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Discussion

Biomarker development targeting unmet clinical needs

Phillip J. Monaghan[a,*], Sarah J. Lord[b,c], Andrew St John[d], Sverre Sandberg[e,f,g], Christa M. Cobbaert[h], Lieselotte Lennartz[i], Wilma D.J. Verhagen-Kamerbeek[j], Christoph Ebert[k], Patrick M.M. Bossuyt[l], Andrea R. Horvath[m,n], for the Test Evaluation Working Group of the European Federation of Clinical Chemistry and Laboratory Medicine

[a] Department of Clinical Biochemistry, The Christie Pathology Partnership, The Christie NHS Foundation Trust, Manchester, UK
[b] School of Medicine, University of Notre Dame, Australia
[c] National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney, Australia
[d] ARC Consulting, Perth, Australia
[e] The Norwegian Quality Improvement of Primary Care Laboratories (NOKLUS), Haraldsplass Deaconess Hospital, Bergen, Norway
[f] Department of Public Health and Primary Health Care, University of Bergen, Norway
[g] Laboratory of Clinical Biochemistry, Haukeland University Hospital, Bergen, Norway
[h] Department of Clinical Chemistry and Laboratory Medicine, Leiden University Medical Center, The Netherlands
[i] Abbott Diagnostics, Wiesbaden, Germany
[j] Medical and Scientific Affairs, Roche Diagnostics International Ltd., Rotkreuz, Switzerland
[k] Medical and Scientific Affairs, Roche Diagnostics GmbH, Penzberg, Germany
[l] Department of Clinical Epidemiology, Biostatistics & Bioinformatics, Academic Medical Center, University of Amsterdam, The Netherlands
[m] SEALS Department of Clinical Chemistry and Endocrinology, Prince of Wales Hospital and School of Medical Sciences, University of New South Wales, Australia
[n] Screening and Test Evaluation Program, School of Public Health, University of Sydney, Australia

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ABSTRACT

Background: The introduction of new biomarkers can lead to inappropriate utilization of tests if they do not fill in existing gaps in clinical care. We aimed to define a strategy and checklist for identifying unmet needs for biomarkers.
Methods: A multidisciplinary working group used a 4-step process: 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.
Results: We used clinical pathway mapping to identify clinical management decisions linking biomarker testing to health outcomes and developed a 14-item checklist organized into 4 domains: 1/ identifying and 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 outcome. We present an outcome-focused approach that can be used by multiple stakeholders for any medical test, irrespective of the purpose and role of testing.
Conclusions: The checklist intends to achieve more efficient biomarker development and translation into practice. We propose the checklist is field tested by stakeholders, and advocate the role of the clinical laboratory professional to foster trans-sector collaboration in this regard.

1. Introduction

Recent calls to increase value and reduce waste in biomedical research have highlighted the need to improve the development and translation of biomarkers into clinical practice [1]. The laboratory medicine profession is in a position to play a pivotal role in improving biomarker translational research to address this challenge.

Common reasons for failed biomarker uptake have been well described. These include inadequate analytical validation, poorly defined clinical indications and inadequate clinical performance [2,3]. Some of these shortcomings can be addressed by improved study design for biomarker evaluation. However, at a more fundamental level, there is also a need to increase research value by better targeting biomarker selection and clinical development towards gaps where more effective or more

* Corresponding author at: Christie Pathology Partnership, The Christie NHS Foundation Trust, Wilmslow Road, Withington, Manchester M20 4BX, UK.
E-mail address: phillip.monaghan@nhs.net (P.J. Monaghan).

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practical options are needed for the diagnosis and management of a condition – referred to as 'unmet clinical needs'.

Market clearance for new in vitro diagnostic (IVD) medical tests in Europe and many other regions does not currently require manufacturers to explicitly state how biomarkers should be used to improve on existing testing strategies, nor to provide evidence for how they add clinical value for the proposed indications. Regulatory approval therefore often leads to early release of biomarkers with an as-yet unproven clinical value. Similarly, biomarkers introduced for specific patient groups may diffuse into practice for other populations with different clinical needs or for off-label use where they subsequently fail to demonstrate adequate effectiveness and may even cause harm. This scenario is illustrated by the examples of PSA for prostate cancer screening [4,5] and CA-125 for ovarian cancer screening [6].

Conversely, where a biomarker is found to improve diagnosis or prognostic classification of disease, there can often be long delays before defining optimal use of the medical test in practice and providing evidence of effectiveness for implementation and re-imbursement. For example, two decades passed between the discovery and clinical validation of B-type natriuretic peptide (BNP) as a marker for heart failure and recommendations for its use in clinical practice [7].

In practice, a major challenge is that biomarkers are usually discovered in response to technological advances – often without a focus on the specific shortcomings in existing clinical practice. This technology 'push' and other non-clinical factors, including financial pressure or reward, can drive technology innovations beyond healthcare needs if inadequate efforts are made to align biomarker development to the 'pull' of clinical needs [1,8,9]. For example, Anderson and colleagues have ascribed a major problem in the current approach to protein biomarker discovery as one of asking an inappropriate clinical question, which they describe as a question that does not seek to determine how well the biomarker can inform a critical clinical decision [8].

Identifying unmet needs presents a practical challenge for those developing biomarkers because it requires close collaboration with health care providers as the potential end-users of medical tests. Unfortunately, there is little guidance to the professions on how to conduct this targeted cross-disciplinary dialogue.

In this paper we define unmet clinical needs for tests. We offer a practical approach with worked examples to assist researchers, clinical scientists, and the IVD industry working with clinicians, to identify unmet needs and improve the targeted development of IVD medical tests that lead to improved health outcomes.

2. Methods

The Test Evaluation Working Group (WG-TE) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) has been formed to facilitate the role of the laboratory profession in translational research involving biomarkers. Building on a methodological framework for test evaluation [10], this multidisciplinary working group of laboratorians, epidemiologists, evidence-based medicine (EBM), health technology assessment (HTA), policy experts, and the IVD industry, aims to provide practical tools that help improve the clinical and cost-effectiveness of biomarkers and facilitate their implementation as medical tests within the clinical pathway.

In this study the WG-TE used a 4-step process. 1/ Following a brainstorming session to define the scope, the WG-TE searched the literature and websites of stakeholder organizations to identify existing tools and processes for defining unmet clinical needs; 2/ held eight face-to-face meetings to discuss the scope, definitions, strategy and checklist items and drafted documents; 3/ circulated the draft checklist within the Working Group and followed an iterative process for feedback and consensus. 4/ On agreeing checklist items, the WG-TE pilot tested and refined the checklist on two case scenarios, involving point-of-care (POC) Nucleic Acid Amplification Testing (NAAT) for chlamydia and fetal fibronectin.

3. Results

3.1. Definition of unmet clinical needs

Assessment of unmet need is widely undertaken across different health sectors to set priorities to improve the effectiveness and cost-effectiveness of health service delivery and planning (health service and policy sector), research funding (academic and research policy sector), and investment into research and development (R&D) and IVD development (industry/business sector). However, despite having a central role in each of these areas, there is no single definition of unmet needs in common use.

Most current definitions of unmet needs focus on the provision of therapeutic interventions. For example, the U.S. Department of Health and Human Services Food and Drug Administration (FDA) defines unmet medical needs as "a condition whose treatment or diagnosis is not addressed adequately by available therapy" [11].

Framing clinical needs only around therapeutic interventions overlooks the potential for innovations in medical testing to improve health outcomes. New tests can improve outcomes by optimizing the selection of treatment, through more accurate or rapid diagnosis, risk classification or prediction of disease, or disease outcomes; or by offering other patient benefits such as replacing a more invasive test. Indeed, the emerging approach of precision medicine requires novel biomarker tests for molecularly targeted therapies, tailored for the individual patient's condition.

In an ideal situation, a well-defined unmet clinical need should act as the architect for biomarker test development. Clinical studies can then be designed in appropriate populations and targeted study designs to validate the biomarker to address this need and to determine analytical and clinical test performance specifications [12].

To recognize these broader potential benefits, we propose the definition of unmet clinical needs should be augmented as follows: *Unmet clinical need refers to any missing or inadequately performing component of a clinical pathway*. The term clinical pathway refers to the standard process of care for managing a specific condition or presentation (current tests and treatment) in a well-defined group of patients and

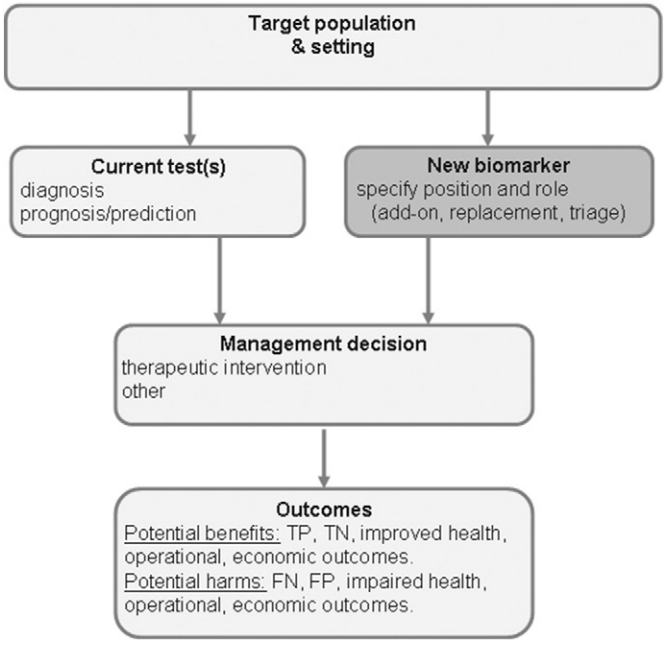

Fig. 1. Clinical pathway mapping to illustrate the intended use of a new biomarker. TP = true positive; TN = true negative; FN = false negative; FP = false positive.