their own statements are scientifically accurate and understandable" [[15], Principle 35]. Moreover, "The physician must support fair and equitable provision of healthcare […] addressing inequities in health and care [and] the determinants of those inequities" [[15], Principle 34].

Then, providing a comprehensible laboratory report is first and foremost an ethical duty. The disintermediation between test producers and interpreters may happen both in Point of Care Tests (POCT), where doctor mediation is provided, but laboratory expert supervision is not, and in Direct to Consumer Testing (DTC), where no medical mediation is provided at all [16, 17]. In these cases, the respect for patient's autonomy must not preclude the principles of non-maleficence (as an individual concern) and justice (as a societal concern), as wrong test interpretation can generate confusion, anxiety, inappropriate social behavior, useless

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medical examinations and considerable cost increase. The National Health Service, for instance, usually bears the cost of both verifying the results generated by DTC tests, and providing secondary and tertiary care access as a consequence of test results themselves (the so-called diagnostic cascade [12]).

Increasing DTC tests can identify monogenic or polygenic disease exposure (e.g., cystic fibrosis, cancer, Parkinson or diabetes), and increasingly faster and cheaper DNA analytic technologies can estimate the individual response to certain drugs. However, the reliability of these tests is unknown. Then, the results should be carefully interpreted under the supervision of the attending physician, in combination with clinical features, individual symptoms and family history. Otherwise, unnecessary worries and further investigations may follow. Ferrari et al. [18] expressed concerns about non-invasive pre-natal screening technologies being performed in absence of adequate gynecological and genetic counselling before and after the examination, which may place additional stress on pregnant women and put normal pregnancies at risk, paving the way for more invasive but useless investigations. Many social determinants were identified by the same authors behind the choice of women opting for certain examinations or other.

In March 2024, a DTC blood test to diagnose Alzheimer's disease was removed from the market, after a number of complaints from scientists and patient associations. Consumers could receive the test at home without visiting a doctor, and asses the risk of developing Alzheimer's based on the simple ratio between amyloid-beta 42 and amyloid-beta 40 measures. The test did not receive approval by the Food and Drugs Administration, in absence of "large-scale, long-term clinical trials that support the idea that the AD-Detect test can predict whether a cognitively unimpaired person will transition to cognitively impaired" [19]. Few months later, however, a paper supported the accurate use of biomarkers p-tau217 and ratio Aβ42/40 for predicting the progression of the Alzheimer [20], and the chief science officer of Alzheimer Association stated that the test should be available for POC use, in a doctor's office, as is the case with cholesterol [21].

Even though a doctor is responsible of test provision, a laboratory medicine expert is needed to maximize the value of medical information by combining test characteristics, analytical findings and quality control, in order to make a positive impact on diagnosis, prognosis and therapy. Numerical ranges marking a reference interval are often old, of uncertain origin and method-dependent. Moreover, the results can be released by different laboratories, using different methods, measurement units and/or acronyms for the same parameter. Considering how different is patient ability to understand test results, if any, and handle any psychological and physical consequence, promoting health literacy and professional laboratory consultation are crucial ethical and professional priorities.

The aims of this review are 1) to describe the importance of health literacy on laboratory test interpretation, medical advice and therapeutic compliance; 2) to discuss doctor-level, patient-level and caregiver-level educational interventions in light of the four principles of the value-based framework (personal value, technical value, allocative value and societal value).

Based on these premises, the authors support the need to enhance health literacy in patients, help doctors improve the communication of results and validate commercial tests by the scrutiny of scientific community.

The importance of health literacy in laboratory medicine

Ordinary visits of patients from different language and culture

In multicultural United States (US), nearly 10 % of the population still have problems with speaking and understanding English, especially among the Spanish-speaking community [22, 23]. Receiving medical information is doubly difficult for these patients. First, they need to understand the spoken language of doctors. Second, they need to understand the relevance of that information to their health. What "reactive" means, along with common referral parameters like "neutrophils, CBC or bilirubin, however you pronounce that", can be difficult and misleading [24]. Even the words "positive" or "negative" can be misinterpreted. For instance, the presence of antibodies against a specific agent may demonstrate immunity against that specific agent. The other way round, resulting positive to a test could mean that the patient is affected by a disease, while resulting negative could mean that the patient is healthy. Specific models to describe results, like dilutions (e.g. 1:80 dilution for antibodies against infectious agents), can also cause pitfalls in data reading and interpreting.

Physicians not necessarily check whether patients really understand medical advice [24], even by a simple confirmation feedback question [25], because of time limitations, because they overestimate patient's literacy [26, 27] or because patients who need most clarification are those who ask the least [28, 29]. The inverse care law applies to health literacy levels in doctor-patient consultation [3, 30, 31]. Second-generation bicultural Latina nurses described the challenges and strategies for working with co-ethnic patients who may be afraid of asking questions, or who may find it difficult to understand basic advice on healthy food habits and behavior [32]. Mexican patients affected by rheumatic diseases reported passive roles in the conversation with doctors and in the decisions made within [33]. While the US are taking some Federal interventions to adopt plain language when communicating public services and benefits, possibly including health information [1], some European countries are just taking ordinary care of second generation immigrants with a different language and culture for the first time in history; and these people are taking ordinary care of elderly, frail patients with poor or no health literacy at all. Therefore, what in the past could represent an occasional communication problem (that additional explanation efforts could solve) will probably become more common in current medical encounters, with less time available to provide in-depth explanations [32] and verify understanding [27]. The rush of modern medical visits can also explain the use of non-conventional care, where time, empathy and shared decision making are particularly appreciated, in addition to conventional treatment [34], in case of ethnically familiar treatments [35, 36] and in case of elderly chronic patients living in rural areas, who find conventional care protocols difficult to comply with [37], even when non-conventional care does not affect the observable health status [38].

These factors make it difficult for patients to take informed decisions and comply with therapy [39], no matter how excellent is care from a technical perspective and how expensive may it be. This is the core problem of value-based care.

Increasing health data digitally at hand of the population

A growing multitude of free, intuitive tools to navigate information with a simple click on the internet enable to seek and receive medical data with unprecedent ease in history, regardless of the user's ability to understand, weigh and contextualize such data: social networks and search engines represent the most common example. Epidemiological and clinical data require some degree of health literacy and numeracy [1, 40, 41] to understand the relevance of information, decrease bias and improve statistical information processing [42–44]. For instance,

- Understanding the different severity of the same symptoms;
- Understanding that the same symptom can be the result of very different causes;
- Weighing the possibility of a certain side-effect to occur against the proved benefits of a certain treatment;
- Overcoming distrust against healthcare professionals, institutions and pharmaceutical companies (and overcoming unconditional trust in their favor, on the contrary)

The one thing is science, another thing is the multitude of environmental and emotional factors systematically influencing our perception, attitudes, thoughts, memories and actions, including medical decisions and laboratory test information understanding [2, 45]. Most of our mental processing takes places unconsciously, based upon automatic responses generated from a lifetime of experiences we may not be aware of, leaving less than 10 % of decisions to reason [46]. This is crucial to deal efficiently with ordinary daily events [2], but may become counterproductive in other situations. Overestimating danger, for instance, is to some extent adaptive to survival, as preventing harm is more important than paying attention to positive experiences, at least in the short or medium term. A single negative episode (e.g. a missed diagnosis, a surgical complication, a drug side-effect, a late rescue) can imprint on memory, influence behavior and health-related choices against dozens of positive episodes silently happening every day (population-scale disease prevention, a life saved, a number of critical patients discharged from hospital in good health). At the same time, we tend to underestimate what we do not see as a threat here and now, no matter how acclaimed is the underlying danger. We may fear and overestimate vaccine side effects, the possibility of a plane to crash or a terrorist attack to occur, but give little importance to well-known environmental and behavioral triggers of life-threatening disease (e.g. smoking, unhealthy diet, poor physical activity and alcohol abuse).

On top of that, mass media sensationalism feeds on common fears to fuel audience, sales and followers, allowing to rapidly share the information we value most (which does not necessarily equate to the facts). One sensational post on a social network (the shorter, the better) is likely to influence more people, decisions and behaviors than a ten-pages technical paper on a prestigious science journal. Artificial intelligence applied to search engines and digital platforms can bring these risks to even greater levels, to the extent that it reproduces content that has already been interacted with; the so-called "loop thinking", from which even scientists are not exempt [47, 48].

Direct-to-patient health information

Point-of-care tests and near-patient tests are performed by medical doctors in absence of traditional laboratory processing, in order to cover underserved healthcare areas, screen a population at risk or provide faster referrals (e.g. rapid antigenic tests during the Covid pandemic or finger-prick samples before blood donation). Patient self-tests (PST), instead, provide health information in absence of medical interpretation, as they monitor chronic disease parameters that patients are supposed to manage on their own. As long as PST should release pressure from hospitals, spare visits, reduce logistical barriers and monitor health information wherever patients are (e.g. at school, work, home, vacation), these tests are expected to improve healthcare efficiency, equity, patients' quality of life and autonomy [16]. On top of that, point-of-care tests and near-patient tests can also be performed by qualified healthcare professionals in absence of conventional laboratory equipment and physician (professional use test, PUT), combining proximity and accuracy.

PUT and PST provide efficient health information for occasional use. In ordinary conditions, however, they should not replace medical consultations, as one thing is understanding that a certain combination of numbers, ranges and asterisks expresses a deviation from the norm; another thing is understanding how relevant is that deviation for the single patient. An interview from a mixed-methods investigation makes this point clear:

"I don't know exactly what [the test result] meant clinically and for my overall health. I just kind of had a general idea. So I'm undergoing cancer treatment and so they're checking my white blood cell counts. Those were low, but I don't really understand are they too low? I don't know necessarily what all of the things are" [49].

People often search the internet to get a second opinion (in case of PUT), a direct test interpretation (in case of PST) or an idea of what a certain deviation can be expression of. The risk of receiving fragmented and/or non-mediated reports is to misunderstand, underestimate or overestimate them, seek further information in search of reassurance – no matter how appropriate and reliable may it be – and take wrong decisions. When artificial intelligence and machine learning technologies are employed to help patients understand reports, the supervision of laboratory experts and/or associations should be mandatory.

Educational interventions

Educational interventions in support of doctors, patients and caregivers can help minimize harm and reduce clinical waste.

Training doctors

"Physicians play an important role in matters relating to health, health education and health literacy", states the International Code of Medical Ethics [15] at Principle 35. Educational interventions to improve the soft skills of doctors, including communication with patients, are described by the literature, either alone [50] or in combination with other healthcare providers [51], either designed for medical students [52] or for graduated physicians only [50].

To make training effective and credible to the audience, make sure that physicians have the possibility to act consistently. Otherwise, the risk is to backfire, as healthcare professionals can perceive soft skills training as "yet another course" irrelevant for practical purposes and/or frustrating [51]. In general, learning the soft-skills on the field by watching expert clinicians at work - or from retired professionals with time on their hands and a willingness to teach [53] – is more effective than learning from trainers with a theoretical background only, and no ordinary experience at all. This is supported by a systematic review on ethical support interventions in elderly care inpatient nursing, according to which educational interventions for healthcare professionals are becoming 1) less theoretical and more integrated in daily care processes, 2) less centrally organized and more context-specific [54], developing in empirical and bottom-up directions more than in formal and top-down directions. When health literacy and compliance issues concern a specific examination, a specific disease or a specific patient (e.g. elderly, foreigners, disabled or child patients), it is possible to tailor and evaluate specific and strategies, which are discussed next.

Considering how wide is the area of laboratory medicine, training doctors to properly interpret and explain uncommon and/or hard to read reports is also important. Increasing type of assays, measurable parameters and complex data group suppliers derived, for example, from microarrays or proteomics make report interpretation difficult for doctors who are not specialists. Imagine two doctor-level educational interventions, both led by laboratory medicine experts: one for specialist physicians, one for non-specialist physicians. The former should introduce the critical thresholds and differences to consider to accurately interpret certain data. The critical difference represents the percentage of variation indicating that certain external factors (disease, therapy, pregnancy or diet) had effectively modified a certain laboratory parameter. The European Federation for clinical chemistry and Laboratory Medicine (EFLM) website offers a complete and informative database for calculating critical differences [55]. Non-specialist physicians, in turn, should receive general training on standards and classifications such as the International Classification for ANA Patterns (ICAP) for antinuclear antibodies and likelihood ratio. Expert patients involved in patient journey definition, clinical trials and ethical committees [56] should receive the same training.

In light of the four principles of value-based care, the expected benefits of doctor-level, educational interventions are:

- gaining patient's trust and improving compliance (personal and technical value);
- reducing health inequalities associated with social determinants (personal and societal value);
- reducing the risk of inappropriate information seeking by patients (personal and technical value);
- reducing inappropriate access to emergency care and clinical waste more in general (technical and allocative value);
- promoting prevention, patient selfcare and responsibility (personal, technical, allocative and societal value).

Training patients and caregivers

Patients and caregivers can receive training to make sense of laboratory tests, improve self-care and compliance, either individually or in group:

- under the supervision of a clinical or case manager (e.g. managed care for chronic patients [57, 58], personal health budgets and integrated care boards [59]);
- specific training for patients' associations in different language on acronyms, test characteristics, clinical significance, critical difference measurement with conversion factors, reference ranges adopted by the literature in multicenter studies;
- specific websites for collecting information, held and controlled by laboratory medicine associations [60];
- providing materials (e.g. booklets) and group sessions in support of specific perioperative elective programs, before surgery (e.g. physical therapist and pre-habilitation) [61] and/or after surgery (e.g. telemedicine and home-based rehabilitation) [62];

In light of the four principles of value-based care, the expected benefits of these interventions are:

- saving healthcare resources, as better compliance usually generates better care outcomes at the same costs, or equal care outcomes at minor costs [58] (personal, technical and allocative value);
- decreasing inappropriate consultations, visits, additional requests of laboratory tests (allocative value)

Impact assessment

The impact of educational interventions for doctors, patients and caregivers could be assessed by similar research programs, possibly combining recipients and outcome indicators. In Table 1, a basic architecture is illustrated.

The correlations between educational interventions (either intended for doctors, patients, care givers or combined) (Column 1) and outcome indicators (Column 2) could be explored through the adoption of different methodologies (Column 3), to capture the benefits for the health of patients in terms of clinical variations (CROMS), quality of life, utility perceived (PROMS) and experience of healthcare treatment (PREMS). Such investigation can help:

Table 1: Educational interventions to improve health literacy: impact assessment.

1 Training recipients	2 Outcome indicators	3 Method
Doctors (soft-skills of communication, e.g. clarity, patience and openness to questions).	Clinician-Reported Outcome Measures (CROMS) e.g. relevant variations in laboratory tests, disease-specific biomarkers and imaging examinations.	Before-after, observational studies (if the educational intervention is occasional or limited in time).
And/or	Patient-Reported Outcome Measures (PROMS) e.g. quality of life; minimal clinically importance difference (MCID) on pain, cognitive, physical, emotional and societal function; side-effects, self-care confidence.	Longitudinal, observational studies (if the educational intervention is repeated across long term and/or chronical care pathways).
Patients and caregivers (health literacy such as comprehension, self-care and compliance).	Patient-Reported Outcome Experiences (PREMS) e.g. clarity of information perceived, possibility to ask questions, receive adequate, plain language explanations; shared decision making, accessibility, considering family and home environment in treatment/pathway design; sense of safety.	Case-control, interventional studies (no intervention group vs control group).

- understand what interventions make a difference (if any), how and when. For instance, improved patient-experience may not correlate with improved clinical outcomes, and improved patient-reported utility may noy correlate with objective clinical outcomes (e.g. the placebo effect);
- find which educational factors improve which care outcomes, in which patient clusters (e.g. classified by age, sex, ethnicity, baseline literacy or comorbidities, even combined);
- retrieve evidence-based data in support of social, ethical and organizational domains of health technology assessment (HTA), which is still unusual in clinical laboratory [63];
- reward healthcare facilities and institutions that invest on quality [64];
- reward medical doctors taking efforts to improve the lifestyle, self-care and health literacy of patients [65] (e.g., primary care physicians). For instance, by helping patients to stop smoking, reduce sugar and fat intake, take appropriate medication (consider the importance of respecting the timing of prescriptions in antibiotic therapy), keep the parameters monitored (e.g. blood pressure, glycemia), invest on physical activity and social engagement.

Searching for specific indicators to estimate the effectiveness of educational interventions is encouraged by Stolt et al. [66] and West et al. [50]. Our recommendation is to include clinician evaluations (CROMS), patient evaluations (PROMS and PREMS) and possibly detail the intervention program, in order to:

a) provide an assessment as comprehensive as possible;
b) evaluate whether a certain intervention can be implemented elsewhere (another context, population, country);
c) pave the way for targeted analyses and improvements.

Administrative outcomes like the cost of the intervention and the use of health care services should also be useful [67–71].

For instance, the observational study of Schillinger et al. [25] assessed the impact of an educational intervention on 38 primary care physicians, based on a communication strategy to enhance the ability of diabetic patients with low health literacy to (really) understand medical advice. The outcomes were the variations in glycemic parameters (CROMS) collected from a clinical and administrative database. Any patient-level perception of improvement was excluded. Objective changes in glycemic parameters are effective proxies of doctor-level educational interventions in such patients, if the former are assumed to follow from the latter. Including PREMS, however, would provide similar studies with stronger evidence that healthier parameters actually depended on greater efforts made by physicians, as these efforts are made explicit by patients.

The quasi-experimental study of Moreira et al. [72] assessed the impact of an intervention on health literacy enhancement on 34 caregivers, with the aim of improving old patients' ADL support. These caregivers were directly asked whether they perceived changes in care attitude, practice and knowledge through semi-structured interviews. The study concluded that the intervention was "effective and viable". We can define care attitude, practice and knowledge *caregiver-reported outcomes* on the educational intervention effectiveness. It would have been interesting to add the variations detected in *their own* quality of life (e.g., more safety, fewer worries and better home care management). Moreover, no PROMS were collected from patients themselves (if cognitively healthy) after the caregiver enhancement, like significant variations in pain (e.g., through the Visual Analog Scale) and quality of life (through the Audit of Diabetes-Dependent Quality of Life); nor are variations confirmed by physicians or any other healthcare professional (CROMS), using general or disease-specific functional scales (e.g. Barthel Index, Hip disability and Osteoarthritis Outcome Score). The value of such complementary investigations would be to confirm the skill variations reported by caregivers, professionally validating the educational interventions.

The systematic review of Sheridan et al. [73] provides a useful overview of 38 educational programs, among which 22 were tested through interventional studies, describing each population, design, contents, controls and outcomes, including CROMS (e.g. biomarker variations), PROMS (e.g. symptoms, quality of life, self-efficacy), PREMS (e.g. knowledge, comprehension, risk perception and adherence) or other (e.g. repeated hospitalizations and costs). No studies adopted all the outcome groups together, few studies adopted two groups in combination, while the vast majority of studies adopted only one group.

The lack of control groups in Schillinger et al. [25] and Moreira et al. [72], and the vast single outcome group adoption reported by Sheridan et al. [73] show significant room for improvement in measuring physician-, caregiver- and patient-level educational interventions. Plenty of outcome sets are available to assess relevant patients' health improvements, classified by disease, age (e.g. pediatric, adults, elderly) or cross-cutting patient clusters (e.g. disabled), including CROMS, PROMS, PREMS and specific health literacy domains. The International Consortium for Healthcare Outcomes (ICHOM), for instance, is set to help doctors, policy makers and healthcare facilities identify in advance where to work and invest to get relevant improvements on patients [74], disclosing additional value from laboratory medicine [75].

Using patient-reported measures can help:

- understand what professional and service characteristics can improve health literacy, accessibility and outcomes;
- estimate the impact of educational interventions;
- provide evidence-based information in support of HTA.

Conclusions

Disease is still, largely a social problem [[76, 77], cited in [41]].

The quality of medical information released from clinical laboratories to users (patients, citizens, care givers) is key to improve healthcare effectiveness (positive impact), efficiency (use of resources) and equity (social gradient of health minimization). The intermediation of laboratory medicine professionals is crucial at this purpose.

Educational interventions can help patients and caregivers better handle the care pathway, and help doctors communicate properly in order to make sure that patients understood. This factors can turn simple numbers into clear health information and informed health decisions, increasing the clinical impact of laboratory medicine.

Joint commitment from professionals, scientists, policy makers and patient associations is needed to protect patient's health and prevent additional pressure on healthcare systems.

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