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Practical guide for identifying unmet clinical needs for biomarkers

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ABSTRACT

The development and evaluation of novel biomarkers and testing strategies requires a close examination of existing clinical pathways, including mapping of current pathways and identifying areas of unmet need. This approach enables early recognition of analytical and clinical performance criteria to guide evaluation studies, in a cyclical and iterative manner, all the time keeping the clinical pathway and patient health outcomes as the key drivers in the process.

The Test Evaluation Working Group of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM TE-WG) https://www.eflm.eu/site/page/a/1158 has published a conceptual framework of the test evaluation cycle which is driven by the clinical pathway, inherent to which is the test purpose and role within the pathway that are defined by clinical need.

To supplement this framework, the EFLM TE-WG has also published an interactive checklist for identifying unmet clinical needs for new biomarkers; a practical tool that laboratories, clinicians, researchers and industry can equally use in a consistent manner when new tests are developed and before they are released to the market. It is hoped that these practical tools will provide consistent and appropriate terminology in this diverse field and offer a platform that facilitates greater consultation and collaboration between all stakeholders. The checklist should assist the work of all colleagues involved in the discovery of novel biomarkers and implementation of new medical tests. The tool is aligned with the IOM recommendations and the FDA and CE regulating body's requirements.

INTRODUCTION

Clinical laboratory scientists and pathologists, responsible for the provision of *in vitro* medical tests, are regularly approached by industry colleagues about the availability of new tests. This late notification sometimes poses problems; e.g. the new test does not seem to fulfil an unmet clinical need, the evidence on the clinical effectiveness of the biomarker is not yet available or controversial and therefore the new biomarker may not be commissioned or get on the reimbursement schedule.

Unmet clinical needs for new biomarkers are often discussed at clinical meetings within the health care setting, yet these perceived needs are rarely communicated to R&D and industry colleagues as key stakeholders in the biomarker development process.

Furthermore, laboratory professionals are more likely to experience pressure from the hospital board to reduce the costs of pathology testing and to rationalize test requesting rather than adding new tests to the laboratory's repertoire; the new test should be shown to improve patient care and outcomes or the cost-effectiveness of care.

To support laboratories in evidencing the value of tests, the Test Evaluation Working Group of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM TE-WG) has published a conceptual framework of the test evaluation cycle which is driven by clinical need and the clinical pathway of managing patients [1].

The aim of the working group is to supplement this framework with practical tools that laboratories, clinicians, researchers and industry can equally use in a consistent manner when new tests are developed and before they are released to the market. The first such tool is a checklist for identifying unmet clinical needs for new biomarkers [2].

The goal of the test evaluation framework and the unmet clinical needs checklist is to provide consistent and appropriate terminology in this diverse field and to offer a platform that facilitates greater consultation and collaboration between all stakeholders.

THE CYCLICAL FRAMEWORK OF TEST EVALUATION

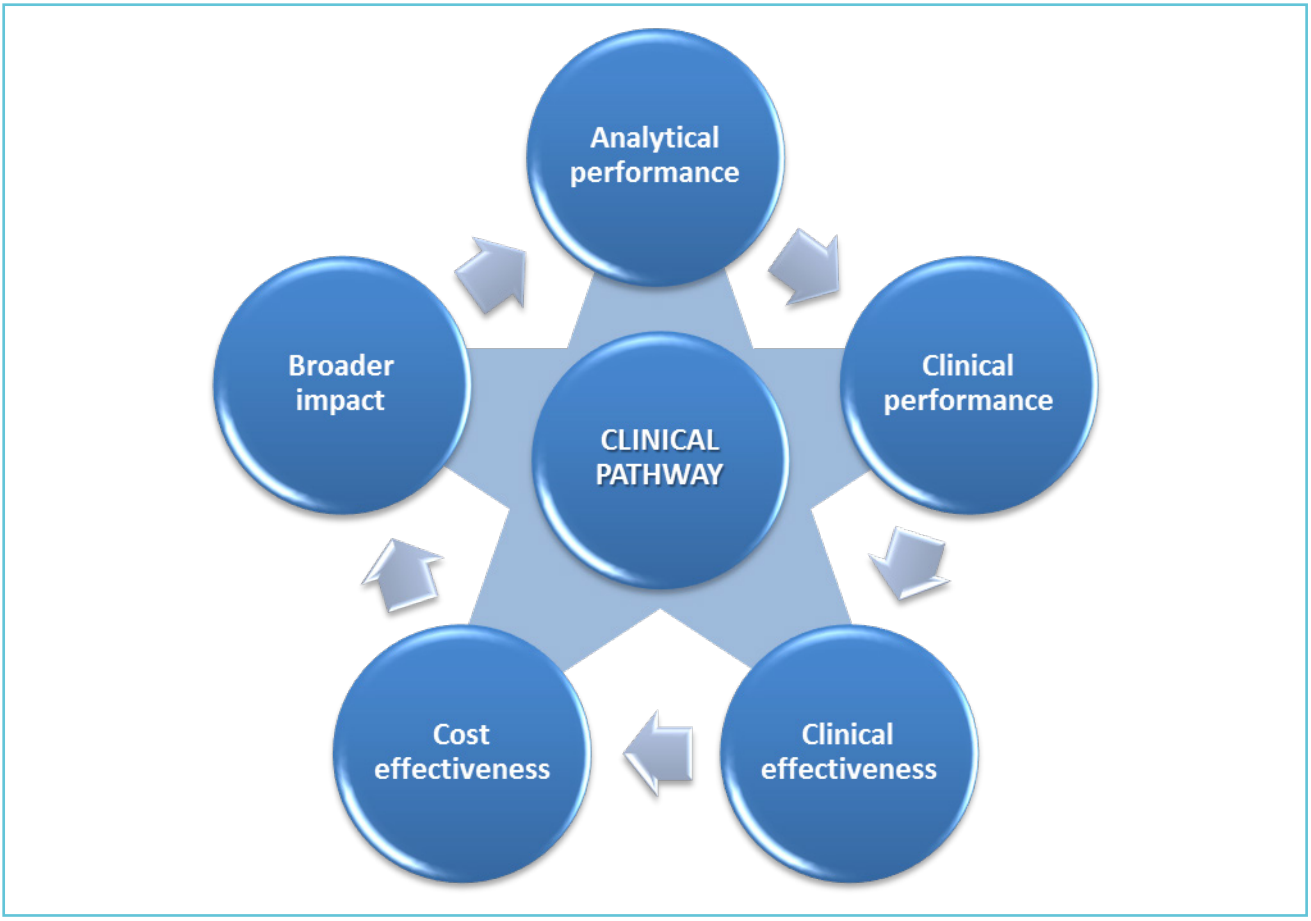
The test evaluation framework of the EFLM TE-WG [1] is intended to be applied after a potential biomarker has been discovered in basic research (so-called 'proof of concept') studies and is ready for further development and evaluation in clinical settings. The framework describes biomarker evaluation as a cycle, where key elements of the process, i.e. assessment of the analytical performance, clinical performance, clinical effectiveness, cost-effectiveness, and overall impact of the new test, are primarily driven by clinical needs and the clinical pathway that should lead to improved health outcomes or greater health care efficiency.

This dynamic framework reflects well-known steps in test evaluation but unlike most other linearly staged test evaluation models, it places the clinical pathway and thus testing-related patient outcomes into the centre (Figure 1).

This is a critical component of the cyclical test evaluation framework, since the relationship between laboratory testing and subsequent patient outcomes is, more often than not, indirect. In most cases, only if test results are utilised to inform and guide effective downstream clinical decisions can patient outcomes be improved.

Thus, clear identification of the test purpose (i.e. intended clinical application and how the test information will be used to improve clinical management; e.g. diagnosis, prognosis, monitoring, screening, treatment selection, etc.) and test role within the clinical pathway (i.e. how the test will be positioned to alter the existing clinical

Figure 1 Framework for the evaluation of *in vitro* medical tests



The cyclical framework illustrates the interplay between the key elements of the test evaluation process and that all are dynamically linked to one another in a cycle driven by the intended use of a test in the clinical pathway.

Adapted from Horvath, et al [1].

pathway; e.g. replacement, triage, add-on test) are essential.

NOVEL APPROACH TO TEST EVALUATION IN PRACTICE

The problem with many frameworks published so far is that they describe what needs to be done, but they do not offer clear explanation of how each of the key steps should be undertaken. The EFLM TE-WG therefore aims to provide practical tools for each step of this framework to help operationalize the theory and the key principles described. The working group found that clinical pathway mapping is a useful method for identifying clinical needs and management decisions and to link information from testing to health outcomes.

Unmet need for medical tests is relatively vaguely defined and its assessment, in general, is a complex process that could be very subjective depending on the background, practice, experience and interest of stakeholders. For example, a representative from a reimbursement organization with strict funding and under government pressure for cost-effectiveness of health care services could see the need for a new biomarker from a very different perspective, compared to a researcher who has just discovered

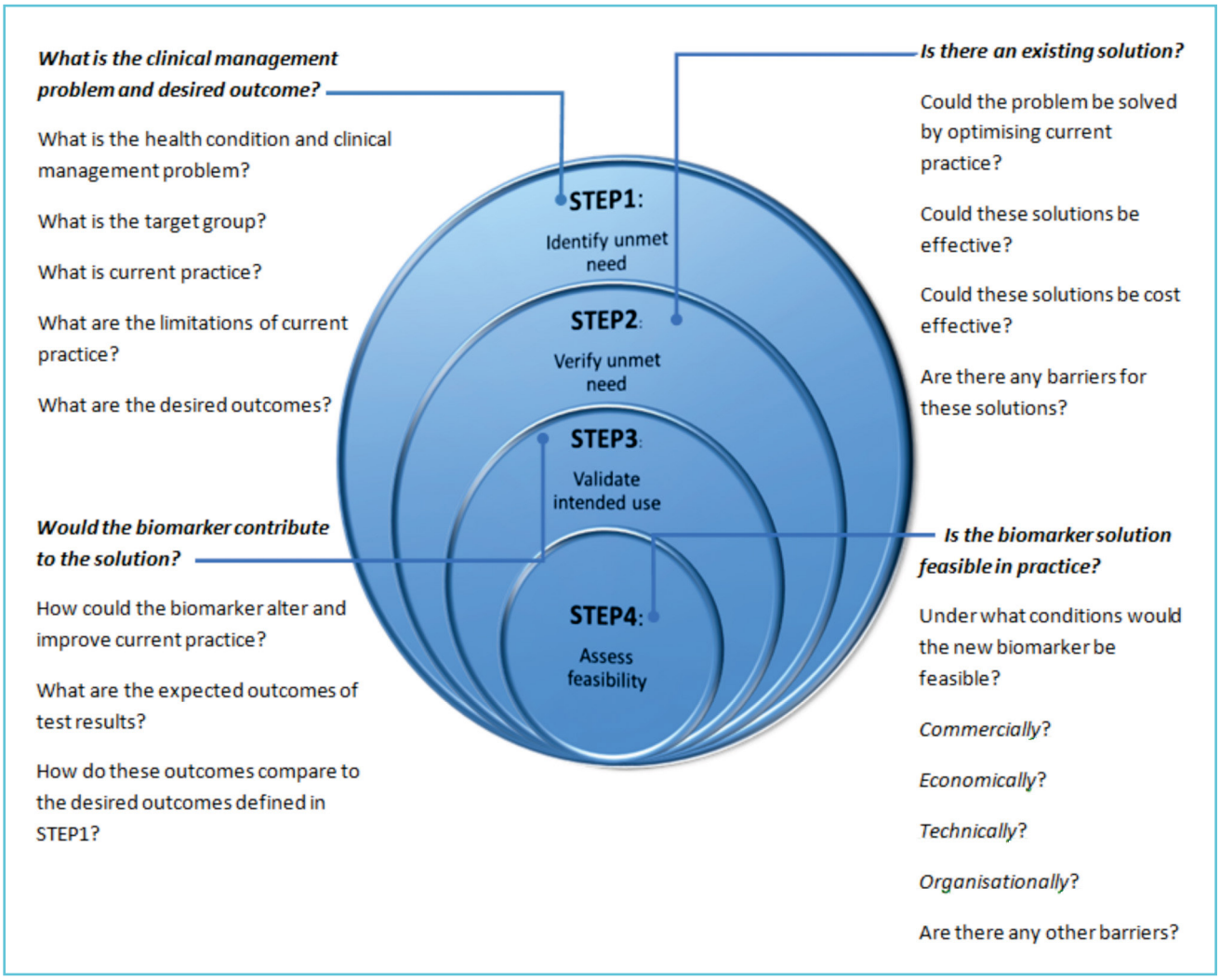
a promising new biomarker of potential clinical effectiveness; or indeed a clinician who is struggling to manage patient treatment in the absence of a reliable biomarker of treatment effectiveness.

To ensure that the differing perspectives of various stakeholders involved in the biomarker translation pipeline are captured, we concluded that a checklist of specific questions, with checkpoints, would be a practical and informative tool, rather than a set of generic recommendations. The checkpoint could also act as a catalyst for open dialogue between various stakeholders to identify and assess unmet needs in view of the clinical pathway.

The TE-WG used a 4-step process to develop the unmet clinical needs checklist:

1. scoping literature review;
2. face-to-face meetings to discuss scope, strategy and checklist items;
3. iterative process of feedback and consensus to develop the checklist;
4. testing and refinement of checklist items using case scenarios.

Figure 2 **The EFLM TE-WG 14-item checklist organized into 4 domains**



The checklist is intended to achieve more efficient biomarker development and translation into practice [2].

Clinical pathway mapping was utilised to identify clinical management decisions linking testing to health outcomes and the 14-item checklist was set around 4 key domains:

1. *Identifying the unmet need in the current clinical pathway;*
2. *Verifying the unmet need;*
3. *Validating the intended use; and*
4. *Assessing the feasibility of the new biomarker to influence clinical practice and health outcomes.*

The checklist presents an outcome-focused approach that can be used by multiple stakeholders for any medical test, irrespective of the purpose and role of testing (Figure 2). In each main domain there are more specific questions that need to be discussed and answered by stakeholders in order to facilitate a structured, considered judgment process. The checklist is built with checkpoints in such a way that if the answers to certain key questions are unfavorable, then the whole process should stop and the medical need for the biomarker and further evaluation of the test are not justified.

Based on the working group's experience, a checklist such as the AGREE checklist to assess the methodological quality of guidelines [3], or the STARD checklist that guides researchers on how to design and report diagnostic accuracy studies [4], is a very effective tool in providing clear guidance and a standardized way of handling complex evidence-based clinical decisions. The central strength of the checklist is that whilst it takes into consideration the perspectives of all stakeholders, it prioritizes the clinical pathway and health outcomes of the patient at the centre of the needs evaluation process.

In collaboration with the EFLM Working Group for Distance Education and e-Learning, we have developed an interactive version of this checklist, now openly available through the EFLM e-Learning platform: https://elearning.eflm.eu/course/view.php?id=11. The platform also contains a short video showing how to use the interactive checklist, including worked examples.

SYNERGY WITH THE NATIONAL ACADEMY OF MEDICINE BIOMARKER REPORT

The National Academy of Medicine (formerly the Institute of Medicine [IOM]) has issued several very useful documents over the years which influenced the development of the unmet clinical needs checklist of the EFLM TE-WG. These include the 2011 IOM report on the "Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease" [5] and recommendations for:

- effective biomarker evaluation and improving evidence-based regulation;
- development of biomarker-based tools for cancer (2006) [6];
- improving diagnosis in health care (2015) [7]; and most recently,
- biomarker tests for molecularly targeted therapies (2016) [8], a document that was issued after the EFLM checklist had already been completed.

Equally the TE-WG was very strongly influenced by the new *in vitro* diagnostic (IVD) regulatory changes in Europe [9] and the US [10], which demand more clinical evidence before new tests enter the market. Significant consideration was also given to the work of the Global Harmonization Task Force (GHTF) [11], which issued a number of valuable documents that have set the definitions, principles and key elements of and proposed processes for more effective biomarker evaluation before market approval.

The EFLM checklist provides a practical 'how to' tool that addresses the goals and principles set out by the above groups and regulatory bodies of the United States Food and Drug Administration (FDA) and Conformité Européenne (CE) in the

European economic area. It is anticipated, that the checklist will facilitate inter-disciplinary, multi-stakeholder collaboration for efficient biomarker development and pre- and post-market evaluation. Critically, the checklist will help to verify and validate the purpose and role of a biomarker in the context of the clinical pathway, thus providing the necessary evidence for the proposed intended use of the test. These important clinical considerations should then guide the analytical and clinical performance requirements and the generation of evidence of clinical effectiveness and value, as promulgated in IOM recommendation 3 [8].

PROFESSIONAL UPTAKE OF THE TOOLS

Initially, it is expected that the checklist will be used by a number of stakeholders such as clinical laboratory professionals, and that it will be pilot-tested with other colleagues, including those staff providing direct clinical care and industry representatives when reviewing the need for new biomarkers or new intended uses of existing medical tests.

Good communication with stakeholders in research and development is needed so that the biomarker development pipeline is aligned with evolving unmet clinical needs. The checklist will ideally drive multidisciplinary collaboration to break down the conventional working silos, and contribute to making biomarker evaluation a more efficient and targeted process, thus becoming an enabler for the adoption of innovative tests. Such collaboration will promote robust implementation planning proportionate to the clinical pathway, so test results are available and acted upon in an appropriate and timely manner, with a strong link to clinical intervention and outcomes.

There are numerous publications reporting biomarker failures and even harm caused by poorly performing biomarkers [12-18].

It is known that only a very tiny fraction of the many newly discovered 'omics' markers find their way 'from bench to the bedside'. Laboratory professionals are under increasing pressure from clinicians and health care administration to prove the value of existing tests in terms of impact on various health, organisational and financial outcomes.

It is also envisaged that IVD companies involved in research and biomarker development will use this checklist before investing in setting up major work for releasing new tests for novel biomarkers to the market.

Due to stricter regulations both by the FDA and CE marking authorities in Europe, IVD companies are under increasing pressure to provide data on the clinical performance of biomarkers before regulatory approval. Such studies are complex, costly and time-consuming. Notwithstanding the complexities of translational research, it has been stated to take on average 17 years for research evidence to reach clinical practice [19].

Therefore, it is in the interest of the IVD industry that the unmet clinical need and the purpose and role of new biomarkers in a clinical pathway and the potential impact of testing on various outcomes are thoroughly considered. This would reduce research waste and prevent the release of useless or even harmful tests to the market.

REGIONAL IMPLEMENTATION, DIFFERENCES AND EXAMPLES OF THOSE USING THE CHECKLIST

The strength of the working group's checklist is that, instead of providing recommendations which may match the healthcare setting of one country or region but not that of another, it asks open questions that can be answered with full consideration given to the local health care setting.

For example, the checklist asks the user of a new test to consider their current local practice, the limitations of current practice and to map out the current clinical pathway to see where the new test would fit in and what value it would add to current practice.

Obviously this clinical pathway can be very different even for the same medical condition in Europe, the US, or Africa or Australia.

Even within one country the care pathway and the utility of or the need for a test may depend on whether the relevant health care is provided in a metropolitan or in a rural care setting.

For example a point-of-care (POC) Troponin test may not fit well into the clinical pathway of a metropolitan hospital, which has 24/7 access to a higher sensitivity and more reliable Troponin assay with a <1hr turn-around-time in its central laboratory. Nevertheless, it may do so in a rural setting where there is limited access to laboratory testing and where a POC Troponin test may save lives by selecting patients who need urgent transport to a hospital, where appropriate care for an acute myocardial injury can be provided.

The checklist also asks whether the new biomarker is feasible in practice technically, commercially, economically, and organizationally, and what other local, cultural, social, etc. barriers may exist to its implementation. These again can be locally determined issues and the answers tailored to each setting may define medical need for the same test completely differently in various countries.

Indeed, unmet clinical need is a crucial primary component of the wider value proposition framework of laboratory medicine [20], taking into account the impact on clinical, operational and economic outcomes to assure feasibility of implementation.

SUMMARY

The unmet clinical need checklist produced by the EFLM TE-WG is a practical tool that should assist the work of all stakeholders involved in the discovery or implementation of new biomarkers and testing strategies.

We encourage pilot testing and regular use of this new interactive tool. The checklist can be used before new biomarkers are developed or fully validated for clinical use as well as when assessing the clinical need for and the clinical utility of existing tests. The TE-WG would appreciate feedback to inform future refinements of the checklist based on user experience.

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