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Towards a framework for outcome-based analytical performance specifications: a methodology review of indirect methods for evaluating the impact of measurement uncertainty on clinical outcomes

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List of Abbreviations

EFLM = European Federation of Clinical Chemistry and Laboratory Medicine

ROC = Receiver operator characteristic

AUC = Area under the curve

CV = coefficient of variation

SD = standard deviation

EQA = External Quality Assessment

QALY = quality adjusted life year

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Abstract

Background: For medical tests that have a central role in clinical decision-making, current guidelines advocate *outcome-based* analytical performance specifications. Given that empirical (clinical-trial style) analyses are often impractical or unfeasible in this context, the ability to set such specifications is expected to rely on indirect studies to calculate the impact of test measurement uncertainty on downstream clinical, operational and economic outcomes. Currently however, a lack of awareness and guidance concerning available alternative indirect methods is limiting the production of outcome-based specifications. Our aim therefore was to review available indirect methods and present an analytical framework to inform future outcome-based performance goals.

Content: 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 downstream outcomes (including clinical accuracy, clinical utility and/or costs). Eighty-two studies were identified, most of which evaluated the impact of imprecision and/or bias on clinical accuracy. A common analytical framework underpinning the various methods was identified, consisting of three key steps: (1) calculation of "*true*" test values; (2) calculation of *measured* test values (incorporating uncertainty); and (3) calculation of the *impact* of discrepancies between (1) and (2) on specified outcomes. A summary of the methods adopted is provided, and key considerations discussed.

Conclusions: Various approaches are available for conducting indirect assessments to inform outcome-based performance specifications. This study provides an overview of methods and key considerations to inform future studies and research in this area.

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Introduction

Although systematic and random variation around measured test values (henceforth, *measurement uncertainty*) is now routinely documented within the clinical laboratory, the potential impact of this uncertainty on downstream clinical, operational and economic outcomes is rarely quantified. Meanwhile, evaluation of the impact of measurement uncertainty on clinical outcomes has become a recurring recommendation in protocols for determining analytical performance specifications. In their recently updated guidance, for example, the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) stipulate that, for medical tests that "have a central role in the decision-making of a specific disease or clinical situation and where cut-off/decision limits are established", specifications should be based on the effect of analytical performance *on the clinical outcome* [termed "Model 1"], as opposed to basing specifications on biological variation ["Model 2"] or state of the art measurements ["Model 3"] *(1)*.

Two types of studies are suggested to inform specifications under Model 1: (i) *direct outcome studies* (i.e. analyses based solely on empirical data, such as randomised controlled trials evaluating the impact of varying analytical procedures on outcomes); or (ii) *indirect outcome studies* (i.e. analyses using non-empirical approaches, such as decision analytic modelling, to determine the impact of varying procedures on outcomes) *(2)*. Since (i) is often unfeasible or impractical due to ethical, financial and time constraints associated with robust end-to-end test-outcome studies, the indirect methods of (ii) are expected to play the dominant role in this context *(3)*.

Despite general agreement that outcome-based specifications provide the best mechanism to ensure tests best serve patients' needs, studies in this area remain uncommon. A primary reason often cited for this concerns the inherent difficulties in conducting direct outcomes

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studies *(1, 3)*. It is likely, however, that a lack of awareness and specific guidance concerning alternative *indirect* methods that may be employed is also a key limiting factor. The aim of this study therefore was to review methodological approaches used in previous indirect assessments and outline an analytical framework to inform future outcome-based performance specifications.

Methods

A literature search was conducted in November 2017 across four databases (Ovid Medline(R), Embase, Web of Science (core collection) and Biosis Citation Index) and covering a 10 year publication period (2008 to November 2017). The search was subsequently updated in 2019 (covering the period 2008 to March 2019). The search strategy (provided in the **Supplemental Appendix**) combined key terms relating to (a) tests, (b) measurement uncertainty, and (c) simulation/ methodology. From those studies identified via the database searches, subsequent citation tracking (including extensive backwards and forwards tracking) was conducted to identify additional studies published on any date (i.e. including studies published before 2008).

Studies were included if they met the inclusion criteria shown in **Table 1**. Studies were required to include an assessment of downstream outcomes including: clinical *accuracy* (the ability of a test to distinguish between patients with and without a specified condition, or identify a change in condition), *clinical utility* (the ability of a test to impact on healthcare management decisions or patient health outcomes) and/or *cost-effectiveness* (the ability of a test to produce an efficient impact on health outcomes in relation to cost). Note that studies using indirect methods *at any stage of the analysis* were eligible for inclusion; this means, for example, that several method-comparison studies (an essentially empirical study design) were

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nevertheless included in cases where an indirect method was subsequently used to assess the impact of identified measurement discrepancies on outcomes.

<<Table 1>>

All screening (including initial title/abstract screening, full text screening, and citation tracking) was conducted by the primary reviewer (AS). A data extraction form was developed (including items on key study, test, and method details) and piloted on the first 10% of included studies. Subsequent full data extraction of included studies was conducted by the primary reviewer and double checked by one of four secondary reviewers (BS, MM, CH and PH). Regular meetings with all authors were conducted to review the ongoing study findings and resolve (via group consensus) any inclusion and/or extraction uncertainties.

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Results

Study characteristics

A total of 82 studies were identified (see **Figure 1**). Regarding data extraction checking, 35 papers (43%) were checked by BS; 16 (20%) by CH; 16 (20%) by MM; and 15 (18%) by PH. Agreement between reviewers across extraction items was >99%.

Study characteristics are summarized in **Table 2**, and details of measurement uncertainty components and test outcomes evaluated are provided in **Table 3**. Most studies focused on evaluating tests or devices used for the purposes of monitoring, diagnosis and/or screening across four key disease areas: diabetes or glycemic control, cardiovascular diseases, cancer and metabolic or endocrine disorders. Imprecision was most commonly addressed, followed by bias and total error, and studies primarily evaluated clinical accuracy outcomes.

<<Figure 1>>

<<Table 2>>

<<Table 3>>

Aim of analyses

Most studies were conducted with the objective of either: (i) determining/ informing analytical performance specifications *(4-22)*; (ii) exploring the impact of uncertainty allowed by *current* performance specifications *(23-34)*; or (iii) evaluating the potential impact of measurement uncertainty on outcomes (without explicitly defining specifications) *(35-78)*. A final group of studies consisted of "incidental" analyses, in which the impact of measurement uncertainty on outcomes was incorporated within the analysis but was not part of the primary study aim *(79-85)*.

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Methodology Framework

Based on the included studies, a common analytical framework underpinning the various approaches to evaluating the impact of measurement uncertainty on outcomes was identified. This framework consists of three key steps: (1) calculation of "*true*" test values; (2) calculation of *measured* test values (i.e. incorporating measurement uncertainty); and (3) calculation of the *impact* of discrepancies between (1) and (2) on the outcome(s) under consideration. An outline of the various methods adopted within this framework is provided below and summarized in **Figure 2**. A summary table detailing the methods used in each individual study is provided in **Supplemental Table 1**.

1. Step one: calculation of "true" test values

Calculation of "true" test values was based either on *empirical* data values *(5, 7, 9-11, 18, 21, 26, 30-32, 34-37, 39-42, 45, 49-53, 56-58, 60, 61, 64, 66-69, 71, 74, 77, 78, 85)* and/or *simulated* values *(4-6, 8, 12-17, 19, 20, 22-25, 27-29, 33, 36, 38, 43, 44, 46-48, 54, 55, 59, 62, 63, 65, 70, 72-76, 79-84).*

Studies using empirical data here included: (i) method comparison and external quality assessment (EQA) studies, which utilized indirect methods to determine the impact of discrepancies between empirical reference (i.e. "true") test measurements vs. index (i.e. uncertain) test measurements on specified outcomes (e.g. using the "error grid" approach outlined in Step 3) *(35, 37, 41, 42, 51, 53, 56-58, 60, 64, 66-69, 71, 75, 78)*; and (ii) studies which derived uncertain measurements from "true" empirical data values using various (non-empirical) approaches outlined in Step 2 *(5, 7, 9-11, 18, 21, 26, 30-32, 34, 36, 39, 40, 45, 48-50, 52, 61, 77, 85).*

Studies using simulation methods here used a range of approaches – the simplest of which was to assume a *fixed set* of individual "true" values specified across the measurement range

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and simulate uncertainty around these values (see Step 2) *(12, 16, 27, 33, 36, 38, 79, 83, 84).* Whilst this approach does not require any simulation for the "true" measurements per se, the values here are nevertheless generated rather than using real-world data directly. An extension of this approach is to assume a *uniform distribution* to describe the "true" frequency distribution(s): that is, assume a constant probability of occurrence for each test value along a specified measurement range, and draw from this distribution within the simulation *(14, 17, 19, 44, 55).* Alternatively, the expected likelihood of test values was often modelled using *Gaussian* (i.e. normal) or *log-Gaussian* frequency distributions, specified using published or empirical data on the expected mean and variance of test values *(4-6, 8, 13-15, 20, 46, 47, 59, 63, 65).* Other infrequently adopted parameterizations included mixed Gaussian distributions *(54, 62),* multivariate Gaussian distributions (where correlations between tests are known *(43)*) and the exponential distribution *(82).* Non-parametric simulation approaches were also used, based on sampling with replacement from an empirical dataset *(18, 30).* Finally, several studies used simulation techniques *(22, 23, 70, 74, 75),* or utilized findings from previously published simulation studies *(24, 25, 73, 76),* but did not clearly report details regarding the calculation of "true" baseline values.

An important issue with respect to the estimation of "true" test values concerns how well the underlying data may be considered a reliable proxy for the truth. A handful of studies attempted to directly address this issue, by "stripping" known measurement uncertainty from baseline "true" test values via statistical adjustment: imprecision, for example, can be removed from the variance term of a specified Gaussian/log-Gaussian distribution using a reverse form of the "sum of squares rule"; whilst bias can be removed from the mean term *(7-10, 13, 15, 31).* In general, however, the likelihood that the adopted "true" test values would in fact be representative of the truth was either implicitly assumed or not discussed.

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2. Step two: calculation of measured test values (incorporating measurement uncertainty)

Approaches to the calculation of measured test values predominantly fell into four broad categories: (1) *empirical assessment (35, 37, 41, 42, 51, 53, 56-58, 60, 64, 66-69, 71, 74, 78)*, (2) *graphical assessment (5, 7, 9-11, 36)*, (3) *computer simulation (4-6, 8, 12, 14-25, 27-31, 34, 38, 39, 44, 46, 49, 50, 52, 54, 55, 59, 61-63, 65, 70, 72-77, 79-85)*, or *regression analysis (26, 32, 43, 47).*

Studies using empirical assessment here included method-comparison studies *(35, 37, 41, 42, 53, 56-58, 60, 64, 66-69, 71, 75, 78)* and an EQA study *(51)* which based "true" test values on the specified reference test and measured values on the index test measurements.

An alternative method, first appearing in 1980, is based on applying hypothetical measurement uncertainty to "true" values via graphical manipulation *(5, 7, 9-11, 36)*. This approach centers on plotting the cumulative percentage frequency of "true" values on the probit scale (x-axis) as a function of "true" values on the logarithmic scale (y-axis); assuming that the log-transformed data are Gaussian, then in the bimodal case (where healthy and diseased populations are modeled separately), cumulating the healthy (diseased) population from high (low) values results in two straight lines sloping in opposite directions for each population (i.e. forming an 'X' on the plot). The addition of negative (positive) bias is then explored by shifting the straight lines to the left (right) on the x-axis; whilst the addition of imprecision is explored by rotating each line around their mean value (i.e. broadening the 95% confidence interval of the values on the probit scale). Given a specified cut-off threshold, the proportion of false positives and negatives at a particular level of bias and imprecision can be read off directly from this plot, by observing the point at which healthy/diseased populations cross the threshold line.

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In response to modern computational capabilities, the graphical method has been superseded by computer simulation approaches which can accommodate more complex specifications of the measurand distribution and measurement uncertainty. The most flexible and widely adopted approach in the identified studies was based on iterative simulation, with uncertainty added on to "true" test values according to a specified *error model* – a function relating measured test values to baseline "true" values plus specified components of measurement uncertainty *(14, 17-19, 28-30, 34, 54, 62, 79, 82-84)*. This method is largely attributed to the seminal 2001 paper by Boyd and Bruns *(14)* – the first study of this kind to clearly specify the error model as a mathematical function (as opposed to earlier *(4-6)* and later *(21-25, 44, 49, 52, 70, 72, 73, 76, 77, 80, 81, 85)* studies limited to textual descriptions or indirect referencing). An example of a typical error model is as follows:

$$\mathbf{Test}_{mesaured} = \mathbf{Test}_{true} + [\,\mathbf{Test}_{true} * \mathbf{N(0,1)} * \mathbf{CV}\,] + \mathbf{Bias} \qquad \mathbf{(1)}$$

where $Test_{true}$ is the "true" measurement value; $Test_{measured}$ is the observed test value measured with imprecision (coefficient of variation [CV%]) and absolute bias (Bias); and N(0,1) is a normal distribution (mean = 0, standard deviation [SD] = 1) applied with the CV% value in order to produce a spread of Gaussian-distributed results around $Test_{true}$.

The error model iterative simulation approach works as follows: (i) a random draw is taken from the distribution of "true" values to generate a value for $Test_{true}$; (ii) components of measurement uncertainty are applied to $Test_{true}$ according to the error model formula to simulate a value for $Test_{measured}$ (this may require random number draws – for example in equation (1) a random draw from N(0,1) is required for the application of imprecision); (iii) points (i) and (ii) are repeated (e.g. 10,000 times to simulate 10,000 $Test_{true}$ and $Test_{measured}$ values) for a given level of measurement uncertainty (e.g. CV% = 5% and Bias = 5%); and (iv) points (i) to (iii) are repeated for varying levels of measurement uncertainty (e.g. CV%

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ranging from 0-20% and Bias ranging from +/-10% in 1% increments). This iterative process can be efficiently implemented using standard statistical software, such as Excel or R.

Rather than iteratively adding on uncertainty via error model simulation, an alternative approach is to incorporate uncertainty directly within a specified probability distribution (e.g. incorporating bias within the mean term, and imprecision within the variance term of a Gaussian or log-Gaussian distribution). This distribution can be applied iteratively around individual "true" values *(12, 16, 18, 27, 30, 38, 46, 59, 61)*, or at a population level, by adjusting a specified "true" population distribution to include additional uncertainty *(8, 15, 31, 63, 65)*.

The remaining studies used regression analysis *(26, 32, 43, 47)*, other one-off methods *(12, 13, 33, 40, 45, 48)*, or reported insufficient details regarding simulation techniques to determine the exact method employed *(74, 75)*. Within the identified regression analyses, bias or total error was applied as a multiplicative factor to baseline measurements within a specified regression model, with the resulting impact on the regression output (e.g. likelihood ratio) explored. Details of studies using other one-off/ indeterminate methods can be found in **Supplemental Table 1**.

3. Step three: calculation of the impact on test outcomes

The final step is to assess the impact of deviations between "true" and measured values on the outcome(s) of interest.

Most studies focused on evaluating clinical accuracy *(4-13, 15, 16, 20, 26-29, 31-33, 38, 39, 43, 45-52, 55, 59, 61-63, 65, 79-85)*. In this case the calculation is generally straightforward: the rate of change in mis-categorizations (e.g. false positive/negative diagnoses) is determined according to the change in the proportion of measured values pushed above or

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below the given test cut-off threshold(s) used to define disease status or inform treatment decisions, compared to the "true" value classifications. This was the typical approach taken in studies using the graphical and simulation approaches outlined in Step 2, for example.

Several studies evaluated the impact of measurement uncertainty on treatment management decisions *(14, 18, 21, 30, 35, 37, 41, 42, 51, 53, 56-58, 60, 64, 66-69, 71, 74, 75, 78)*. Most of these were method-comparison studies which determined the impact of measurement deviations on treatment decisions using error grid analysis *(35, 37, 41, 42, 53, 56-58, 60, 64, 66-69, 71, 74, 78)*. Two studies similarly employed the error grid approach, but used simulated (rather than empirical) reference and index test measurements *(74, 75)*. First developed in the 1980s, the original error grid aimed to evaluate the potential impact of measurement discrepancies between self-monitoring blood glucose devices and laboratory reference measurements in terms of insulin dosing errors *(35)*. Using a scatter plot of reference vs. index test measurements, the plot was divided into five error grid "zones" according to assumed severity of associated dosing errors (from zone A = clinically accurate results; to zone E = erroneous results leading to dangerous failure to detect and treat). More recently studies have attempted to build on this approach, for example by expanding on the small sample of experts used to define the initial error grid *(37, 74, 75)*, accounting for temporal aspects of measurement *(41)*, or applying the same methodology to alternative clinical settings *(64)*.

Others have attempted to incorporate the impact of measurement uncertainty on patient health outcomes *(17, 19, 22, 23, 44, 54, 70, 72)*. All of these studies related to evaluations of monitoring devices for glycemic control, in which health outcomes such as hypoglycemia and hyperglycemia were determined using decision analytic models based around sequential glucose measurements (incorporating measurement uncertainty via the error model simulation approach, for example). Combined with data on insulin dose administrations

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(resulting from measured values), and additional factors such as patient insulin sensitivity and gluconeogenesis, these models were used to track patients' response to administered doses and resulting health outcomes.

Nine final studies included an assessment of costs or cost-effectiveness *(7, 8, 11, 24, 25, 40, 73, 76, 77)*. Four were based on a simple assignment of expected costs of misdiagnoses to rates of false positive/negative results *(7, 8, 11),* or expected costs of adverse events applied to simulated health outcomes data *(77).* One study included a more comprehensive costing analysis, in which the potential financial implications of calibration bias in serum calcium testing was explored *(40)*. The remaining four studies all utilized the previous work of Breton and Kovatchev (2010), in which the impact of reduced glucose meter imprecision on glycemic events was simulated using a published simulation platform *(23)*. Two studies constructed simple cost-consequence decision models, combining the Breton and Kovatchev (2010) findings with data on patient population numbers, glucose meter costs, and the rate of myocardial infarctions resulting from glycemic outcomes, to estimate annual cost savings associated with improved meter precision *(73, 76).* Two more recent studies conducted full cost-effectiveness analyses, using cohort Markov (i.e. state-transition) models to link the data on improved glycemic control and reduced glycemic event rates, with data on diabetes complication rates, patient health-related quality of life and health service costs *(24, 25)*. Using these models the authors were able to estimate the incremental cost per additional quality adjusted life year (QALY) associated with reduced device error.

<<**Figure 2**>>

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Discussion

Review findings

Based on our methodology review findings, a three-step analytical framework underpinning the various approaches to determining the impact of measurement uncertainty on outcomes was identified (see **Figure 2**). Key points for consideration within this framework are discussed below.

With regards to Step 1 (calculation of "true" test values), the primary advantage of using either empirical data or informed parametric distributions is that, by accounting for the expected frequency of values, population-level conclusions (such as analytical performance specifications) may be derived. In contrast, the primary drawback of the fixed-values approach, and by extension the uniform distribution approach (assuming this is not a realistic parameterization), is that population-level conclusions cannot be derived. Nevertheless, such approaches may be useful for exploring the impact of measurement uncertainty in specific scenarios – for example, to explore the impact of uncertainty on test values close to the test cut-off threshold.

A question that must be considered when using either empirical or parametric distributions, is how well the underlying data may be considered to represent the truth. If values used to inform the "true" distributions are themselves subject to measurement uncertainty (even if this uncertainty is expected to be small), then all subsequent analyses may be affected by this confounding factor and care should be taken when asserting absolute maximum bounds for imprecision and bias. A handful of studies did attempt to address this issue using statistical adjustment methods however this approach depends on having reliable information on the expected measurement uncertainty contained in the baseline "true" measurement values and can only be used when modelling test values as parametric distributions *(7-10, 13, 15, 31)*.

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A second consideration in the adoption of parametric distributions concerns the appropriateness of the assumed parametric form. Whilst a minority of studies provided some form of justification for the parametric choice (e.g. using the Kolmogorov–Smirnov test for normality), a common implicit assumption was that data would be likely to be Gaussian or log-Gaussian distributed. The validity of this assumption is not always clear, however.

Within Step 2 (calculation of *measured* test values) computer simulation methods offer the most flexible approach for exploring alternative specifications and levels of measurement uncertainty. In the context of setting performance goals, studies based on method-comparison analyses are of limited use given the fact that alternative levels of measurement uncertainty cannot be efficiently explored, and analyses using the graphical method suffer from the issue that non-Gaussian parameterisations or non-constant/ non-linear specifications of bias or imprecision cannot be accommodated. The error model approach is particularly useful in this respect. While the example formula provided in Equation (1) specifies one CV% element representing total imprecision, additional elements of imprecision (e.g. pre-analytical, analytical and biological) may be separately specified. Alternative characterisations of imprecision may also be defined: for example, using (i) a fixed SD, (ii) different SD/CV values for different sections of the measurement range, or (iii) imprecision defined as a linear/ non-linear function of $Test_{true}$. Similarly bias may also be characterised in alternative ways.

With regards to Step 3 (calculation of the impact on *outcomes*), a further advantage of the simulation approach is that, by sampling over a range of bias and imprecision values, the joint impact of these components on outcomes can be clearly explored. In particular, several studies used *contour plots* to present their findings *(14-19, 21, 30, 34, 62)*: an example, provided in **Figure 3**, represents a hypothetical case in which bias and imprecision have been applied (according to equation (1)) to normally distributed healthy [N(30,5)] and diseased

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[N(60,10)] populations. The plotted lines indicate at which values of imprecision and bias a given value of clinical sensitivity/specificity is maintained. For example in this case, at imprecision=0, increasing positive bias decreases clinical specificity and increases clinical sensitivity, whilst negative bias has the opposite effect. Based on this plot, we expand on the typical contour plot to show how maximum allowable bounds for imprecision and bias can be identified according to specified minimum requirements for clinical accuracy. Suppose, for example, that we require sensitivity to remain above 90% and specificity to remain above 80% in order to maintain expected health utility gains. The region of acceptable analytical bias and imprecision values for this specification of clinical accuracy is illustrated by the shaded region of the contour plot – from this we can see that, if bias is zero we can tolerate up to 20% imprecision, whilst if imprecision is zero we can tolerate -8 to +6 units of absolute bias. Plots such as this one offer an effective means of highlighting acceptable bounds for measurement uncertainty.

<<Figure 3>>

Whilst most studies focused on the intermediate outcome of clinical accuracy, ideally technologies should be evaluated in terms of their influence on "end-point" outcomes i.e. health outcomes (clinical utility), operational and/or cost-effectiveness outcomes. Several of the identified studies utilized analytic decision modeling techniques to determine the impact of measurement uncertainty on health outcomes: while these all related to the context of glycemic control devices, decision models can feasibly be used to explore any clinical pathway of interest, subject to data availability. Within the field of health technology assessment, for example, decision models are routinely employed to evaluate the expected clinical utility and cost-effectiveness of novel tests, by linking data on disease prevalence and test clinical accuracy (e.g. the proportion of correct and incorrect diagnoses), with downstream data on the expected change in patient management, patient compliance to

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treatment and treatment effectiveness (often referred to as the "linked-evidence approach") *(86-88)*. Although this approach is more resource- and data-intensive, and care must be taken to ensure that the model structure appropriately reflects key aspects of the clinical pathway, it nevertheless has the advantage of explicitly capturing the impact of additional parameters (e.g. treatment effectiveness) on end-point outcomes (which may not always produce expected or intuitive results) and uncertainty around the exact values of these parameters can be quantitatively characterised in the model framework *(89)*. We identified two recent studies which utilized health-economic models to estimate the cost-effectiveness of improved analytical performance *(24, 25)*. These studies explored a limited set of fixed imprecision levels relating to pre-existing performance specifications: future studies could extend this methodology to explore a broader range of measurement uncertainty values (e.g. by linking error-model simulations with the downstream health-economic modelling) and derive de novo performance specification based on maintaining or optimizing cost-utility and cost-effectiveness outcomes.

Strengths and limitations:

In light of the sustained international focus on outcome-based analytical performance specifications, it is expected that the indirect approaches outlined in this study will become increasingly important. The analytical framework presented in this study provides a useful starting point to inform future studies in this area, by clearly outlining available methods in sufficient detail to enable practical implementation, and highlighting possible advantages and limitations to consider under each approach. Whereas previous studies have provided commentaries and general reviews of various approaches to setting analytical performance specifications *(3, 90, 91)*, this is the first methodology review to focus specifically on indirect methods for setting outcome-based performance specifications.

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As a methodology review, the aim of this study was not to systematically identify all evidence, but rather to ensure that key examples of relevant methods were identified. While we attempted to make the database search as sensitive as possible, due to the vast volume of literature in this area we necessarily had to focus the search strategy by: (i) concentrating on terms related to in-vitro biomarkers, (ii) including a filter for simulation and methodology terms, and (iii) restricting the initial database search period to 10 years. Extensive citation tracking was additionally conducted, extending into preceding years, in order to ensure that seminal papers informing modern practices would be identified in addition to current state-of-the-art methodology. Although we believe that this two-stage strategy will have captured key methodologies, not all relevant material relating to each method will have been identified and we cannot therefore draw definitive conclusions regarding the frequency that each method has been used. Nevertheless, we believe our findings provide a valuable overview of indirect study methods and an informative starting point for future studies in this area.

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Tables

Table 1. Review inclusion criteria

Population	Any human population with any indication
Intervention	In-vitro test (excluding imaging) or any kind of medical device used for the purpose of screening, diagnosis, prognosis, monitoring or predicting treatment response
Comparator	Any
Outcomes	(a) Clinical accuracy e.g. - Diagnostic sensitivity and/or specificity - Positive/negative predictive values - ROC curve/ AUC analysis - Relative risks - Likelihood ratios (b) Clinical utility - Impact on treatment management decisions - Impact on patient health outcomes (c) Costs (d) Cost-effectiveness
Method	Analysis includes indirect methods (i.e. excluding purely empirical analyses) to incorporate or assess the impact of one or more components of measurement uncertainty (below) on one or more outcomes (above): - Bias (e.g. calibration or method bias) - Imprecision (e.g. repeatability, within-laboratory or between-laboratory imprecision) - Pre-analytical or analytical effects - Summary metrics (e.g. total error [TE] or uncertainty of measurement [U_M])
Study type	Full paper relating to an original study
Language	Full text in English
Year of publication	Database search: January 2008 – March 2019 Citation tracking: any data
ROC = Receiver operator characteristic; AUC = Area under the curve	

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712 ***Table 2. Study characteristics***

	N	%
Year of publication		
Pre-2008 (identified via citation tracking alone)	25	30%
2008 – 2009	3	4%
2010 – 2011	7	9%
2012 – 2013	9	11%
2014 – 2015	18	22%
2016 – 2017	13	16%
2018-2019	7	9%
Clinical area[a]		
Diabetes & glycemic control	43	52%
Cardiovascular diseases	17	21%
Cancer	10	12%
Metabolic & endocrine disorders	8	10%
Kidney disorders	3	4%
Prenatal screening	3	4%
Noise induced hearing loss	2	2%
Role of test[a]		
Monitoring	44	54%
Diagnosis	24	29%
Screening	11	13%
Prognosis	7	9%

[a]Several studies included a test or tests used in multiple clinical areas or roles (hence total percentages under these categories sum to >100%).

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714 ***Table 3. Components of measurement uncertainty included and test outcomes assessed***

	N	%
Component(s) of measurement uncertainty included[a]		
Imprecision:		
Analytical	31	38%
Pre-analytical / combined pre-analytical and analytical	8	10%
Non-specific	11	13%
Total	**50**	**61%**
Bias:		
Analytical	18	22%
Calibration bias	9	11%
Non-specific	9	11%
Pre-analytical / combined pre-analytical and analytical	2	2%
Between-method bias	1	1%
Total	**39**	**48%**
Total error:		
Method-comparison study	18	22%
EQA study	2	2%
Other	6	7%
Total	**26**	**32%**
Biological variation included?		
Yes - included as a separate element	13	16%
Yes - combined with imprecision	5	6%
Total	**18**	**22%**
Primary test outcome assessed[a]		
Clinical accuracy	45	55%
Clinical utility:		
Impact on treatment management	23	28%
Impact on health outcomes	13	16%
Costs	7	9%
Cost-effectiveness	2	2%

[a] Several studies included multiple components of measurement uncertainty or assessed multiple test outcomes (hence total percentages under these categories sum to >100%).

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Figure captions

Figure 1. PRISMA flow diagram of included studies

Figure 2. Summary box outlining the three-step analytical framework, primary methods identified for each step in the framework, and key questions for consideration in future analyses

Figure 3. Example contour plot based on simulations using the error model approach (adding increasing magnitudes of bias and imprecision onto assumed "true" measurand values). The contour lines indicate what level of clinical accuracy is achieved across the range of bias and imprecision inputs explored: varying sensitivity levels as a function of bias and imprecision are represented by the solid contour lines, whilst varying specificity levels are represented by the dashed contour lines. The grey region represents an "acceptability region" for bias and imprecision, which maintains sensitivity ≥ 90% and specificity ≥ 80%.

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