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An evidence-based laboratory medicine approach to evaluate new laboratory tests

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ABSTRACT

The evidence-based recommendations for the evaluation of new tests to be used in practice are a key issue to improve diagnostic clinical pathway inducing effective care. Emerging precision or personalized medicine requires innovative and pioneering biomarker tests for molecularly targeted therapies, possibly fitted for the individual patient's condition. Beyond the traditional analytical specifications that should guarantee the proper clinical diagnostic performances in response to a specific clinical question, the outcomes of a new test should be clearly defined and evaluated. Analytical and diagnostic performances such as sensitivity, specificity, imprecision, positive and negative predictive values are traditionally established measures but the clinical impact and the healthcare outcomes, to which these accuracy measures are related, are complex to measure. The extent of the improvement of the patients' health due to a diagnostic test remains a "holy grail" notwithstanding it should be the ultimate goal.

HARMONIZATION AND RISK MANAGEMENT POLICIES IN LABORATORY MEDICINE

Harmonization and risk management policies represent the key-issues in laboratory medicine as they directly rely on a patient-centred delivery of laboratory information based on the recognition of the importance of the total testing process for assuring healthcare quality and patient safety.

The term "harmonization" is intended to assure that the results of a test are equivalent, being either traceable to a reference material and based on a consensus approach in agreement with the mean values obtained with different methods (1-3).

Nevertheless, the concepts of commutability, uncertainty and reference intervals to harmonize laboratory results are well known issues, a growing body of evidence demonstrates that clinical benefits can be achieved only by focusing on the total testing process, where the appropriateness of test request and interpretation are the main steps. If the scope of harmonization goes beyond method and analytical results to consider all the other aspects of laboratory testing, including strategies for test demand and criteria for result interpretation (1,2), robust and methodologically high-quality recommendations to evaluate new tests are pivotal tools to promote the cooperation at the clinical-laboratory interface to guarantee a valuable medical decision-making process.

In risk management, the new approaches to quality and patient safety in the healthcare system emphasize that diagnostic improvements are based on the assurance of the desired outcomes rather than on the sole identification of the errors. The outcome-based approach proposed by Epner et al. (4) on testing-related diagnostic errors appeals for a more effective selection and interpretation of useful biomarkers in order to prevent adverse events, failure to diagnose and to provide the appropriate treatment. Patient safety is compromised by inappropriately requested tests or by misinterpretation of the results so harmonization and risk management policies in the laboratory increasingly recognizes the need to consider patient outcomes in the assessment of tests and test strategies (4,5). The development of high-quality recommendations may be the common framework to promote harmonisation and risk management in diagnostic pathway by evaluation of proposed innovative diagnostic tests translated in clinical practice from research (6).

THE TEST EVALUATION WORKING GROUP (WG-TE) OF THE EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE (EFLM): IDENTIFYING UNMET CLINICAL NEEDS FOR NEW BIOMARKERS

The Test Evaluation Working Group (WG-TE) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM), a working group composed of laboratorians, epidemiologists, evidence-based medicine (EBM) methodologists, health technology assessment and policy experts and the IVD industry, delivered practical tools to improve the clinical and cost-effectiveness evaluation of new biomarkers to facilitate their implementation as medical tests within the clinical pathway (7-8). It proposed an outcome-focused approach that can be used by stakeholders for any medical test, irrespective of the purpose and role of testing to identify clinical management decisions, linking biomarker testing to health outcomes. This method including worked examples are suggested to assist researchers, clinical scientists, and the IVD industry working with clinicians, to identify unmet clinical needs to improve the development of IVD medical tests to improved health outcomes.

The 14-item checklist is organized into 4 domains: 1/ identifying the clinical management problem and desired outcome and 2/ verifying the unmet need and an existing solution; 3/ validating the intended use, how the biomarker contributes to the solution; and 4/ assessing the feasibility of the new biomarker to influence clinical practice and health outcome. A more efficient biomarker development and translation into practice are the purpose of the proposed checklist as it was field tested to promote the role of the clinical laboratory specialist to forward interdisciplinary and multi-professional collaboration. A complete picture of the guide to identify unmet clinical needs for new biomarkers is described in a recent paper (9), this checklist proposed by EFLM TE-WG is aimed to assist all stakeholders engaged in the discovery or implementation of new biomarkers or new diagnostic pathway.

THE GRADE APPROACH: THE GRADING OF RECOMMENDATIONS ASSESSMENT, DEVELOPMENT AND EVALUATION

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty in evidence and to develop recommendations is a widely, patient-centred method (10). This approach is presently used by over 100 organizations worldwide and has become one of the reference standard for providing health care recommendations (11).

The GRADE methodology is increasingly used in the area of medical testing where the GRADE framework is turning away from simple test accuracy to incorporate main health outcomes in light of the resulting downstream clinical actions. Since direct studies assessing the impact of diagnostic tests or strategies on patient important outcomes are rarely available, the GRADE process requires two main steps. The first is the judgments about directness in assessing the link between test accuracy and the evaluated health outcomes and the second aims to the criteria used in moving from evidence to a recommendation (12).

THE GRADE EVIDENCE TO DECISION (ETD) FRAMEWORKS

EtD frameworks may be utilized to assess the certainty of the evidence and to model the consequences of a decision about a test. The frameworks include not only the traditional criteria to assess test analytical and diagnostic performances but also the assessment of the certainty of evidence to estimate if the test effects match patient outcomes. At first a clear clinical question and related outcomes (important to the patient) are defined and then a structured systematic review of the available evidence is performed. Diagnostic test performances are then judged by taking eight criteria into consideration, of which five are to downgrade the quality of evidence, such as risk of bias, indirectness, inconsistency, imprecision, and publication bias. The last three criteria are to upgrade evidence quality, such as the magnitude of the effect, dose response in relation to the effect, and opposing plausible residual bias or confounders.

The GRADE evidence to decision (EtD) frameworks (6) for tests offer a structured approach as described as follow.

Formulating the question

Formulating a question needs a clear problem draw and the definition of purpose, type and role of a test and alternative intervention(s), the main outcomes focused and the expected setting. PICO, the population intervention comparison outcome format is a suitable method for formulation of the question (13).

Making an assessment

The problem

A definition of the magnitude and the priority of the problem should be established depending on the setting in which the test will be used and the influence on current or future practices.

Test accuracy

A summary of findings from systematic reviews is the means to interpret the accuracy of a test. An acceptable overall accuracy is the starting point for entering a laboratory test into an EtD framework evaluation.

Benefits & harms

The judgment about the benefits and harms to introduce a new test is based on findings about desirable and undesirable effects. Evidence should be derived from up-to-date systematic reviews and summarized in a table of findings (14).

Certainty of the evidence

The GRADE overall rating the certainty of the evidence about the effects of a new test and the subsequent management decisions on patient-important outcomes is now extensively used by guideline developers (15) and a complete report of this approach can be found elsewhere (16).

EtD tests framework includes five criteria for reaching judgments and making assessment of the evidence certainty: 1) test accuracy, 2) any critical or important direct benefits, adverse effects or burden of the test, 3) effects of natural history or the management that is guided by the test results, 4) the link between the test results and the management decisions and 5) the evidence about the effects of the test.

Values

The perceived value of the main outcomes includes test downstream outcomes. For example, a blood test may replace more dangerous interventions, such as bowel biopsy in coeliac disease diagnosis, tumor prostate biopsy, or fetal cell genotyping through maternal blood sampling instead of amniocentesis.

Balance between the desirable and undesirable effects

Desirable and undesirable effects following the introduction of a new test need to be judged in comparison to the old or traditional test through either formal or informal modeling evaluating the actions due to a new test.

Resource use

In the case of the selection of the proposed diagnostic test, judgments about the magnitude of costs, certainty of evidence of resource requirements and the cost-effectiveness of interventions should include the evaluation of the impact both within the laboratory and the downstream consequence. The great challenge is to identify the overall health care cost and not only the plan cost of the test itself (17).

Equity, acceptability and feasibility

Assessments of equity, acceptability and feasibility comprise both the test and the consequent interventions. The use or misuse of tests for a specific clinical presentation in different professional settings affects equity of access to clinical care. For example, in the same healthcare setting, the introduction of a new test may vary from one hospital to another.

CONCLUSION

High quality and evidence-based recommendations may support a transparent clinical governance policy where the introduction of new laboratory test based on assessed outcome for patients is a value allowing the laboratory people to contract with the management the allocation of resources in terms of health priorities (18).

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