Beyond the laboratory: methods to assess the impact of test measurement uncertainty on outcomes

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Background
For medical tests that have a central role in clinical decision-making, international laboratory guidelines advocate *outcome-based* analytical performance specifications (APS) – i.e. measurement performance goals derived from the expected impact of measurement uncertainty on clinical outcomes. The identification of outcome-based APS relies on indirect studies (e.g. simulation) to assess the impact of test measurement uncertainty on outcomes. Currently however, there is limited awareness of available methods in this context. Increased awareness and understanding of indirect study methods could further inform test evaluation methodologies.

Aim
To identify indirect methods for assessing the impact of measurement uncertainty (i.e. bias and imprecision) on outcomes (clinical performance, clinical utility and/or costs).

Methods
A methodology review consisting of database searches and extensive citation tracking was conducted to identify studies using indirect methods to incorporate or evaluate the impact of test measurement uncertainty on outcomes.

Results
Eighty-two studies were identified, most of which evaluated the impact of imprecision and/or bias on clinical accuracy. A common three-step analytical framework underpinning the various methods was apparent: (1) estimation of "true" test values; (2) estimation of measured test values (incorporating uncertainty); and (3) estimation of the impact of discrepancies between (1) and (2) on specified outcomes. Simulation techniques have become a common approach over the past two decades; the most flexible method – the *error model simulation approach* – is based on the iterative application of bias and imprecision onto baseline "true" values. Whilst previous studies have focused on clinical performance (e.g. diagnostic accuracy), evaluations can be feasibly extended to clinical-utility and cost-effectiveness outcomes using decision analytic models.

Conclusions
Various approaches are available for conducting indirect assessments to inform outcome-based APS and test evaluations. This study provides a useful overview of methods and key considerations for future research.

Keywords
Measurement uncertainty, methodology review, analytical performance specifications, test evaluation