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Setting minimum clinical performance levels to develop biomarkers for clinical use

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Background

Biomarker discovery studies often claim clinically important findings, motivating further studies and marketing, however few have led to improvements in clinical care. This failing has been largely attributed to poor study design and inadequate validation of findings; both recognised as major causes of research waste. Missed opportunities for implementing validated biomarkers to improve clinical care are more difficult to estimate but equally important.

To improve this situation, studies of biomarker performance should mirror how it is intended to be used to improve patient care. Further, by specifying minimum clinical performance levels a biomarker must achieve to allow it to represent a potentially useful test, researchers can prioritise good performers for validation, and discard poor performers. However, this approach is rarely used and there is limited guidance to encourage its use.

This presentation aims to provide practical guidance for setting and applying minimum clinical performance levels for tests to improve biomarker development and evaluation.

Methods

We draw on established principles of test evaluation and clinical trial phased design to describe the process for setting minimum clinical performance levels for biomarkers proposed for use as clinical tests. We describe three basic methods to determine the minimum acceptable cut-off for a given clinical indication with illustrative examples; and explain how to apply this cut-off to guide biomarker development.

Results

The process can be summarised in 5 steps: Step 1. Define desired outcomes for the biomarker based on deficiencies in current practice. For example: (a) improve disease outcomes by earlier or more accurate rule-in of disease for treatment; (b) reduce iatrogenic harm by earlier or more accurate rule-out of disease; or (c) other benefits without compromising accuracy; Step 2. Describe current practice for the proposed indication using clinical pathway mapping to list key clinical management decisions, existing tests, treatments and outcomes; Step 3. Define the intended purpose (eg. screening, diagnosis, prognosis, monitoring, predict treatment response) and role of the test (replacement, triage, add-on, new pathway) to alter the current clinical pathway to achieve the desired outcomes. Step 4. Identify the key measures to assess proposed benefit and potential benefit-harm trade-off – for example, difference in true positive versus false positive rates, difference in true negative/false negative rates versus the existing test strategy. Step 5. Set the minimum acceptable cut-off for key performance measure/s by: (i) comparing to the existing test strategy as a benchmark; (ii) a clinician survey to determine acceptable risk; or (iii) a decision-analytical approach to estimate acceptable harm:benefit trade-off. We discuss consideration of blood biomarkers as a replacement test for faecal occult blood testing for colorectal cancer screening, troponin as a triage test for ruling out acute coronary syndrome and CA 125 as a new test pathway for ovarian cancer screening to describe how the method used depends on the intended role, comparator, desired outcomes and potential harms of the new test.

Conclusions

We suggest laboratory professionals, clinicians, researchers and the in-vitro-diagnostic industry can use this approach to guide the efficient development of new biomarkers to meet clinical needs. For biomarkers achieving minimum performance levels, a randomized controlled trial may still be necessary to assess improved patient outcomes.