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Discussion

Biomarker development targeting unmet clinical needs

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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

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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

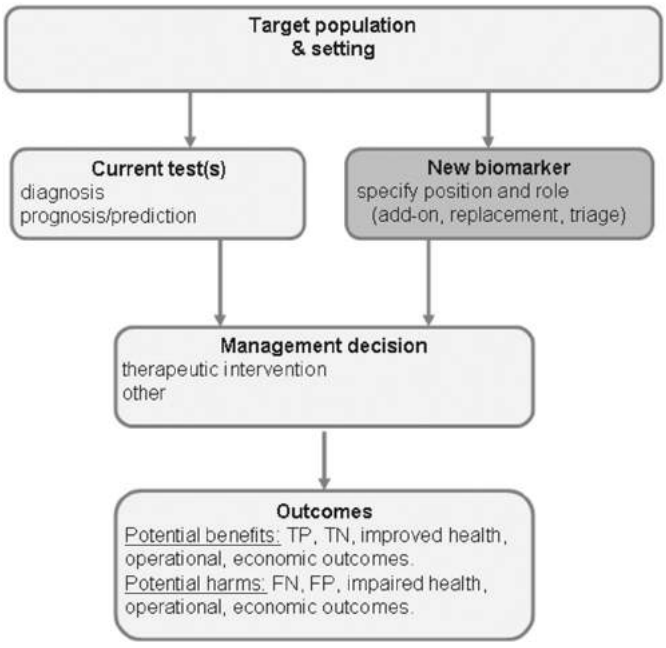

Fig. 1. Clinical pathway mapping to illustrate the intended use of a new biomarker. TP = true positive; TN = true negative; FN = false negative; FP = false positive.

the associated health outcomes (Fig. 1). Thus the definition of unmet clinical needs requires explicit mapping of current practice to identify opportunities for improving management and thereby outcomes. We propose that when a new biomarker is marketed as a medical test, the intended use, stated within the assay documentation, clearly defines the unmet need that the new test is anticipated to address.

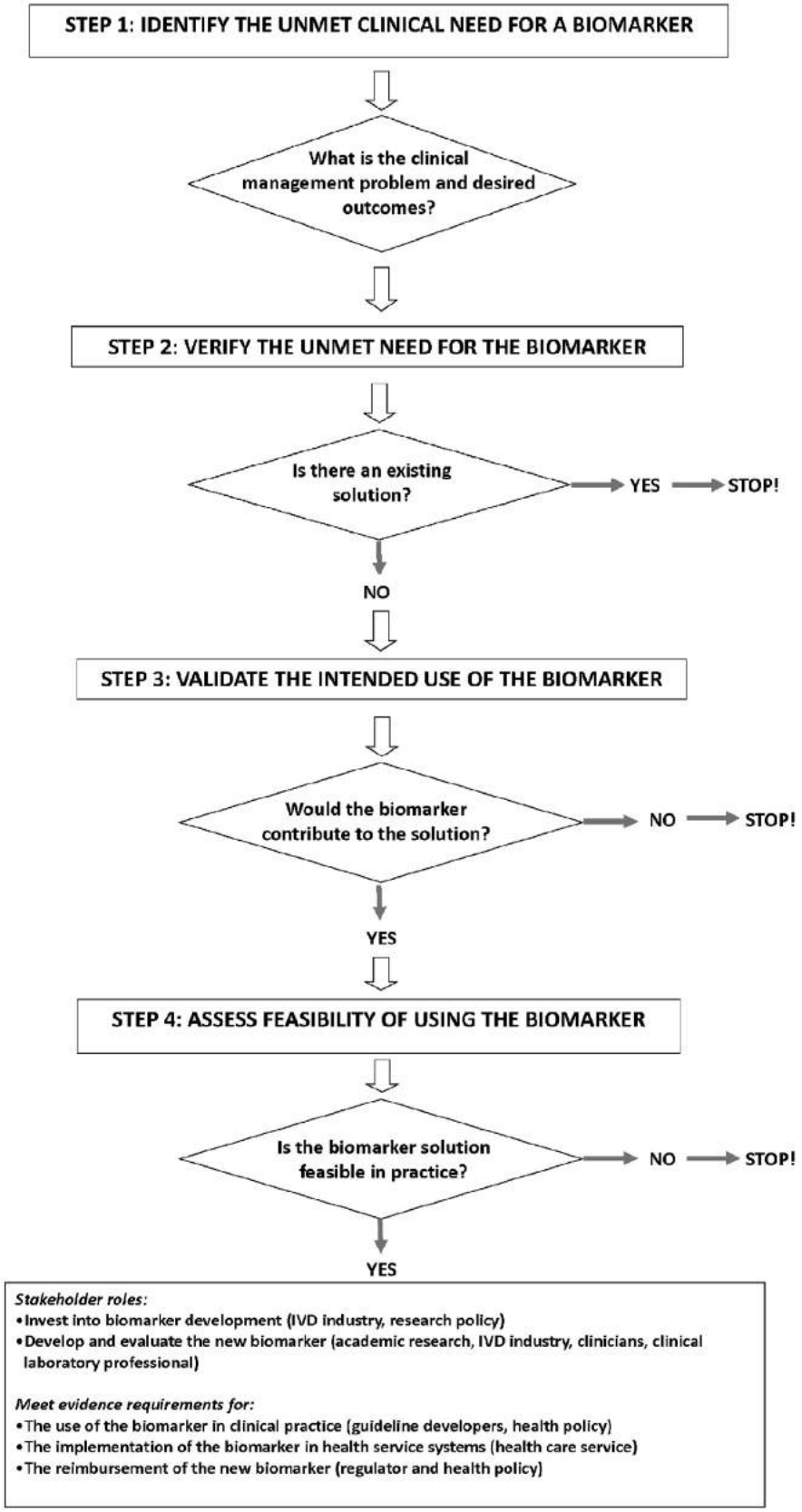

Fig. 2. The process of identifying unmet clinical needs for a biomarker.

Fig. 3. Unmet clinical needs checklist for diagnosis and management of chlamydia infection using POC Nucleic Acid Amplification Testing (NAAT) as a replacement for laboratory based NAAT.

Fig. 4. Unmet clinical needs checklist for fetal fibronectin as a triage test to predict preterm labor.

Explicitly defining how a biomarker could be used to improve health outcomes can guide further evaluation of potential benefits and harms. In some situations, the new biomarker may demonstrate similar diagnostic accuracy to the currently available test but is less invasive, with the proposed benefits of improved patient safety with no change in diagnosis and subsequent clinical decisions anticipated.

3.2. A practical tool

We propose a checklist of questions that can be used to guide discussion between multidisciplinary groups to define the unmet needs for, and the potential clinical use of, a medical test (Fig. 2). Checklist questions are organized around a 4-step process: 1/ Identify the unmet clinical need for a biomarker; 2/ Verify the unmet need for the biomarker; 3/ Validate the intended use of the biomarker; 4/ Assess feasibility of using the biomarker. The same process can be followed regardless of the proposed purpose (screening, diagnosis, prognosis) and role (add-on, triage, replacement) of the biomarker within the clinical pathway [10,13]. The checklist is designed to be used by any stakeholder group and perspective (i.e. clinician, allied health professional, health service and policy, academic and research policy, or industry/business sector). We describe these steps with examples below (Fig. 3–4).

3.3. Step 1: identify the unmet clinical need fora biomarker

3.3.1. Key question 1: what is the clinical management problem and desired outcomes?

The first step in the checklist is to identify the unmet need. This involves defining the condition, describing the patient group(s) involved, current practice for this condition, and the outcomes of current practice where improvement is desired. The latter involves identifying the specific type of disease events or other health related issues for improvement.

To determine opportunities for improved testing, current practice should be described by defining what tests are currently used. It is mandatory to identify the key management decisions that are supported by the actual test and may require better information, or other desirable attributes such as improved safety or convenience. We recommend drawing the elements (population, test(s), management, outcomes) on a simple clinical pathway (Fig. 1). The act of drawing up a pathway to map out current practice is helpful to initiate discussions with clinicians and clarify unmet needs where improvements in outcomes are desired. The pathway can then be used to focus discussion about the potential benefits of the new biomarker in terms of what management decision and outcomes it should aim to improve; and how the new biomarker is best positioned to alter current practice to achieve these outcomes (see Step 3). The positioning in the pathway will allow the definition of required performance characteristics. Clinical pathway mapping can follow the same process regardless of the proposed purpose (e.g. screening, diagnosis, prognosis) of the biomarker.

One example is the rapid diagnosis of Chlamydia infection which was one of the top priorities identified by primary care physicians in a survey of their unmet needs [14]. Here, the desired outcome is reduced Chlamydia complication rates such as pelvic inflammatory disease, achieved through immediate access to diagnostic information to initiate prompt appropriate treatment and reduce the problem of missed treatment due to patient loss to follow-up. A second example is the need for improved tests for women presenting with symptoms of threatened preterm labor to identify those at very low risk of progressing to labor who can safely avoid admission and treatment [15]. Here, the desired outcome is reduced unnecessary hospital observation and patient inconvenience, achieved through improved diagnostic information for timely triage of very low risk women. We present both examples to show how the checklist can be used (Figs. 3–4), and also show how the clinical pathway can be mapped to display the intended role of these biomarkers (Fig. 5–6).

In some cases, it may not be so easy to identify unmet needs and careful enquiry will be needed to identify opportunities for biomarkers to improve current practice. Questions can include, what patients do poorly and what information could help management; or more generally, in managing this problem, what would make the patient's life or your clinical task easier?

3.4. Step 2: verify the unmet need for the biomarker

3.4.1. Key question 2: is there an existing solution?

The second step is to identify whether other interventions or changes in current practice could improve the unsatisfactory situation. If the unfavorable outcomes can be avoided or improved by changing current practice, for example by better adherence to guidelines or recommendations, reducing practice variability or by involving an existing technology, then the need, though present, cannot be called an unmet clinical need. Existing methods can meet it.

In the examples shown in Figs. 3 and 4, alternative interventions or options within current practice to improve outcomes were not identified. In the case of Chlamydia (Fig. 3), point of care or rapid tests for Chlamydia have not, until recently, had sufficient diagnostic accuracy to diagnose infection to replace laboratory-based testing. In the second example, for women with threatened preterm labor with negative findings on clinical examination alone (Fig. 4), the risk of progression to labor is not judged to be adequately safe to replace admission for observation. Transvaginal ultrasound measurement of cervical length is the best available test for assessing risk of birth within 48 h but is not part of routine antenatal care and requires specialized equipment and expertise [16].

3.5. Step 3: validate the intended use of the biomarker

3.5.1. Key question 3: would the biomarker contribute to the solution?

The third step is to identify how the biomarker is proposed to improve current practice, thereby validating its intended clinical use. This involves defining any direct impact on outcomes, for example by providing reassurance to patients with a negative result; and all indirect impacts, for example by informing decisions about the need for further tests and treatment for patients with a positive result.

This information should be displayed on the clinical pathway to show the proposed position of the biomarker. The new test can be positioned before, after or at the same time as current tests. Its proposed role can be one of an add-on, replacement or triage test. The anticipated consequences of test results on patient management and subsequent outcomes can be identified, which can be classified as potential benefits and harms (Fig. 1).

In Fig. 3 we describe how a sensitive rapid test for Chlamydia is intended to facilitate timely treatment of patients with outcomes including reduced risk of pelvic inflammatory disease and associated serious complications [17]. In general, evaluation of the new test will be required to demonstrate improved performance over current practice for these claimed benefits.

Sometimes the potential harms of using the new test to guide management are clinically significant. For example, a false negative result of a biomarker used to exclude preterm labor could lead to significant adverse events and complications. In those cases, the checklist can be used to discuss the minimally required clinical performance the test should achieve such that the benefits outweigh the harms (Fig. 4).

3.6. Step 4: assess feasibility of using the biomarker

3.6.1. Key question 4: is the biomarker solution feasible in practice?

In the final step, the technical, commercial and organizational feasibility of the biomarker for the intended use requires thorough consideration. In Fig. 3 we show that organizational changes are required in order to introduce a point-of-care test for Chlamydia to ensure that the results of the test can be used in the subsequent consultation and treatment instituted.

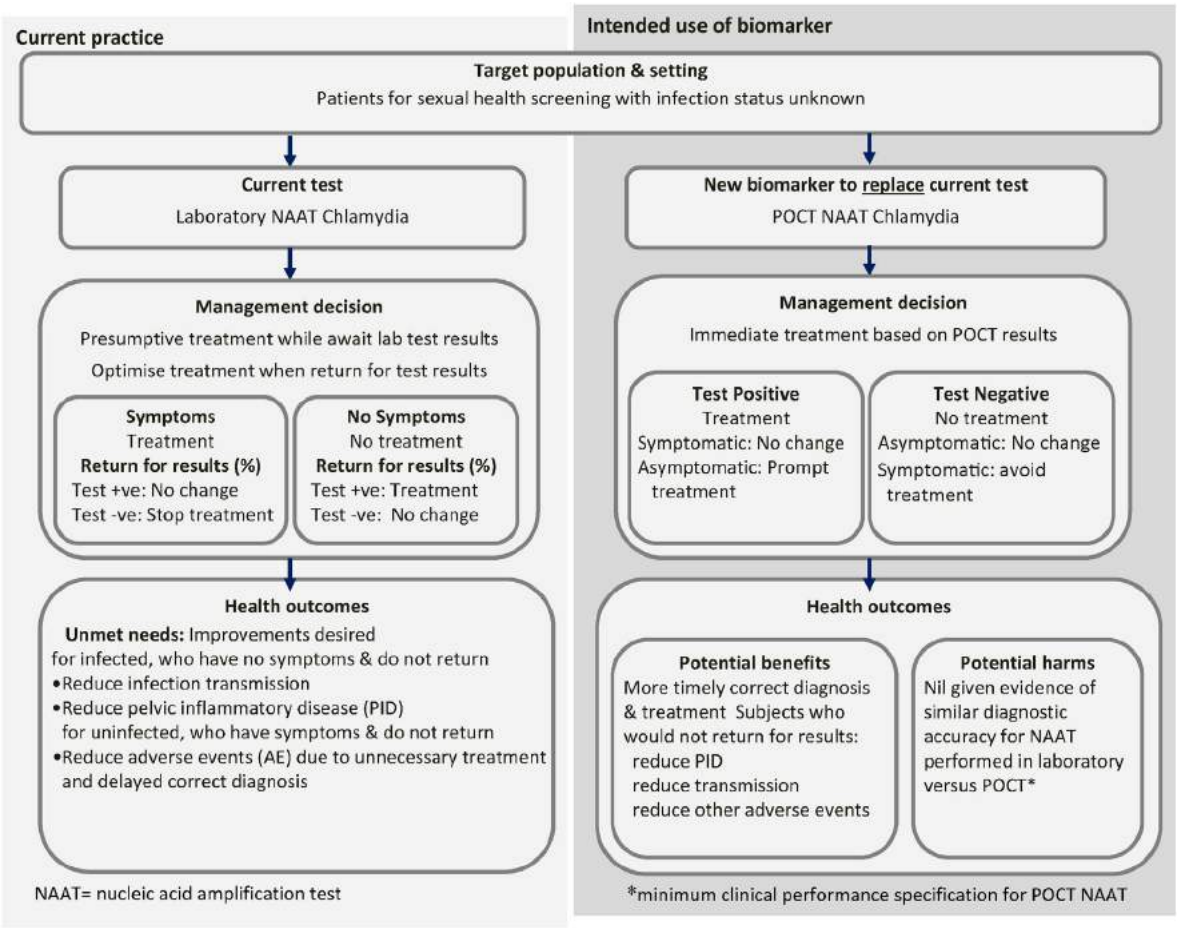

Fig. 5. Clinical pathway mapping of point of care testing as a replacement for laboratory testing for Chlamydia.

The economic feasibility of introducing biomarkers is another critical consideration. Many new tests only offer marginal improvements in health outcomes compared to current practice, and therefore may not be cost-effective. Approaches to select economically viable markers, at least for companion diagnostics, have been attempted through the development of rank order estimates, by therapeutic area, for scientific potential and economic attractiveness for companion diagnostics development [18].

4. Discussion

While the concept of unmet need is well recognized, it has been poorly defined for biomarker tests. The few papers that explain the importance of defining the unmet need in the development of biomarkers [19] do not provide a practical approach. To address this problem, we have provided a checklist as a tool to help assess whether a new biomarker would provide clinical benefit, and if implementation would be feasible.

We believe this checklist provides a valuable addition to ongoing initiatives to promote the assessment of unmet need to guide research and health policy. In the field of medical testing, the UK National Institute for Health Research (NIHR) has developed a clinical research infrastructure to foster partnerships of the medical device and diagnostic sectors and clinicians. Consumer advocacy groups and patient focused clinician-patient partnerships, such as the James Lind Alliance and the USA Patient-Centered Outcomes Research Institute (PCORI), also provide leadership in identifying high priority unmet patient needs that help guide research. However, to date, no simple generic methods or tools have been available to help health profession groups to identify unmet clinical need, in particular for medical tests.

We describe how the clinical pathway should be mapped to identify unmet needs. The use of clinical pathways, also referred to as test-treatment pathway, clinical algorithms or care maps [10], has been well described for the development of quality improvement activities and clinical guidelines. However, their role in the validation of new biomarkers is complex because the relationship between testing and outcomes is usually indirect. Important questions to resolve are: 1) What is the proposed role of the new tests in relation to existing tests, 2) What is the impact on decisions for further testing and/or treatment, and 3) What are the consequences for outcomes compared to existing care?

In developing this checklist we have focused on unmet needs from the clinician perspective of improving health outcomes. A similar approach can be used to identify unmet needs from other perspectives, such as the health care funder perspective where cost reduction without compromising clinical performance may be desired, or from the societal perspective where more equitable access to healthcare is desired.

The Institute of Medicine (IOM) has also emphasized the need for improved inter-professional communication and collaboration of all stakeholders involved in the clinical pathway to support approaches for biomarker development and evaluation in order to provide benefits to clinicians, patients and the health care system and society [20]. Initiating forums that foster inter-professional collaboration is one possible solution. In addition to investigator- and industry-led initiatives for specific projects, opportunities to initiate multidisciplinary discussion and collaboration include hospital grand rounds, local health district forums, inter-professional academic working groups and scientific expert meetings. We hope that the unmet needs checklist will be useful as a platform to facilitate these collaborations and stimulate productive discussion between groups with diverse roles using a common terminology.

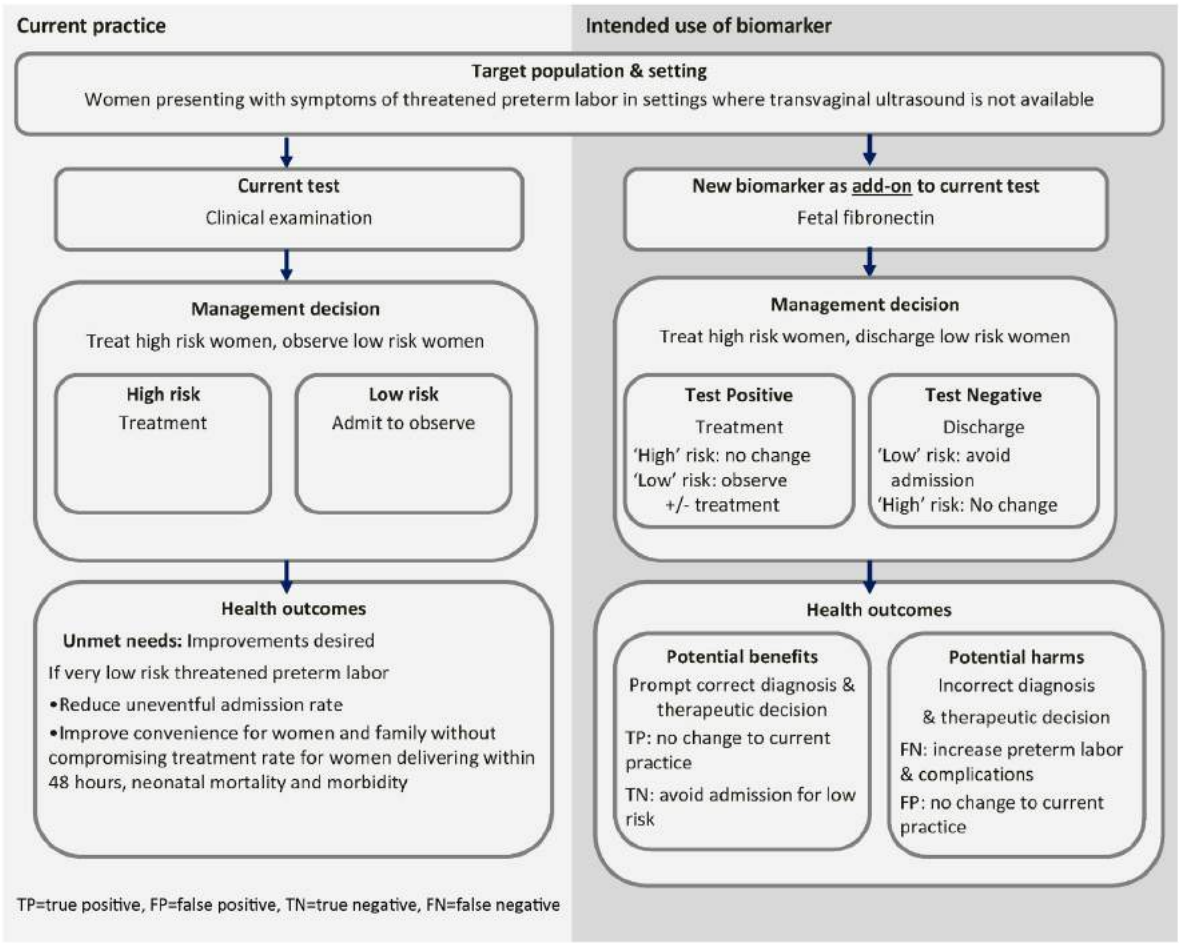

Fig. 6. Clinical pathway mapping of a biomarker for threatened preterm labor as an addition to clinical examination.

Agencies investing in biomarker research should demand better returns on investment [21], which could be attainable through more efficient discovery and test evaluation networks. To increase the value of biomarker research one approach to drive efficiency gains in this field would be to require researchers and manufacturers, when reporting on the clinical value and utility of new biomarkers, to include a discussion of the most promising proposed use of the biomarker in the context of the clinical pathway. At a minimum, researchers and those responsible for bringing new tests to the market should be required to identify the proposed purpose and role of a new test within an existing or in a new pathway as part of the evidence of clinical performance when seeking marketing approval (IOM recommendation 3 [20]).

In the post-marketing phase the laboratory medicine profession can help optimize biomarker evaluation and improve value through other approaches as well. Medical laboratories can play an important role in identifying unmet clinical needs through audit or active post-market surveillance of the clinical performance and effectiveness of existing tests. By identifying poorly performing medical tests, laboratory professionals may assist in both removing biomarkers from the test repertoire and replacing them with better performing tests, or exploring novel test purposes where appropriate. To achieve this, the laboratory information system and the electronic health record of patients need to be better integrated to support the systematic collection of biomarker utility data in a publicly accessible data base that ideally would be shared nationally and internationally (IOM recommendation 6 [20]).

We would like to advocate that the checklist presented here is field tested and validated by various stakeholder groups. We believe that clinical laboratory professionals, acting at the interface between the clinic, academia and industry, are well positioned to coordinate multidisciplinary networks, and to facilitate and direct a tailored approach for more efficient biomarker test development based on the assessment of unmet clinical needs for medical tests.

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References

[1] M.R. Macleod, S. Michie, I. Roberts, U. Dirnagl, I. Chalmers, J.P. Ioannidis, R. Al-Shahi Salman, A.W. Chan, P. Galsziou, Biomedical research: increasing value, reducing waste, Lancet 383 (2014) 101–104.
[2] E.P. Diamandis, The failure of protein cancer biomarkers to reach the clinic: why, and what can be done to address the problem? BMC Med. 10 (2012) 87.
[3] J.P.A. Ioannidis, Biomarker failures, Clin. Chem. 59 (2013) 202–204.

[4] V.A. Moyer, Screening for prostate cancer: U.S. preventive services task force recommendation statement, Ann. Intern. Med. 157 (2012) 120–134.
[5] S.E. Eggener, A.S. Cifu, C. Nabhan, Prostate cancer screening, JAMA 314 (2015) 825–826.
[6] V.A. Moyer, Screening for ovarian cancer: U.S. preventive services task force reaffirmation recommendation statement, Ann. Intern. Med. 157 (2012) 900–904.
[7] NICE CG187, Acute Heart Failure: Diagnosis and Management, https://www.nice.org.uk/guidance/cg187 2014 (accessed; 28.06.16).
[8] N.L. Anderson, A.S. Ptolemy, N. Rifai, The riddle of protein diagnostics: future bleak or bright? Clin. Chem. 59 (2013) 194–197.
[9] B.M. Hofmann, Too much technology, BMJ 350 (2015) h705.
[10] A.R. Horvath, S.J. Lord, A. St John, S. Sandberg, C.M. Cobbaert, S. Lorenz, P.J. Monaghan, W.D.J. Verhagen-Kamerbeek, C. Ebert, P.M.M. Bossuyt, From biomarkers to medical tests: the changing landscape of test evaluation, Clin. Chim. Acta 427 (2014) 49–57.
[11] U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Guidance for Industry Expedited Programs for Serious Conditions — Drugs and Biologics, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf 2014 (accessed; 28.06.16).
[12] T.A. Metcalfe, Development of novel IVD assays: a manufacturer's perspective, Scand. J. Clin. Lab. Investig. Suppl. 242 (2010) 23–26.
[13] P.M. Bossuyt, Comparative accuracy: assessing new tests against existing diagnostic pathways, BMJ 332 (2006) 1089–1092.
[14] J. Howick, J.W. Cals, C. Jones, C.P. Price, A. Pluddemann, C. Heneghan, M.Y. Berger, F. Buntinx, J. Hickner, W. Pace, T. Badrick, A. Van den Bruel, C. Laurence, H.C. van Weert, E. van Severen, A. Parrella, M. Thompson, Current and future use of point-of-care tests in primary care: an international survey in Australia, Belgium, The Netherlands, the UK and the USA, BMJ Open 4 (2014), e005611.
[15] S.N. Deshpande, A.D. van Asselt, F. Tomini, N. Armstrong, A. Allen, C. Noake, K. Khan, J.L. Severens, J. Kleijnen, M.E. Westwood, Rapid fetal fibronectin testing to predict preterm birth in women with symptoms of premature labour: a systematic review and cost analysis, Health Technol. Assess. 17 (2013) 131–138.
[16] NICE NG25, Preterm Labour and Birth, https://www.nice.org.uk/guidance/ng25 2015 (accessed; 28.06.16).
[17] E.J. Adams, A. Ehrlich, K.M. Turner, K. Shah, J. Macleod, S. Goldenberg, R.K. Meray, V. Pearce, P. Horner, Mapping patient pathways and estimating resource use for point of care versus standard testing and treatment of chlamydia and gonorrhoea in genitourinary medicine clinics in the UK, BMJ Open 4 (2014), e005322.
[18] J.C. Davis, L. Furstenthal, A.A. Desai, T. Norris, S. Sutaria, E. Fleming, P. Ma, The microeconomics of personalized medicine: today's challenge and tomorrow's promise, Nat. Rev. Drug Discov. 8 (2009) 279–286.
[19] J.W. Zolg, H. Langen, How industry is approaching the search for new diagnostic markers and biomarkers, Mol. Cell. Proteomics 3 (2004) 345–354.
[20] National Academies of Sciences, Engineering, and Medicine, Biomarker Tests for Molecularly Targeted Therapies: Key to Unlocking Precision Medicine, The National Academies Press, Washington, DC, 2016.
[21] G. Poste, Bring on the biomarkers, Nature 469 (2011) 156–157.