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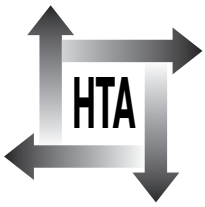

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Evaluation of diagnostic tests when there is no gold standard. A review of methods

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The research reported in this monograph was commissioned by the National Coordinating Centre for Research Methodology (NCCRM), and was formerly transferred to the HTA Programme in April 2007 under the newly established NIHR Methodology Panel. The HTA Programme project number is 06/90/23. The contractual start date was in October 2005. The draft report began editorial review in March 2007 and was accepted for publication in April 2007. The commissioning brief was devised by the NCCRM who specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Evaluation of diagnostic tests when there is no gold standard. A review of methods

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Objective: To generate a classification of methods to evaluate medical tests when there is no gold standard.

Methods: Multiple search strategies were employed to obtain an overview of the different methods described in the literature, including searches of electronic databases, contacting experts for papers in personal archives, exploring databases from previous methodological projects and cross-checking of reference lists of useful papers already identified.

Results: All methods available were classified into four main groups. The first method group, impute or adjust for missing data on reference standard, needs careful attention to the pattern and fraction of missing values. The second group, correct imperfect reference standard, can be useful if there is reliable information about the degree of imperfection of the reference standard and about the correlation of the errors between the index test and the reference standard. The third group of methods, construct reference standard, have in common that they combine multiple test results to construct a reference standard outcome including deterministic predefined rules, consensus procedures and statistical modelling (latent class analysis). In the final group, validate index test results, the diagnostic test accuracy paradigm is abandoned and research examines, using a number of different methods, whether the results of an index test are meaningful in practice, for example by relating index test results to relevant other clinical characteristics and future clinical events.

Conclusions: The majority of methods try to impute, adjust or construct a reference standard in an effort to obtain the familiar diagnostic accuracy statistics, such as sensitivity and specificity. In situations that deviate only marginally from the classical diagnostic accuracy paradigm, these are valuable methods. However, in situations where an acceptable reference standard does not exist, applying the concept of clinical test validation can provide a significant methodological advance.
All methods summarised in this report need further development. Some methods, such as the construction of a reference standard using panel consensus methods and validation of tests outwith the accuracy paradigm, are particularly promising but are lacking in methodological research. These methods deserve particular attention in future research.

Contents

List of abbreviations

BCG	Bacillus Calmette–Guérin
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CT	computed tomography
ED	emergency department
EIA	enzyme immunoassay
DOR	diagnostic odds ratio
FN	false negative result
FP	false positive result
LR	likelihood ratio
LTBI	latent tuberculosis infection
MAR	missing at random
MCAR	missing completely at random
MRI	magnetic resonance imaging
NMAR	not missing at random
NPV	negative predictive value
NT-proBNP	N-terminal pro-brain natriuretic peptide
PCR	polymerase chain reaction
PE	pulmonary embolism
PET	positron emission tomography
PPV	positive predictive value
RCT	randomised controlled trial
ROC	receiver operating characteristic
TN	true negative result
TP	true positive result
TST	tuberculin skin test

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

The classical diagnostic accuracy paradigm is based on studies that compare the results of the test under evaluation (index test) with the results of the reference standard, the best available method to determine the presence or absence of the condition or disease of interest. Accuracy measures express how the results of the test under evaluation agree with the outcome of the reference standard. Determining accuracy is a key step in the health technology assessment of medical tests.

Researchers evaluating the diagnostic accuracy of a test often encounter situations where the reference standard is not available in all patients, where the reference standard is imperfect or where there is no accepted reference standard. We use the term 'no gold standard situations' to refer to all those situations. Several solutions have been proposed in these circumstances. Most articles dealing with imperfect or absent reference standards focus on one type of solution and discuss the strengths and limitations of that approach. Few authors have compared different approaches or provided guidelines on how to proceed when faced with an imperfect reference standard.

Objectives

We systematically searched the literature for methods that have been proposed and/or applied in situations without a 'gold' standard, that is, a reference standard that is without error. Our project had the following aims:

1. To generate an overview and classification of methods that have been proposed to evaluate medical tests when there is no gold standard.
2. To describe the main methods discussing rationale, assumptions, strengths and weaknesses.
3. To describe and explain examples from the literature that applied one or more of the methods in our overview.
4. To provide general guidance to researchers facing research situations where there is no gold standard.

Methods

We employed multiple search strategies to obtain an overview of the different methods described in the literature, including searches of electronic databases, contacting experts for papers in personal archives, exploring databases from previous methodological projects (STARD and QUADAS) and cross-checking of reference lists of useful papers already identified.

We developed a classification for the methods identified through our review taking into account the degree to which they represented a departure away from the classical diagnostic accuracy paradigm.

For each method in our overview, we prepared a structured summary based on all or the most informative papers describing its rationale, its strengths and weaknesses, its field of application, available software and illustrative examples of the method.

Based on the findings of our review, discussions about the pros and cons of different methods in various situations within the research team and input from expert peer reviewers, we constructed a flowchart providing general guidance to researchers faced with evaluation of tests without a gold standard.

Results

From 2200 references initially checked for their usefulness, we ultimately included 189 relevant articles that were subsequently used to classify and summarise all methods into four main groups, as follows.

Impute or adjust for missing data on reference standard

In this group of methods, there is an acceptable reference standard, but for various reasons the outcome of the reference standard is not obtained in all patients. Methods in this group either impute or adjust for this missing information in the subset of patients without reference standard outcome. Researchers should be careful with these

methods if (1) the pattern of missing values is not determined by the study design, but is influenced by the choice of patients and physicians, or (2) the fraction of patients verified with the reference standard is small within results of the index tests.

Correct imperfect reference standard

In this group, there is a preferred reference standard, but this standard is known to be imperfect. Solutions from this group either adjust estimates of accuracy or perform sensitivity analysis to examine the impact of this imperfect reference standard. The adjustment is based on external data (previous research) about the degree of imperfection. Correction methods can be useful if there is reliable information about the degree of imperfection of the reference standard and about the correlation of the errors between the index test and the reference standard.

Construct reference standard

These methods have in common that they combine multiple test results to construct a reference standard outcome. Groups of patients receive either different tests (differential verification and discrepant analysis) or the same set of tests, after which these results are combined by: (1) deterministic predefined rule (composite reference standard); (2) consensus procedure among experts (panel diagnosis); (3) a statistical model based on actual data (latent class analysis). The prespecified rule for target condition makes the composite reference standard method transparent and easy to use, but misclassification of patients is likely to remain. Discrepant analysis should not be considered in general, as the method is likely to produce biased results. The drawback of latent class models is that the target condition is not defined in a clinical way, so there can be lack of clarity about what the results stand for in practice. Panel diagnosis also combines multiple pieces of information, but experts may combine these items in a manner that more closely reflects their own personal concept of the target condition.

Validate index test results

The diagnostic test accuracy paradigm is abandoned in this group and index test results are related to relevant other clinical characteristics. An important category is relating index test results with future clinical events, such as the number of events in those tested negative for the index test results. Test results can also be used in a randomised study to see whether the test can predict who will benefit more from one intervention than the other. Because the classical accuracy paradigm is not employed, measures other than accuracy measures are calculated, including event rates, relative risks and other correlation statistics.

Conclusions

The majority of methods try to impute, adjust or construct a reference standard in an effort to obtain the familiar diagnostic accuracy statistics such as pairs of sensitivity and specificity or likelihood ratios. In situations that deviate only marginally from the classical diagnostic accuracy paradigm, for example where there are few missing values on an otherwise acceptable reference standard or where the magnitude and type of imperfection in a reference standard is well documented, these are valuable methods. However, in situations where an acceptable reference standard does not exist, holding on to the accuracy paradigm is less fruitful. In these situations, applying the concept of clinical test validation can provide a significant methodological advance. Validating a test means that scientists and practitioners examine, using a number of different methods, whether the results of an index test are meaningful in practice. Validation will always be a gradual process. It will involve the scientific and clinical community defining a threshold, a point in the validation process, whereby the information gathered would be considered sufficient to allow clinical use of the test with confidence.

Recommendations for further research

All methods summarised in this report need further development. Some methods, such as the construction of a reference standard using panel consensus methods and validation of tests outwith the accuracy paradigm, are particularly promising but are lacking in methodological research. These methods deserve particular attention in future research.

Chapter 1
Background

"Accuracy is telling the truth … Precision is telling the same story over and over again."

Yiding Wang

Introduction and scope of the report

As with all other elements of healthcare, medical tests should be thoroughly evaluated in high-quality studies. Biased results from poorly designed, conducted or analysed studies may trigger premature dissemination and implementation of a medical test and mislead physicians to incorrect decisions regarding the care for an individual patient.[1–3] Avoidance of these perils requires a proper evaluation of medical tests.[4]

Several authors have proposed a staged model for the evaluation of medical tests.[5–7] Technical evaluations dominate in the early phases, in which the reproducibility under different conditions of biochemical tests and the intra- and inter-observer variation of tests are evaluated. A key phase in the clinical evaluation of a test is determining its diagnostic accuracy: the ability to discriminate between patients who have the condition of interest (target condition) and those who have not.[8] The target condition can refer to a disease, syndrome or any other identifiable condition that may prompt clinical actions such as further diagnostic testing, or the initiation, modification or termination of treatment.

By themselves, accuracy studies cannot always answer the question whether a medical test is useful or not. More informative accuracy studies can be designed by taking into account the likely future role of the test under evaluation. Three possible roles are replacement, addition or triage.[9] In comparative accuracy studies, the accuracy of the test under evaluation is compared against that of existing diagnostic pathways, leading to more informative and possibly more efficient diagnostic accuracy studies.[9]

The clinical value of a test will ultimately depend on whether it is able to improve patient outcome. In most cases this will be by guiding subsequent decision-making. Accuracy studies may not be sufficient to evaluate the clinical value of a test, especially if the new test is more sensitive than the existing test(s).[10] The reason is that the results from current intervention studies may not apply to those additional cases detected. Results from randomised studies assessing response to therapy in these additional cases are then required. Later stage evaluation studies may focus on determining the societal costs and benefits of a test.

The focus of this report is on problems related to diagnostic accuracy studies. The key challenge in diagnostic accuracy is to determine in all patients whether the target condition is present or absent. The reference standard should provide this classification. As such, the reference standard plays a crucial role in accuracy studies.

Problems with the reference standard abound in diagnostic accuracy studies. (http://www.fda.gov/cdrh/osb/guidance/1428.pdf). The outcome of the reference standard may not be available in all patients, it may be unreliable, it may be inaccurate or there could be no acceptable reference standard at all. As in any other form of epidemiological research, outcome data that are missing or misclassified pose a great threat to the validity of such studies, and diagnostic accuracy studies are no exception.[11–15] We will use the term 'no gold standard situations' to refer loosely to all these situations where the outcome of the reference standard is missing, the reference standard is imperfect or there is no acceptable reference standard.

This report gives an overview of solutions that have been proposed to overcome no gold standard situations in diagnostic accuracy research. Because the scope of this report is limited to problems related to diagnostic accuracy studies, we will not discuss the broader issue of determining the most appropriate type of evaluation given a specific diagnostic research question.

Before explaining our methods (Chapter 3) and reporting our results (Chapter 4), in the next section we first explain the key features of diagnostic accuracy studies and in the subsequent section discuss the various mechanisms that can

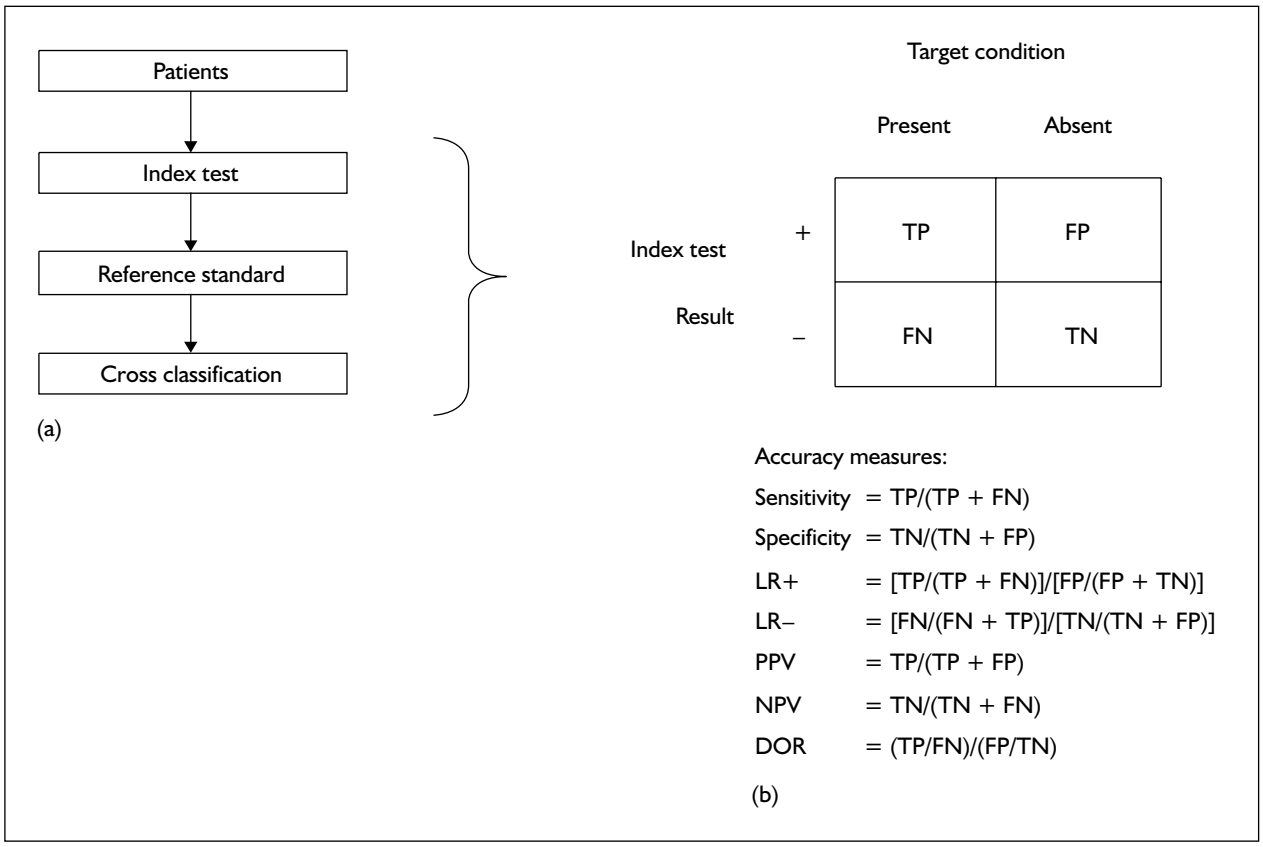

FIGURE 1 *(a) Classical design of a diagnostic accuracy study and (b) results of an accuracy study in the case of a dichotomous index test result. TP, true positive result; FP, false positive result; FN, false negative result; TN, true negative result; LR, likelihood ratio; PPV, positive predictive value; NPV, negative predictive value; DOR, diagnostic odds ratio.*

lead to no gold standard situations. In Chapter 5 we provide guidance on selecting the most appropriate method for a given situation by addressing some key questions. In addition, we sketch possible research alternatives in situations where the diagnostic accuracy paradigm is unlikely to be useful.

Key concepts in diagnostic accuracy studies

Diagnostic accuracy studies aim to measure the amount of agreement between index test results and the outcome of the reference standard. The classical outline of an accuracy study is given in *Figure 1(a)*. The starting point is a consecutive series of individuals in whom the target condition is suspected. The index test is performed first in all subjects, and subsequently the presence or absence of the target condition is determined by the outcome of the reference standard. In the case of a dichotomous index test result, the results of an accuracy study can be summarised in a 2-by-2 table, as shown in *Figure 1(b)*. Several measures of accuracy can be calculated from this table, as also shown in *Figure 1(b)*.

The term accuracy has been borrowed from measurement theory, where it is defined as the closeness of agreement between an analytical measurement and its actual (true) value.[16] The first publication mentioning accuracy and the associated statistics sensitivity and specificity to express the performance of a medical test was by Yerushalmy,[17] followed by the landmark publication of Ledley and Lusted.[18] In these publications, test results in patients known to have the disease of interest were compared with test results in subjects not having the disease. Since then, various other measures of accuracy have been introduced, including likelihood ratios, predictive values and the diagnostic odds ratio.[4] All of these accuracy measures have in common that they need a classification of patients in those with and those without the condition of interest. In other words, index test results are verified by comparing them with the outcome of the reference standard. Based on this concept, we can formulate the properties of the ideal reference

standard and verification procedure. The ideal verification protocol would fulfil the following criteria:

1. The reference standard provides error-free classification.
2. All index test results are verified by the same reference standard.
3. The index test and reference standard are performed at the same time, or within an interval that is short enough to eliminate changes in target condition status.

Empirical studies have shown that estimates of diagnostic accuracy are directly influenced by the quality of the verification procedure.[1,3,19]

Problems in verification

In practice, researchers may encounter situations where the ideal verification procedure cannot be achieved. Based on the first two criteria for an ideal verification procedure, we will briefly discuss the key mechanisms why verification procedures can produce errors.

Classification errors by the reference standard

Within the accuracy concept, the reference standard is judged by its performance in producing error-free classification with respect to the presence or absence of the target condition. Even if a reference standard has no analytical error but the target condition does not produce the biochemical changes of interest, we consider it a 'failure' of the reference standard. Other examples of imperfections of the reference standard are tumours that are missed because they are below the level of detection in case of a radiological reference standard, or the presence of an alternative condition that is misclassified as the target condition because it produces similar changes in a biomarker as that of the target condition.

One inherent difficulty in accuracy studies is that we use the dichotomy of target condition present or absent, whereas in reality the target condition varies from very early and minor changes to severe and advanced stages of the disease, thus covering a wide spectrum of disease. For some conditions, defining the lower end of disease is difficult. This can be illustrated with the example of appendicitis. In the majority of accuracy studies evaluating non-invasive imaging techniques for the diagnosis of appendicitis, histological examination of the removed appendix is used as reference standard. This requires defining a threshold for the type and amount of inflammatory changes above which we will classify a patient as having appendicitis. Different reference standards may apply a different threshold before classifying patients as having the target condition. In the example of appendicitis, clinical follow-up and observing whether the symptoms of the patients improve or deteriorate will probably mean a higher threshold for disease, resulting in some patients being classified differently between these two reference standards; for example, some patients with inflammatory changes at histological examination would have recovered in a natural way without intervention. This requires proper thinking by the researcher of what is the right definition of the target condition and then choosing the most appropriate reference standard in the light of this target condition.

Additional sources of misclassification are failures in the reference standard protocol and interpretation errors by observers. These errors in misclassification could be preventable by stricter adherence to protocol or better training of observers. Examples include failure of detecting cancer cells after fine-needle aspiration because the biopsy was performed outside the tumour mass or overlooking a small pulmonary embolism in spiral computed tomography (CT) images.

Furthermore, for several target conditions there is no reference standard based on histological or biochemical changes. In some of those cases, the condition is defined by a combination of symptoms and signs. Migraine is an example. The presence or absence of this and similar conditions has been based on criteria developed by individual researchers or on criteria established during a consensus meeting. Such classifications can vary over time or across countries, and cannot be error-free.

Given the many potential factors that can lead to errors in the classification of the target condition by a reference standard, a perfect reference standard (e.g. providing error-free classification) is unlikely to exist in practice. The shift in terminology from 'gold standard', suggesting a standard without error, to the more neutral term 'reference standard', indicating the best available method, has been initiated by these observations. It means that researchers should always discuss the quality of the reference standard and the potential consequences of misclassification by the reference standard.

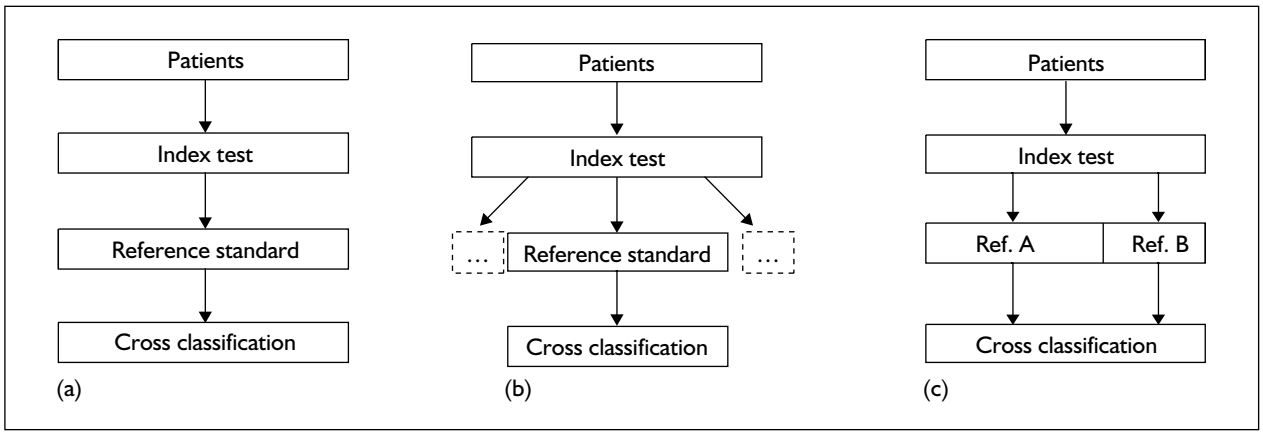

FIGURE 2 *(a) Diagnostic accuracy study with complete verification by the same reference standard (classic design), (b) study with partial verification and (c) study with differential verification.*

Whatever the cause of errors in classification of target condition status by the reference standard, it will directly lead to changes in the 2-by-2 classification table (*Figure 1b*). Within the classic accuracy concept, any disagreement between the reference standard and the index test will be labelled as a 'false' result for the index test. The net effect of the misclassification by the reference standard can either be an upward or downward bias in estimates of diagnostic accuracy. The direction depends on whether errors by the index test and imperfect reference standard are correlated. If errors are positively correlated, it will erroneously increase agreement in the 2-by-2 tables and estimates of accuracy will be inflated.[11–15] The magnitude of the biasing effect depends on the frequency of errors by the imperfect reference standard and the degree of correlation in errors between index test and reference standard.

Partial and differential verification

Even if a near perfect reference standard exists, it may be impossible, unethical or too costly to apply this standard in all patients. In the case of target conditions that can produce multiple lesions that need histological verification, it is often impossible to verify (the countless) negative index test results. An example is 18-fluorodeoxyglucose-positron emission tomography (PET) scanning to detect possible distant metastases before planning major curative surgery in patients with carcinoma of the oesophagus: only PET hot spots can be verified histologically.

Ethical reasons play a role in the choice of reference standard in pulmonary embolism. Angiography is still considered the best available method for the detection of pulmonary embolisms, but because of the frequency of serious complications it is now considered unethical to perform this reference standard in low-risk patients, for instance in patients with low clinical probability and negative D-dimer result. Other reasons for missing data on the outcome of the reference standard are situations where the reference standard is temporarily unavailable or when patients and doctors decide to refrain from verification.

One solution is to leave the unverified patients out of the 2-by-2 table, which is referred to as partial verification (*Figure 2b*). Omitting unverified patients from the 2-by-2 table may generate a bias. The direction and magnitude will depend on (1) the fraction of patients that are unverified; (2) the ratio between the number of patients with positive and negative index test results that remain unverified; and (3) whether the reason for not verifying is related to the presence or absence of the target condition.[20]

Because omitting patients from the 2-by-2 classification table can lead to bias, researchers have strived to obtain complete verification by applying an alternative reference standard in the initially unverified patients. The use of different reference standards between patients is known as differential verification (*Figure 2c*). An example of differential verification that is fairly common is where follow-up is used as the alternative reference standard in patients not verified by the preferred reference standard. In these studies, clinical follow-up is used as a proxy to obtain the information of true status at the moment of the index test; the term delayed-type cross-sectional accuracy study has been introduced for this design.[8] For all studies with differential verification where the alternative reference standard provides imperfect classification, it may affect the 2-by-2

table and generate bias along the same lines as discussed earlier in the previous section on errors in classification by the reference standard. Empirical studies have shown that studies with differential verification produce higher estimates of diagnostic accuracy than studies with complete verification by the preferred reference standard.[1,3]

Given these diverging reasons for imperfections in the verification procedure, it is not surprising that different solutions have been suggested to remedy the effects of verification procedures that are not based on using a single gold standard in all patients. We have systematically searched the literature to identify and summarise the solutions that have been proposed. We have developed a classification of these methods based on their figurative distance, that is, the extent to which they depart from the classical diagnostic accuracy paradigm described in *Figure 1*.

Chapter 2

Aims of the project

Several methods have been proposed to deal with situations where the reference standard is partially unavailable or imperfect or where there is no accepted reference standard. These methods vary from relatively simple correction methods based on the expected degree of imperfection of the reference standard, through more complex statistical models that construct a pseudo-reference standard, to methods that validate index test results by examining their association with other relevant clinical characteristics. Most articles dealing with imperfect or absent reference standards focus on one type of solution and discuss strengths and limitations of that particular approach.[21–23] Few authors have compared different approaches or have provided guidelines on how to proceed when faced with an imperfect reference standard[24–26] (http://www.fda.gov/cdrh/osb/guidance/1428.pdf).

Aims

In this project, we systematically searched the literature for methods to be used in situations without a 'gold' standard. Our project had the following aims:

1. To generate an overview and classification of methods that have been proposed to evaluate medical tests when there is no gold standard.
2. To describe the main methods discussing rationale, assumptions, strengths and weaknesses.
3. To describe and explain examples from the literature that applied one or more of the methods in our overview.
4. To provide general guidance to researchers facing research situations where there is no gold standard.

Outline of the report

Chapter 1 provides background information about the key concepts in diagnostic accuracy studies, in particular the role of the reference standard and the problems that can be encountered in the verification of index tests results. The methods chapter (Chapter 3) describes the strategies that we employed to identify and assess methodological papers on methods relevant for this project. The results chapter (Chapter 4) has the following structure: the first section presents the results of the literature search; an overview and classification of the different methods that we encountered is given in the second section; and a description of each of the methods discussing strengths and limitations is given in the third section. In Chapter 5 we provide general guidance to researchers when faced with research situations where there is no gold standard. In addition, we discuss some alternative options when repairing or hanging on to the accuracy paradigm is not helpful.

Chapter 3
Methods

In our systematic review, we modified the recommendations set out by the Cochrane Collaboration and the NHS Centre for Reviews and Dissemination[27] to make them more applicable for a review of methodological papers.

Our approach consisted of the following steps:

1. literature search and inclusion of papers
2. assessment of individual studies
3. overall classification of methods
4. structured summary of individual methods
5. expert review on individual methods
6. development of guidance statements
7. peer review of total report.

Literature search and inclusion of papers

Searching for methodological papers in electronic databases is difficult because of inconsistent indexing and the absence of a specific keyword for the relevant publication types. Several methods for conducting diagnostic research when there is no gold standard have been developed in other areas of epidemiological, biomedical or even non-medical research. Conducting a broad literature search to capture every single potentially relevant paper would be inappropriate, especially since precise estimation is not the objective of a review of methodological papers. Once a set of comprehensive papers has been obtained about a methodological issue, there is no additional value in reviewing additional papers explaining the same concept. This is known as theoretical saturation,[28] a principle that guided our search and selection.

Based on these considerations, we relied on multiple strategies to obtain an overview of the different methods described in the literature and to maximise the likelihood of identifying those papers that provide the most thorough and complete description:

- Restricted electronic searches in the following databases: MEDLINE (OVID and PubMed), EMBASE (OVID), MEDION, a database of diagnostic test reviews (www.mediondatabase.nl), and the Cochrane Library (DARE, CENTRAL, CMR, NHS). The exact terms of the search strategy are given in Appendix 1.
- Searching databases that have been established in earlier methodological projects, including STARD and QUADAS.
- Searching personal archives.
- Contacting other experts in the field of diagnostic research to establish whether they had additional relevant papers, especially aimed at retrieving articles within the grey literature.
- To locate additional information on specific methods, we checked reference lists, used the citation tracking option of SCISEARCH and applied the 'related articles' function of PubMed.

Inclusion of papers

Publications in English, German, Dutch, Italian, and French were included. One researcher (AWSR) reviewed the identified studies for inclusion in the review and this process was checked by another reviewer (JBR). The only reason for exclusion was if the article did not address a method that could be used in a no gold standard situation.

Assessment of individual studies

We extracted a limited set of standard items from each included paper. These included the strategy that identified the paper, the type of journal, the type of article and the type of method proposed. Other items were the rationale and structure of the article, a description of its usefulness and remarks about the overlap in relation to other papers (all free text fields). The information extracted in this way was used to organise papers within each method. The main function of this step was to categorise papers in order to facilitate the writing of a structured summary of each method.

Overall classification of methods

We classified all methods into groups that addressed diagnostic research in situations where there is no gold standard in an analogous way. The purpose of this classification was to give an

overview of methods and to serve as a starting point for formulating guidance. The key element in the classification was the underlying mechanism leading to the absence of perfect reference standard information (see also Chapter 1).

Structured summary of individual methods

For each method in our overview, we made a structured summary based on all or the most informative papers describing that method. Each summary starts with a description of the method and its rationale, avoiding technical language where possible. In subsequent sections, the strengths and weaknesses of the methods are described; the field of application of the method in terms of the circumstances in which the method should or should not be used; available software; and an illustrative example of the method. One member of the research team (AWSR or AC) wrote the first draft of a summary, which was then reviewed and modified by another team member (JBR, PMMB, AC, KSK). These two reviewers continued exchanging drafts, held face-to-face meetings or had teleconference meetings until they agreed that the version was ready for expert review.

Expert review on individual methods

We assembled a list of potential reviewers outside our research team to review each method. These experts were selected based on their knowledge and/or expertise in relation to a specific method. This group included epidemiologists, statisticians and clinicians (see Appendix 2). Each expert was contacted by electronic mail or by telephone and was asked to comment on at least one method. These experts received a brief description of the project, its objectives and the summary of a specific method. They were asked to review this first version, paying particular attention to the following issues:

- Is the method accurately described?
- Are the main characteristics of the method described?
- Are key strength and weaknesses mentioned?
- Are key references missing?
- Are tables and/or figures understandable?
- Do you have any other suggestions how the summary can be improved?

Based on the comments from the expert, a final version of each method was prepared. Because of time constraints, the revised version was not sent back to the expert.

Development of research guidance

The research team held face-to-face meetings to discuss the pros and cons of different methods in different situations. Prior to this meeting, we had contacted and interviewed a few general experts about their preferred solutions when faced with research situations where there is no gold standard. Based on the discussion, a first version was drafted and circulated among the research members. Further comments were incorporated to produce a final version.

Peer review of report

The full report was reviewed by general experts identified by the research team and peer reviewers assigned by the NHS Research Methodology programme.

Chapter 4

Results

Search results and selection of studies

The references retrieved by the electronic searches were assembled in a single database. After duplicate references had been deleted, the abstracts of 2265 references were assessed for eligibility. Of those, 134 were labelled potentially relevant. Twenty-three references were excluded because they could not be retrieved or inspection of the full article revealed that the topic was not test evaluation. Contact with experts in the field resulted in an additional seven references to books and 50 reference to articles. Reference checking at various stages of preparing the report yielded a total of 11 additional relevant articles.

As the number of references was limited for imputation methods and the panel consensus method, we conducted additional electronic searches. Using the 'related articles' approach in PubMed we identified 10 additional references relevant for imputation. For the panel consensus method, an additional search in PubMed was performed with the search term Delphi[textword], resulting in no relevant references. The final number of relevant articles included was 189. A flowchart of the retrieval and inclusion of studies is given in *Figure 3*.

Classification of methods

Many methods have been described for no gold standard situations. An exact number is difficult to provide because many methods can be viewed as variations or extensions of a single underlying approach. For this report, we classified the methods into four main groups (*Table 1*). These four groups differ in their distance or extent of

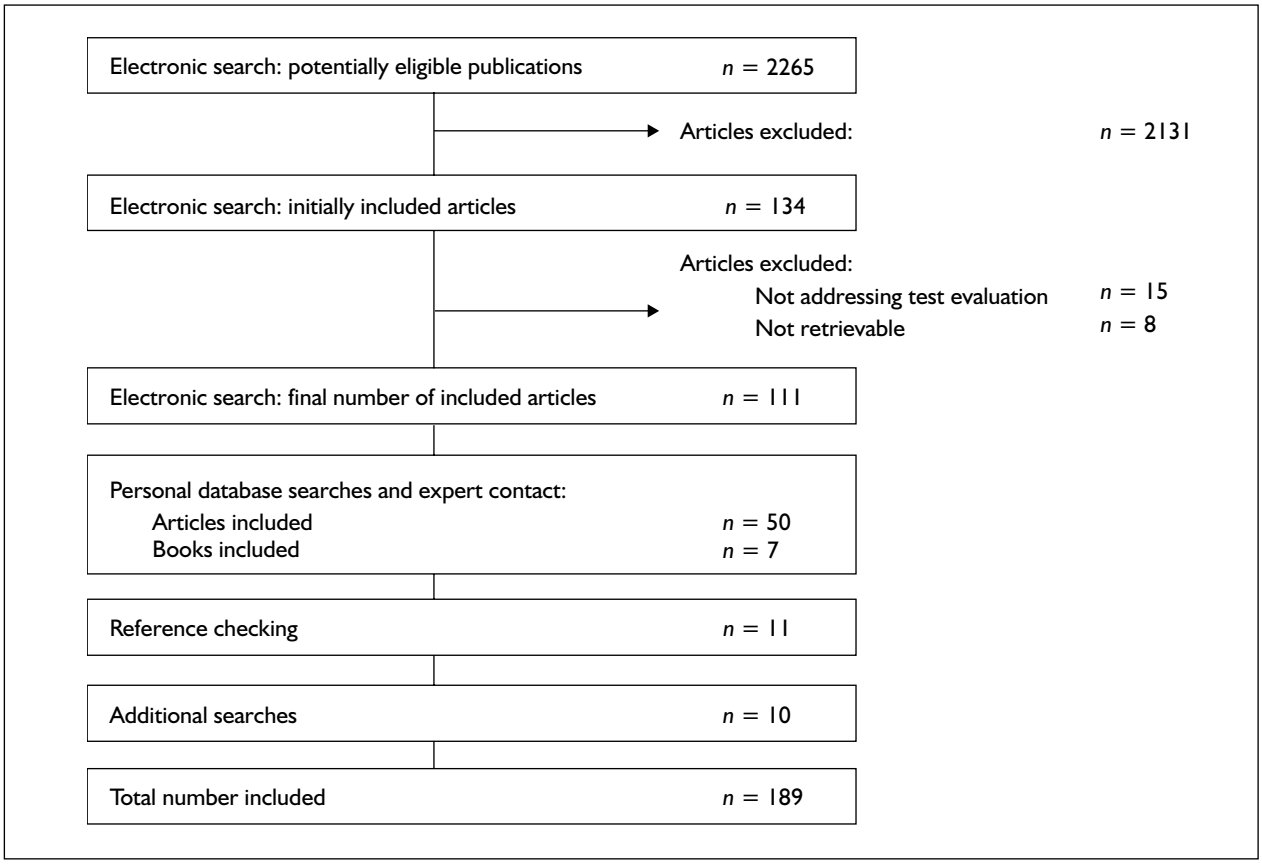

FIGURE 3 *Flowchart of the selection process of articles*

TABLE 1 *Classification of methods for diagnostic research where there is no gold standard*

Main classification *Subdivision*	**Main characteristic**	**Section in Chapter 4**[a]
A. Impute or adjust for missing data on reference standard	Impute the outcome of the reference standard in those patients who did not receive verification by the reference standard or adjust estimates of accuracy based on complete cases	A
B. Correct imperfect reference standard	Correct estimates of accuracy or perform sensitivity analysis to examine the impact of using imperfect reference standard based on external data about the degree of imperfection	B
C. Construct reference standard *Differential verification* *Discrepant analysis* *Composite reference standard* *Panel or consensus diagnosis* *Latent class analysis*	Information from different tests is combined to construct the reference standard outcome. Groups of patients receive either different tests (differential verification and discrepant analysis) or the same set of tests after which these results are combined by: (a) deterministic predefined rule (composite reference standard) (b) consensus procedure among experts (panel diagnosis) (c) a statistical model based on actual data (latent class analysis)	C D E F G H
D. Validate index test results *Examine patient outcomes*	Explore meaningful relations between index test results and other relevant clinical characteristics. An important way to validate is to use dedicated follow-up to capture clinical events of interest in relation to index test results, including randomised diagnostic studies	I

[a] A, 'Impute or adjust for missing data on reference standard' (p. 13); B, 'Correct imperfect reference standard' (p. 16); C, 'Construct reference standard' (p. 18); D, 'Differential verification' (p. 18); E, 'Discrepant analysis' (p. 19); F, 'Composite reference standard' (p. 21); G 'Panel or consensus diagnosis' (p. 24); H, 'Latent class analysis' (p. 26); I, Validate index test results' (p. 29).

departure from the classical diagnostic accuracy paradigm including a gold standard, as explained in Chapter 1. Our classification is neither exhaustive nor mutually exclusive. Researchers can also use a combination of methods within a single study.

In the first group of methods, **Group A: Impute or adjust for missing data on reference standard**, there is a reference standard providing adequate classification, but for various reasons the outcome of the reference standard is not obtained in all patients (see Chapter 1 for an overview of reasons). The methods in this group impute or adjust for this missing information in the subset of patients without reference standard outcome. Methods within this group differ in the way in which they impute or adjust for this missingness.

In the second group, **Group B: Correct for imperfections in reference standard**, there is a preferred reference standard, but this standard is known to be imperfect. Solutions from this group either adjust estimates of accuracy or perform sensitivity analysis to examine the impact of using this imperfect reference standard. The adjustment is based on external data (previous research) about the degree of imperfection.

Methods in the third group, **Group C: Construct a reference standard**, have in common that they combine multiple pieces of information (test results) to construct a reference standard outcome. The methods differ as to whether they use a predefined deterministic rule to classify patients as having the target condition (composite reference standard), whether only discordant results are retested with a second reference standard (discrepant analysis) or whether the different tests are combined through a statistical model (latent class analysis). Also, a panel of experts can be used to determine the presence or absence of the target condition in each patient.

The diagnostic test accuracy paradigm is abandoned in the fourth group, **Group D: Validate index test results**. In these studies, index test results are related to other relevant clinical characteristics. An important category is relating index test results with future clinical events, such as the number of events in those tested negative for the index test or a randomised comparison between testing and non-testing. Any relevant clinical information could be used to validate index test results, including cross-sectional or historical data. Because this group departs completely from the classical accuracy paradigm,

measures other than accuracy measures are calculated, including event rates, relative risks and correlation statistics.

Impute or adjust for missing data on reference standard

In some studies, an accepted reference standard providing adequate classification is available, but for a variety of reasons not all patients receive this standard, leading to missing data on whether the target condition is present or absent. The general problem of missing data is well established in epidemiology and biostatistics, and many statistical methods have been developed to deal with missing data.[29] Most literature focuses on missing values on predictors, but a fair amount of literature is available on missing data of outcome variables, including papers dealing with diagnostic research.[22,23,30–41] Missing data on the reference standard have been labelled partial or incomplete verification in the diagnostic literature, and the bias associated with it is known as partial verification bias or sequential ordering bias.[19,20]

Imputation methods use a mathematical function to fill in each missing value, whereas correction methods use a mathematical function to correct the indexes of accuracy directly. Three main patterns of partial verification or missingness have been described: missing completely at random (MCAR), missing at random (MAR) and not missing at random (NMAR).[29]

In MCAR, missing values are unrelated to the status of the target condition, index test results and other patient characteristics. Hence the occurrence is a true random process and therefore the frequency of missing values is similar among patients with positive or negative index test results. This situation can occur due to unavailability of the reference standard because of technical failures.

More often, missing values for the reference standard do not occur completely at random, but are related to the results of the index test (more frequent in patients with negative index test result) and to other patient characteristics. If the mechanisms that have led to the missing values on the reference standard are known and observed, then the technical term 'missing at random' (MAR) is used. This term is used because within strata of the mechanisms leading to missing values, the pattern is random. This also forms the basis for predicting and subsequently imputing missing values.

If the pattern of missing values is related to the target condition, but through mechanisms that we have not observed, it is called NMAR. This situation can occur when incomplete verification is not design based, but determined by the choice of patients and physicians. In these situations, the mechanisms leading to missing values are difficult to determine, especially when additional patient characteristics such as symptoms, signs or previous test results have not been recorded.

Imputation methods

Imputation methods comprise two phases, an imputation phase where each missing value is replaced, and an analysis phase, where estimates of sensitivity and specificity are computed based on the now complete dataset. Many variants of imputation are possible, ranging from single imputations of missing values to multiple imputations.[42–46] Instead of filling in a single value for each missing value, multiple imputation procedure replaces each missing value with a set of plausible values that represent the uncertainty about the correct value to impute. These multiple imputed data sets are then analysed (one by one) by standard procedures for complete data sets. In a next step, the results from these analyses are combined to produce estimates and confidence intervals (CIs) that properly reflect the uncertainty due to missing values.

The choice of imputation method is largely based on the pattern of missingness. Basically, the associations between patient characteristics and the outcome of the reference standard are evaluated through a statistical model, like logistic regression, subsequently to impute missing values. In the NMAR setting, it is very rare to identify an appropriate model for the missingness mechanism. Consequently, the validity of the model is uncertain. For further information on dealing with missingness and imputations, readers are referred to Little and Rubin.[29]

Correction methods for missing data on reference standard outcome

In correction methods, no effort is made to impute missing values. The notion is that estimates of diagnostic test accuracy are likely to be biased if only patients who received verification with the reference standard (complete cases) are analysed. A mathematical correction of these

estimates and their CIs is warranted based on the mechanism of missingness.

The first publications about correction for partial verification were based on the MCAR assumption.[39] If missings occur completely at random and the fractions of persons missing in each of the cells of the two-by-two table are likely to be comparable, estimates (but not CIs) of accuracy can be easily recalculated without any statistical model. As this pattern is not likely to occur often, mathematical correction methods have been developed that can deal with MAR. In MAR, estimates of accuracy can be corrected if verification is random within specific patient profiles, based on patient characteristics or (index) test results, and the number of patients not verified within each stratum is known. Here, several methods to correct estimates of sensitivity and specificity based on this assumption have been described.[13,22,23,32,47,48] The same is true for the correction of receiver operating characteristic (ROC) curves and associated indexes.[38,47,49]

Strengths and weaknesses

Both methods aim to alleviate the bias that is potentially introduced by analysing only cases with complete data on the reference standard. The strengths of each method are determined by how accurately the mechanism behind missing values is known. If the mechanisms that lead to missing values on the reference standard are (partially) unknown, the correction or imputation methods are prone to bias. Moreover, correction and imputation methods are based on statistical modelling of the data, which requires sufficiently large sample sizes.[50] The potential of bias can be large when correction methods are used in studies with relative small sample sizes, or if the fraction of patients receiving the reference standard is small. Imputation methods, especially multiple imputation methods, seem to be more robust in these situations than correction methods.[23]

Application

These methods can be used when a preferred reference standard is available, but has not been applied in all patients enrolled in the study. Ideally, partial or incomplete verification should be planned by design, so that the pattern of missingness is known. Researchers should be very careful with these methods if missingness is uncontrolled and open to influence by patient and practitioner choice, if the sample size is small or if the fraction of verified patients is small within test categories.

Software

Software for dealing with missing data is now embedded in the main statistical software packages.

Clinical example

Harel and Zhou used two real data examples to illustrate the results of multiple imputation and correction methods for missing data on the outcome of the reference standard.[23] We present a brief summary of their results.

The first example addresses hepatic scintigraphy, an imaging scan procedure, for the detection of liver cancer.[51] Out of 650 patients, 344 were referred to liver pathology, which was considered the reference standard (*Table 2*). The MCAR assumption does not hold here, as 39% of the index test positives and 63% of the index test negatives are not verified. Either MAR or NMAR is true, and Harel and Zhou used the MAR assumption that non-verification occurred randomly within index test positives and negatives, respectively. *Table 3* presents summary estimates of sensitivity, specificity and CIs as computed by eight different methods. The first method concerns a 'complete case' analysis, where the 306 patients without liver pathology are ignored and estimates are based on the remaining 344 patients only. This method gives a higher estimate of sensitivity and lower estimate of specificity in comparison with all other methods. The two correction methods, as proposed by Begg and Greenes,[22,48] produce comparable estimates, with lower sensitivities and higher specificities compared with the complete case analysis. In comparison with the remaining five multiple imputation methods, however, the sensitivities are lower and the specificities are higher.

In the second example, Harel and Zhou used data of a study evaluating diaphanography as a test for detecting breast cancer.[52] Of the 900 patients enrolled, 812 were not verified. The pattern of missingness was either MAR or NMAR, as 55% of the diaphanography positives and only 6% of the diaphonography negatives were verified (*Table 4*). Again, Harel and Zhou chose to use the MAR assumption that is related to index test results only. *Table 5* shows the estimates computed by the eight methods. Here the differences between the complete case analysis, the correction and imputation methods are more prominent, while the estimates of multiple imputations are fairly close to each other. In the light of the sample size and their previous simulation work, Harel and Zhou concluded that the estimates of multiple imputations are more representative of the data.

TABLE 2 *Hepatic scintigraphy data: outcome of reference standard in those verified and fraction of unverified test results (adapted from Harel and Zhou[23])*

	Liver pathology positive	Liver pathology negative	Liver pathology not performed
Hepatic scintigraphy positive	231	32	166
Hepatic scintigraphy negative	27	54	140
Total	258	86	306

TABLE 3 *Estimates with 95% CIs of sensitivity and specificity for different methods to adjust or impute missing data on reference standard outcome (based on data from* Table 2*)*

Procedure	Sensitivity		Specificity	
	Estimate	95% CI	Estimate	95% CI
Complete cases	0.895	0.858 to 0.932	0.628	0.526 to 0.730
Begg and Greenes[a]	0.836	0.788 to 0.884	0.738	0.662 to 0.815
Logit version Begg and Greenes[a]	0.836	0.835 to 0.838	0.738	0.735 to 0.741
A&C[b]	0.869	0.820 to 0.918	0.672	0.571 to 0.772
Rubin (logit)[b]	0.872	0.817 to 0.912	0.675	0.567 to 0.797
Wilson[b]	0.869	0.837 to 0.901	0.672	0.610 to 0.733
Jeffrey[b]	0.872	0.838 to 0.901	0.675	0.611 to 0.734
Z&L[b]	0.872	0 to 1	0.675	0 to 1

A&C, Agresti-Coull; Z&L, Zhou and Li method.
[a] Correction method.
[b] Multiple imputation method.

TABLE 4 *Diaphanography data: outcome of reference standard in those verified and fraction of unverified test results (adapted from Harel and Zhou 2006[23])*

	Breast cancer positive	Breast cancer negative	No verification
Diaphanography positive	26	11	30
Diaphanography negative	7	44	782
Total	33	55	812

TABLE 5 *Estimates with 95% CIs of sensitivity and specificity for different methods to adjust or impute missing data on reference standard outcome (based on data from* Table 4*)*

Procedure	Sensitivity		Specificity	
	Estimate	95% CI	Estimate	95% CI
Complete cases	0.788	0.649 to 0.927	0.800	0.694 to 0.906
Begg and Greenes[a]	0.280	0.127 to 0.434	0.974	0.960 to 0.989
Logit version Begg and Greenes[a]	0.280	0.275 to 0.285	0.974	0.973 to 0.975
A&C[b]	0.706	0.560 to 0.852	0.861	0.753 to 0.970
Rubin (logit)[b]	0.717	0.548 to 0.841	0.869	0.721 to 0.944
Wilson[b]	0.706	0.601 to 0.812	0.861	0.839 to 0.884
Jeffrey[b]	0.718	0.603 to 0.815	0.863	0.839 to 0.885
Z&L[b]	0.717	0 to 1	0.869	0 to 1

A&C, Agresti-Coull; Z&L, Zhou and Li method.
[a] Correction method.
[b] Multiple imputation method.

Complete case analysis seems to overestimate sensitivity and underestimate specificity, whereas Begg and Greenes's correction methods seem dramatically to underestimate sensitivity and overestimate specificity.

Harel and Zhou used the MAR assumption where missingness is related to index test results only. In practice, factors other than index test results, such as symptoms, signs, co-morbidity or other test results, may have driven the decision to apply or to withhold the reference standard. Imputation models can be extended to incorporate these additional sources of information, if known and collected, in an effort to improve the prediction of the reference standard outcome in unverified patients.

Correct imperfect reference standard

Description of the method

If a true gold standard does not exist, a logical next step is to search for the best available procedure to verify index test results. This is the rationale behind the concept of reference standard: the best available method to determine the presence or absence of the target condition, not necessarily without error. However, imperfection of the reference standard leads to bias known as reference standard bias.[11,19,53] If knowledge about the amount and type of errors of the imperfect reference standard is available, then this information can be used to correct estimates of diagnostic accuracy. We assume that all patients have received the imperfect reference standard, so there are no missing data in contrast to the correction methods described in the previous section.

Basic model

The basic model assumes that the error rates of the reference standard are known and that algebraic functions can be used to recalculate estimates of accuracy. Key publications by Hadgu and colleagues[54] and Staquet and colleagues[55] provide several algebraic functions, all based on the assumption of conditional independence between the index test and reference standard results. The assumption implies that the errors of both tests are independent of the underlying true status of the target condition, hence the index test and reference standard do not tend to err in the same patients.

Sometimes, the exact sensitivity and specificity of the imperfect reference standard are not known, but a range of plausible values are available. This range of values can then be applied in a sensitivity analyses that will produce a range of estimates of accuracy for the index test.

Extensions of the basic model

In many clinical situations, the assumption of conditional independence is unlikely to be true. Often the index test and reference standard have a tendency to make errors in the same (difficult) patients, particularly when index test and reference standard are methodologically related or measure the same physiologic alteration.[56] In the detection of cancer, for example, both the index test and reference standard may have difficulties in detecting early stages of cancer, and in clinical chemistry, contamination of body fluid samples may affect both the index test and reference standard. Algebraic functions have therefore been developed that build in the conditional dependence, such as the correlation in errors.[57] Unfortunately, the amount of correlation between errors is rarely known, hence this parameter is often varied over a wide range of plausible values.

Strengths and weaknesses

These correction methods can easily be applied using simple algebraic functions. The main limitation is that in most situations the true sensitivity and specificity of the imperfect reference standard are not known, nor does one know the amount of correlation among errors of the index test and the reference standard. If the chosen values do not match the true values, the resulting estimates of diagnostic test accuracy would still be biased or could become even more biased than the unadjusted ones.[58] For these reasons, researchers have tried to generalise the algebraic correction functions to avoid making untenable assumptions.[54] Latent class analysis subsequently evolved, which can be viewed as an extension of this method for situations where there is no information available on either the error rates of the reference standard or the true prevalence (see the section 'Latent class analysis', p. 26). In latent class analysis, the result of the (imperfect) reference standard is incorporated as just one source of information about the true disease status.

Applicability

The basic correction method can be applied in any situation if the following conditions are met: reliable information on the magnitude of the error rates of the reference standard is available and the conditional independence assumption is likely to be true, or there is reliable information about the

correlation between errors in the index test and the reference standard. In all other situations, the method is likely to render accuracy estimates that are biased, despite the use of a correction method.

Software

The algebraic functions can be used in widely available software programs such as Excel or any other statistical program.

Clinical example

The development of sensitive tests for bladder cancer is critical for its early detection. A gold standard does not exist for the evaluation of endoscopic tests as ideally this would necessitate removing the bladder for detailed pathological examination, a procedure that would not be ethically justifiable. Therefore, pathological evaluation is done only on biopsy or surgically removed tissue. In other words, only positive findings during endoscopy (index test) are verified. Histological examination alone is therefore not a reference standard providing perfect classification because of the unknown likelihood of missing cancerous lesions because they were not biopsied. This is the downside of not being able to verify negative findings of the index test.

Assumptions are necessary to correct for biases inherent in this approach. Schneeweiss and colleagues[59] provide an example of derivation of an interval of sensitivity estimates that includes the true value. They compared the ability of 5-aminolevulinic acid-induced fluorescence and white light endoscopy to detect bladder cancer. This is an example of a comparative diagnostic accuracy study with two index tests. They hypothesised that 5-aminolevulinic acid-induced fluorescence endoscopy is of superior diagnostic value. A total of 208 patients under surveillance after superficial bladder cancer were included. Multiple evaluations over time within the same patient were included, leading to a total of 328 endoscopic evaluations in which both procedures (index tests) were performed. They used sensitivity as the main accuracy parameter as the consequences of false negative cases would be worse and these results should be minimised by a good test.

The effect of having no gold standard is that there can be misclassification among the four cells in the 2-by-2 table. The observed true positive cell consists of lesions that are positive with the index test and confirmed on biopsy. It is unlikely that any observation in this cell should belong in another cell because we assume that cancer cells identified by pathological evaluation always indicate to cancer. However, in reality, there could be more observations in the true positive cell when some observations were wrongly classified as false positives, which can happen when not enough or not the correct biopsies were taken from a lesion. These observations would be classified as false-positives when in reality they belong in the true positive cell. The magnitude of this type of misclassification is assumed to be small but unknown.

For the false negative and true negative cells, the mechanism is analogous. If cancerous lesions are missed by both index tests, they are classified as true negatives, but in reality they are false negatives. False negatives can be observed in this study because of the paired design of this study; for example, patients underwent both index tests so that a true positive finding with one technique can be considered a false negative finding for the other technique if that technique missed that lesion. The magnitude of this misclassification of negative index test results is also assumed to be small but larger than the misclassification in the positive tests.

The following misclassification model was used to correct the counts in the observed 2-by-2 table and recalculate sensitivity based on these corrected counts. Let $p(\mathrm{A})$ be the probability of misclassifying true positives as false positive results and $p(\mathrm{B})$ be the probability of misclassifying false negative as true negative results. A more general equation can now be derived for estimating test sensitivity:

$$\text{Sensitivity} = \frac{\text{'true positive'} + p(\mathrm{A}) \times \text{'false positive'}}{\text{'true positive'} + p(\mathrm{A}) \times \text{'false positive'} + \text{'false negative'} + p(\mathrm{B}) \times \text{'true negative'}}$$

If it were assumed that there would be no misclassification, sensitivity could be easily calculated from the observed numbers in the 2-by-2 table, the so-called naive estimate. The analysis that Schneeweiss and colleagues propose comprises most optimistic, most pessimistic and some realistic assumptions to generate an interval of sensitivity.[59,60] The maximum interval of observable sensitivity for 5-aminolevulinic acid-induced fluorescence endoscopy ranged between 78 and 97.5%, and the best estimate for sensitivity based on realistic assumptions was 93.4% (95% CI 90 to 97.3). The best sensitivity estimate for white

light endoscopy was 46.7% (95% CI 39.4 to 54.3, maximum range 47.2–53%).

This method to determine the maximum possible range of sensitivity estimates in studies in which negative findings cannot all be verified is easily applied. Depending on the assumptions, a range of reasonable scenarios can be constructed and the corresponding sensitivities can be reported.

Construct reference standard

Differential verification

Description of the method

Instead of ignoring, imputing or correcting the non-verified results in the analysis, a second reference standard can be used to achieve complete verification. Use of different reference standards in this way is also known as differential verification (see also *Figure 2*, p. 4).[19] The second reference standard is usually a less invasive test and is less costly or less burdensome to patients. In the detection of pulmonary embolism (PE), for example, it is nowadays considered unethical to perform pulmonary angiography in patients with a low suspicion of PE and a negative D-dimer test result.[61] In many of these studies, only patients at high-risk for PE receive the best available reference standard (angiography), whereas 'low-risk' patients are likely to receive a different reference standard, such as clinical follow-up.

The use of different reference standards between patient groups is frequently encountered in the literature. In a survey of 31 diagnostic reviews, differential verification was present in 99 out of 487 (20%) primary diagnostic accuracy studies.[3] In most cases, incomplete verification is neither specified in the design nor completely at random. Triggers to perform the preferred reference standard in some patients and not in others include a positive result on the index test, positive results from other tests or the presence of risk factors for the condition of interest. This means that differential verification is selective and shows a non-random pattern, being based on decisions by the practitioner or patient.

Differential verification has been shown to lead to higher estimates of accuracy than studies using a single reference standard in all patients.[1,3] This type of bias is known as differential verification bias, or different reference standard bias, work-up bias or selection bias.[19,62] The effect of differential verification on estimates of accuracy is difficult to predict, as it depends on the proportion of patients verified differently, the selection process behind patients verified differently, the properties of the reference standards involved and their relation with the index test.[20]

Strengths and weaknesses

Differential verification appears to escape the bias of incomplete (partial) verification, but can lead to estimates of diagnostic accuracy that differ from those obtained with full verification by the preferred reference standard.[1,3] Moreover, estimates of sensitivity and specificity are more difficult to interpret, as they are based on multiple index test–reference standard combinations.[20] If complete verification by the preferred reference is not possible and different reference standards have to be used, the best approach is to incorporate differential verification in the design. This means prespecifying the group of patients that will receive the first reference standard and the group that will receive the second. An example could be that all patients with a positive index test are verified by one reference standard and all negative patients are verified by the second reference standard. In that case, the appropriate measures of accuracy are the positive and negative predictive values, calculated with corresponding reference standards. Because these measures are directly influenced by changes in prevalence the right design has to be chosen, such as cohort rather than case–control.

Field of application

Differential verification can be a reasonable option if several acceptable diagnostic tests are available that can serve as the reference standards. A prerequisite, however, is that the verification scheme is preplanned (design-based). As in any design, authors should report the rationale for each reference standard. Moreover, results should be reported separately for each index test–reference standard combination.

Software

Studies with differential verification produce standard accuracy results. No additional programming is necessary.

Clinical example

An illustrative example of differential verification that was (partly) design based can be found in the publication of Kline and colleagues.[63] The objective of the study was to evaluate the diagnostic accuracy of the combination of D-dimer assay with an alveolar dead-space measurement for rapid exclusion of pulmonary embolism.

In this multicentre study, V/Q scans, helical computed tomography, ultrasonography, clinical follow-up, angiography, death, events of deep venous thrombosis or new events of pulmonary embolism and combinations of these tests were used as diagnostic criteria to determine the presence or absence of pulmonary embolism. The authors describe a verification scheme to establish the final diagnosis that at first seems to be design based, but later on they state that the decision to order further imaging in patients with non-diagnostic V/Q scans was at the discretion of the attending physician.

The authors provide a table describing the different criteria for the presence of PE and the matching number of patients. Unfortunately, the corresponding results of the combined D-dimer–alveolar dead-space measurement were not stated in this table. In the results section, sensitivity, specificity, negative and positive likelihood ratios and the corresponding CIs were calculated in the usual way.

In the discussion, the authors do address the problem of differential verification. They state that computed tomography, for example, performs differently from angiography, and may have wrongly diagnosed some patients with PE who may have been free from PE.

The results of this study may not be very helpful to clinicians in practice, as it is unclear to which patients the estimates of diagnostic accuracy apply.

Discrepant analysis

Description of the method

Discrepant analysis, also referred to as discrepant resolution or discordant analysis, uses a combination of reference standards in a sequential manner to classify patients as having the target condition or not.[22,64,65] Discrepant analysis can provide estimates of prevalence and estimates of sensitivity and specificity of the index test without statistical modelling.

Initially, all patients are tested with the index test and one imperfect reference standard (*Figure 4*). Since the imperfect reference standard is known to be imperfect, the discordant or discrepant results (cases where index and first reference standard disagree) are retested (resolved) with an additional reference standard, frequently called the resolver test. The resolver test is usually a more invasive, more costly or otherwise burdening test, with better discriminatory properties than the first reference standard. The results of the resolver test are then used to update the final 2-by-2 table. Based on this final 2-by-2 table, estimates of accuracy for the index test are calculated.

Strengths and weaknesses

The method is straightforward and easy to carry out without statistical expertise. At first sight, this design seems to provide an efficient alternative to reduce the number of patients who have to be tested with the best available reference standard when this standard is either invasive or costly to apply. Yet a fundamental problem of discrepant analysis is that the verification pattern is dependent on the index test results.[64,66] Although discrepant analysis provides the status of the target condition for those who are retested, it does not provide that information for those not retested, which is usually the majority. Discrepant analysis therefore has the potential to lead to serious bias.[64,65,67–71]

The potential for bias has been demonstrated algebraically and numerically in the estimation of sensitivity and specificity in a situation where the resolver test is a perfect gold standard.[66,68,69] In this situation, discrepant analysis will lead to estimates of sensitivity and specificity for the index test that are biased upwards, so that the index test appears to be more accurate than it really is. The magnitude of this bias depends on the absolute number of errors of the index tests (false positive and false negative index test results) and the amount of correlation between the errors of the index test with the results of the first reference standard. These are correlated errors that will erroneously appear as either true positives or true negatives in the final 2-by-2 table as these patients will not enter the second stage and therefore will not be corrected by the perfect resolver test.

Green and colleagues showed that when the resolver test is not a perfect gold standard, even larger biases are possible, as the second imperfect reference standard can lead to further misclassification of the discordant results.[72] If errors of the stage 2 resolver test are correlated with errors of either the index test or the stage 1 imperfect reference standard, the diagnostic accuracy of the stage 2 reference standard will be biased in the assessment of discordant results. In other circumstances, the measured values may actually be closer to the true values.[66] In general, situations where the errors of the index test and the resolver test are related are of particular concern.

A method to correct for the potential bias in the discrepant analysis has been proposed,[66,73] but this

method is considered to be of limited applicability. The method requires that a random sample of patients with concordant results of the index test and the initial reference standard is tested by the resolver test. From this sample, the concordance rate of false results is estimated and the observed sensitivity and specificity are corrected accordingly. This procedure is adequate only if the resolver test is (nearly) perfect, a situation which occurs infrequently.

Field of application

Although discrepant analysis has been most frequently applied in the field of microbiology (detection of infections),[64,66] it can, in theory, be applied in all other medical fields. The general notice is to refrain from discrepant analysis because of the fundamental problem of the implicit incorporation of index test results in the definition of the true disease status leading to potential bias.[64,65] (http://www.fda.gov/cdrh/osb/guidance/1428.pdf). Only in special situations can the choice for discrepant analysis be defended if there is a perfect resolver test and a random sample of concordant results is also verified by the resolver test using the correction method proposed by Begg and Greenes.[22,48]

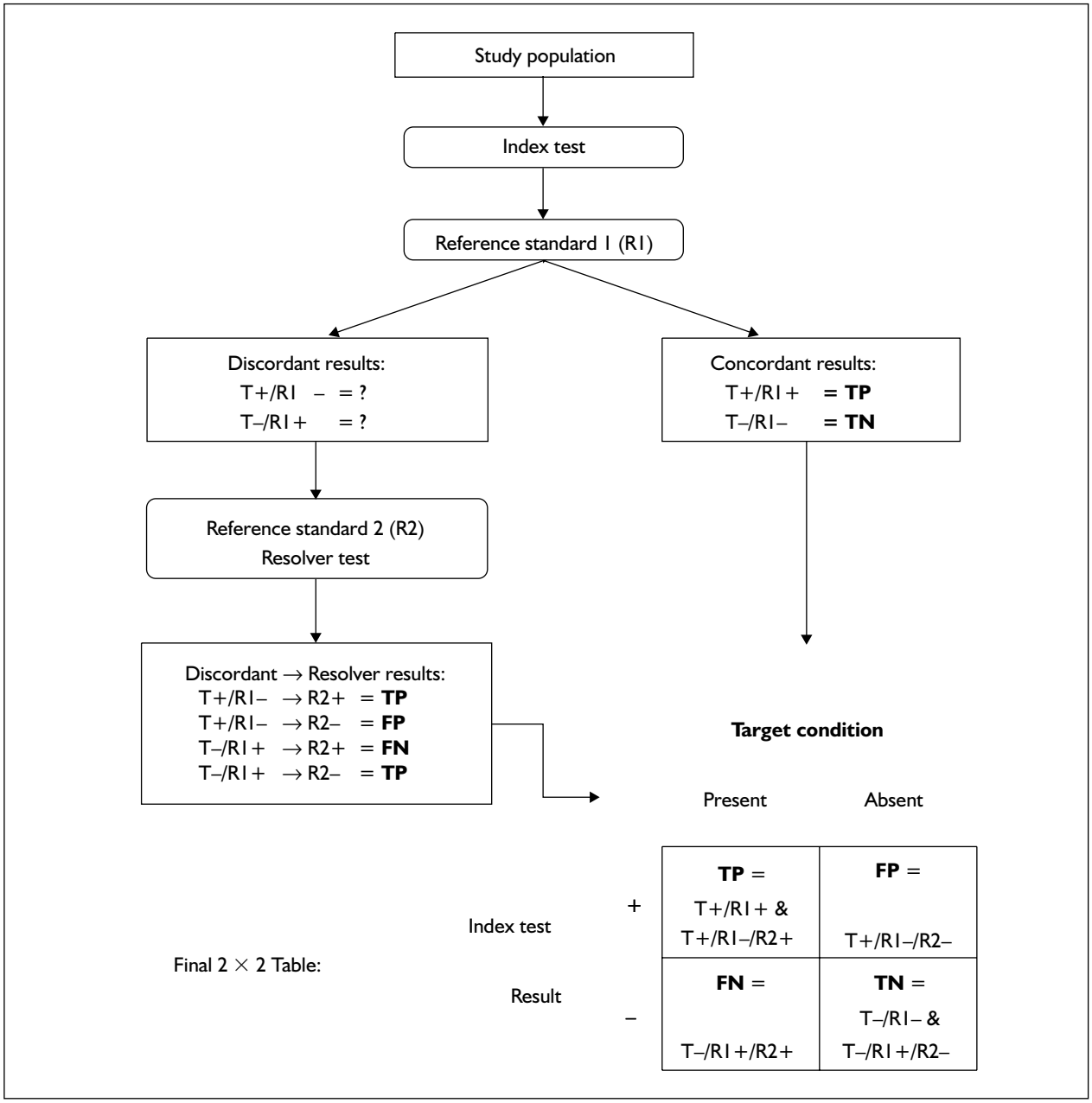

FIGURE 4 *Flow of patients and final 2-by-2 table in a study using discrepant analysis*

Software

Any statistical package can be used. The calculations can also be done with a pocket calculator.

Clinical example

To diagnose *Chlamydia trachomatis* infection, culture, DNA amplification methods such as polymerase chain reaction (PCR) and antigen detection methods such as enzyme immunoassay (EIA) are used (the same example is also used in composite reference standard and latent class analysis). Alonzo and Pepe[25] discuss the problems of assessing the accuracy of EIA (index test) as neither of the two other methods can be considered 'gold standards'. Culture is believed to have nearly perfect specificity, but also misses patients with *Chlamydia* infection (false negatives). PCR is believed to be more sensitive than culture to detect *Chlamydia trachomatis*. Alonzo and Pepe use the method of discrepant analysis to assess the accuracy of EIA by using culture as the initial reference test and PCR to resolve the discrepant results in the second stage (resolver test).[25]

The data are derived from the study of Wu and colleagues.[74] In the first stage, all 324 specimens are tested by EIA (index test) and culture (*Table 6*). In the second stage, only the discrepant results, for example, specimens which are positive by EIA and negative by culture ($n = 7$) or vice versa ($n = 3$), are retested with the resolver, PCR. The concordant results directly enter the final 2-by-2 table as true positives ($n = 20$) and true negatives ($n = 294$).

In the second stage, the 10 discordant results are tested with PCR and the outcome of the PCR test determines the classification in the final 2-by-2 table (*Table 7*). The EIA positive and culture negative results become either true positives if the PCR is positive ($n = 4$) or false positives if the PCR outcome is negative ($n = 3$). The same rule applies for the EIA negative and culture positive results ($n = 3$): the outcome of the PCR determines the final classification as either true negative if PCR is negative ($n = 1$) or false negative if PCR is positive ($n = 2$).

TABLE 6 *Initial classification using culture as the first (imperfect) reference standard*

	Culture	
EIA	+	–
EIA+	20	7
EIA–	3	294

Combining the results from the initial stage (*Table 6*) and the second resolver stage (*Table 7*) leads to the final 2-by-2 table (*Table 8*) on which the accuracy can be calculated.

The estimates of accuracy after retesting the 10 discordant results with PCR are as follows:

prevalence is $26/324 = 0.080$
sensitivity is $(20 + 4)/(20 + 4 + 3 - 1) = 24/26 = 0.923$
specificity is $(294 + 1)/(294 + 1 + 7 - 4) = 295/298 = 0.990$.

If we would have calculated the estimates of accuracy directly after using culture as a single reference standard, they would have been as follows:

prevalence is $23/324 = 0.071$
sensitivity is $20/23 = 0.870$
specificity is $294/301 = 0.977$.

Changes in this case are small because the frequency of discordant results was relatively low (3.1%). The validity of the approach depends on the error rate of the resolver test and the frequency of errors in the concordant results in the initial stage.

Composite reference standard

Description of the method

In the absence of a single gold standard, the results of several imperfect tests can be combined to create a composite reference standard. The results of the component tests of the composite

TABLE 7 *Results of the second stage: selective testing of discrepant results with PCR, the resolver test*

Discrepant results	Resolver test PCR	
	+	–
EIA+ and culture – ($n = 7$)	4	3
EIA– and culture + ($n = 3$)	2	1

TABLE 8 *Final classification based on discrepant analysis method*

EIA	Final classification	
	+	–
EIA+	20 + 4	3
EIA–	2	294 + 1

reference standard determine the presence of the target condition based on a prespecified rule. Such a composite reference standard is believed to have better discriminatory properties than each of the reference standards components in isolation.[24,25,64,66,75]

Basic model
A basic model is where two tests are applied in all patients and a prespecified (deterministic) rule is used to classify patients as having the target condition. Several definitions for the presence of the target condition can be used, depending on whether emphasis should be given to detecting or excluding the target condition and on the characteristics of the available reference tests. Most frequently, researchers define the target condition to be present if either one of the reference tests is positive. In the evaluation of the diagnostic accuracy of EIA in the detection of *Chlamydia trachomatis*, for example, a composite standard of two reference tests has been used: culture and PCR.[76] EIA and the two reference tests were applied in all patients and infection with *Chlamydia trachomatis* was diagnosed if either culture or PCR was positive. If both reference tests were negative, the person was labelled free of *Chlamydia trachomatis*.

It is important to note that the composite reference standard approach differs from discrepant analysis (see the section 'Discrepant analysis', p. 19), as the results of the index test themselves play no role in the verification procedure of the composite method. The difference between using a composite reference standard and differential verification is that in the composite method each patient receives all (necessary) components of the composite reference standards whereas in differential verification subgroups of patients are verified by one reference standard and other subgroups by a **different** reference standard (see also the section 'Differential verification', p. 18).

Extensions of the basic model
The composite reference standard approach can be extended to include more than two reference tests, as for instance in the detection of myocardial infarction, where chest pain, serological markers and electrocardiograms are used to define the presence or absence of the disease.[77] Increasing the number of reference tests amplifies the number of ways to define the presence of the target condition. If six reference tests are combined, for example, one possibility is the 'any test positive' definition of disease. Another definition was used in a study evaluating *Helicobacter pylori*, where a patient was regarded infected whenever two or more of the six available tests were positive.[78]

The efficiency of the composite reference standard can often be improved by avoiding redundant testing. If the classification rule is based on one of the two reference tests being positive, there is no need to perform a second reference test once the outcome of the first reference test is positive. Hence retesting is only necessary in patients with a negative result on the first reference test. Performing the more accurate reference test first lowers the number of patients needing additional testing.

Another extension is the use of statistical models to combine several reference test results to define disease status as in latent class analysis. This approach is discussed separately, as it does not use a prespecified deterministic rule for classifying patients having the target condition or not (see the section 'Latent class analysis', p. 26, for more details).

Strengths and weaknesses
The method is straightforward and easy to understand. It allows one to combine several sources of information in order to assess whether the target condition is present. The prespecified rule to define when the target condition is present increases transparency and avoids problems of incorporation and work-up bias. Unlike discrepant analysis, the application of the second reference standard is independent of the index test result.

A major issue is whether the combination of reference test results is a meaningful way of defining the target condition and whether residual misclassification is likely to be present. Do different reference standard tests look at the same target condition, but with different error rates, or do they define the target condition differently? The latter is thought to reduce the clinical usefulness.[24] The inclusion of more than two reference tests in the composite reference standard may then obscure the final definition of the disease.

A general problem is the determination of the 'cut-off value' to classify patients as having the target condition when several imperfect reference tests are available. Several suggestions have been made in literature. Alonzo and Pepe referred to latent class analysis as a tool for finding an optimal cut-off to define the target condition, but

TABLE 9 *Contingency table summarising composite reference for the* Chlamydia *data: EIA is the index test and the elements of the composite reference standard are culture and PCR.*

EIA	Culture		Composite reference standard: culture + PCR	
	+	–	+	–
EIA+	20	7	20 + 4	7 – 4
EIA–	3	294	3 + 2	294 – 2

they concluded against its use, as they see the model as being prone to bias due to its assumptions[64] (see also the 'Latent class analysis', p. 26). Some authors have suggested to use all possible 'cut-off values' to define the target condition rather than choosing a single one. They evaluate the index test against all these definitions and show how the accuracy of the index test varies across these definitions.[75,79]

Field of application

The composite reference standard method can be considered in all situations where a single gold standard does not exist, but several imperfect reference tests are available. One potential benefit is that it allows the researcher to 'adjust' the threshold for disease depending on the clinical problem at hand. In situations where missing the target condition outweighs the risk of wrongfully labelling persons as diseased, using a cut-off of 'any result positive indicates disease' can be advantageous. The composite reference standard method has been used in many areas, including infectious diseases[64,75,76] and gastroenterology.[79]

Software

The method is based on simple predefined classification rules, and requires no additional software. Measures of accuracy including CIs are calculated in their traditional way.

Clinical example

To diagnose *Chlamydia trachomatis* infection, culture, DNA amplification methods such as PCR and antigen detection methods such as EIA are used. (The same example is used in discrepant analysis and latent class analysis.) Alonzo and Pepe discuss the problems of assessing the accuracy of EIA (index test) as neither of the two other methods can be considered 'gold standards'.[25] Culture is believed to have nearly perfect specificity. PCR is believed to be more sensitive than culture to detect *Chlamydia trachotomatis*.

Alonzo and Pepe provide an example of assessment of EIA's accuracy using a composite reference standard based on culture and PCR.[25] They use the either positive rule to classify patients as having *Chlamydia* infection meaning that any specimen that is culture positive **or** PCR positive is composite reference standard positive and any specimen that is culture negative **and** PCR negative is composite reference standard negative. This approach allows one to use several sources of information in order to assess if an infection is present based on an *a priori* rule.

Because they use the either positive rule, there is no need to test all specimens with both reference tests of the composite reference standard: if a specimen is positive on the first reference test it will be positive on the composite reference standard and no further testing is therefore required. In the *Chlamydia* setting, in the first stage all specimens are tested by EIA (index test) and culture. In the second stage, only those specimens which are culture negative at the first stage are tested with PCR.

Considering the data from the study by Wu and colleagues[74] a contingency table summarising the two stages of composite reference standard is given in *Table 9*. After the first stage in assessing the performance of EIA using the composite reference standard, the 301 culture negative specimens (7 + 294) were tested with PCR. Six of these specimens were PCR positive and therefore considered to be infected based on the composite reference standard. The final estimates of accuracy are as follows:

prevalence is 29/324 = 0.090
sensitivity is (20 + 4)/(20 + 4 + 3 + 2) = 24/29 = 0.828
specificity is (294 – 2)/(294 – 2 + 7 – 4) = 292/295 = 0.990.

Because there is an *a priori* rule involving only the two reference test, the results of the index test (EIA) play no role in the classification of patients. This is different from the discrepant method because there the index test does play a role as only discrepant results move on to the second stage. To put it differently, in the composite

example the classification would not have changed if all specimens had been tested by both reference tests (culture and PCR). Because of the nature of the *a priori* rule (either positive), redundant testing can be avoided to gain efficiency.

One drawback of the composite reference standard is that it requires testing the typically large number of specimens negative by culture.

Panel or consensus diagnosis

Description of the method

In a panel or consensus diagnosis, a group of experts determines the presence or absence of the target condition in each patient based on multiple sources of information. These sources can include general patient characteristics, signs and symptoms from history and physical examination, and other test results. Information from clinical follow-up may also be included as an additional source of information to improve the classification of patients by the experts.

Variation exists in how to synthesise the input from different experts. Experts can discuss the information on each patient directly in a meeting and produce a consensus diagnosis using majority voting in case of disagreement. In other studies, experts determined the final diagnosis independently from each other and patients were only discussed in a consensus meeting in case of disagreement among experts. The final diagnoses from individual experts can also be combined using a statistical model.

Because a final diagnosis is determined in all patients, researchers can calculate estimates of accuracy in the traditional way without the use of specialised software.

Several practical decisions have to be made in setting-up a panel method. These include:

- the choice of experts: number and background
- the number of items to be considered in reaching a diagnosis and the way to present them
- whether or not to include the results of the index test
- combining the input from experts
- training and piloting.

Surprisingly little has been written in the medical literature about these practical decisions and how they can affect the final outcome. The discussion that follows is therefore largely based on theoretical considerations.

In the selection of experts, the qualities of the experts are expected to be of greater importance than the number of experts in a panel. Judgements by specialists may come closer to the true status of patients than a random or convenience sample of physicians. An uneven number of experts is sometimes recommended as it facilitates decision-making in case of majority voting.[80]

In general, all information relevant for the classification of patients is presented to the experts in a standardised way. Especially, subtle information from history taking might be difficult to get across on paper. Video footage of the original history taking or video films of dynamic radiological examinations might be an option.

Special care should be given to the role of the index test result in a panel diagnosis. If the index test result is given to the experts, its importance may be overestimated, leading to inflated measures of accuracy. This is known as incorporation bias.[2] On the other hand, the final classification in patients with and without the target condition may become better if the results of the index tests are disclosed to the experts. This would then reduce the problem of misclassification of the disease status. Most authors advise withholding the index test result from the experts. An attractive alternative is to use a staged approach where experts make a final diagnosis without the index test results first and then reveal the index test result and ask whether experts would like to change their classification.

As stated before, several methods of synthesising the input from different experts have been applied. Standard consensus meetings have been questioned because of problems arising from powerful personalities and also peer or group pressures. The Delphi procedure is a formal technique to collect and synthesise expert opinions anonymously to overcome these types of problems.[81]

Offering training and piloting sessions to experts can be used to increase agreement among experts. Piloting of the disease classification process may unearth problems that can then be addressed prior to the actual consensus process. Whether or not fixed decision rules need to be established during this piloting process is a matter of debate.

Strengths and weaknesses

Consensus diagnosis is an attractive alternative if a generally accepted reference standard does not

exist and multiple sources of information have to be interpreted in a judicious way to reach a diagnosis. Examples include target conditions that can lead to a wide range of symptoms and that cannot be diagnosed histologically. In those cases, the target condition can be defined by the clinicians, who take into account items of history, clinical examination, other test results and clinical follow-up, in order to determine clinical management. In such cases, the panel method closely reflects the clinically relevant concept of target condition. The accuracy statistics calculated in a study that relies on panel method to classify disease are likely to have high levels of generalisability to clinical practice.

Other advantages of this approach are the flexibility in determining conditions that have been poorly defined and the option of classifying conditions in a binary (target condition present or absent) and also in a multi-level way (as in severe, moderate, mild, no disease, indeterminate, etc.).

The downside of this method can be poor inter- and even intra-rater agreement, leading to discordance in disease classification between and within the experts. The levels of inter- and intra-rater agreements for the experts can be measured and should be reported in the study as part of validation of the consensus method.

Second, the subjectivity of the disease classification process may introduce bias. Incorporation bias or test review bias looms if the result of the index test is disclosed to the experts.

Third, the absence of a strict definition of disease in panel-based methods may be responsible for a divergence in the definition of 'disease' in the group of experts, who may have a different view of what constitutes the target condition of interest. Piloting and some form of standardisation can help in remedying this problem.

Fourth, the panel method can become a laborious enterprise if many items of information per patient need to be summarised and if many patients have to be discussed among several experts.

Finally, domination by assertive members of the panel can weaken any consensus procedure, although formal techniques such as the Delphi method are available to reduce this problem.

Application

The panel diagnosis method is well suited when there is no generally accepted reference standard procedure and multiple sources of information have to be interpreted in a judicious way to reach a diagnosis. In particular, the panel method is suited for target conditions that cannot be unequivocally defined. Examples in which panel diagnoses have been used include heart failure, the underlying causes in patients with syncope and underlying conditions in patients presenting with dyspnoea.

Software

No specialised software is needed, unless advanced procedures such as latent class analysis are used as a method of combining the results from various experts (for details, see the section 'Latent class analysis', p. 26).

Clinical example

Echocardiography is considered an imperfect reference standard test for heart failure. The European Society of Cardiology recommends that the diagnosis of heart failure be "based on the symptoms and clinical findings, supported by appropriate investigations such as electrocardiogram, chest X-ray, biomarkers and Doppler-echocardiography". Convening a consensus panel to establish the presence or absence of the target condition is then an appropriate approach to address the issue of imperfect reference standard in this study.

Rutten and colleagues evaluated which clinical variables provide diagnostic information in recognising heart failure in primary care patients with stable chronic obstructive pulmonary disease (COPD), and whether easily available tests provide added diagnostic information, in particular N-terminal pro-brain natriuretic peptide (NT-proBNP.[82] They studied patients over the age of 65 years with stable COPD diagnosed by a general practitioner without a previous diagnosis of heart failure made by a cardiologist. Clinical variables included history of ischaemic heart disease, cardiovascular medications, body mass index, displacement heart and heart rate. The tests included NT-proBNP, C-reactive protein, electrocardiography and chest radiography. An expert panel made up of two cardiologists, a pulmonologist and a GP determined the presence or absence of heart failure by consensus. The panel used all available information, including echocardiography, but did not use NT-proBNP in making the diagnosis. When there was no consensus, the majority decision was used to allocate the diagnostic category. Whenever a situation of evenly split votes arose, the majority decision amongst the two cardiologists and the GP

was used to reach a diagnosis, thus leaving out the vote of the pulmonologist. The situation of split vote only occurred in a minority of the cases (5/405, 1%). The authors re-presented a random sample of patients to the expert panel, blinded to the original decision, and found excellent level of reproducibility (Cohen's $k = 0.92$).

A limited number of items from history could help GPs identify those with heart failure. NT-proBNP and electrocardiography were the two tests that were found to be useful in improving the accuracy of diagnosis. As fully appreciated by the study authors, the study suffers from the possibility of incorporation bias, except in the case of the index test of NT-proBNP, as results of this test were not made available to the consensus panel. The authors postulated that the magnitude of the incorporation bias is likely to have been small as most diagnostic determinants were not crucial in the panel diagnosis process. This postulate is supported by the use of echocardiography, which is central in the diagnosis of heart failure, only as part of the reference standard, and not as one of the index tests.

No specific algorithms or guidelines were given in the article on how the panel weighted and combined the various items of history, examination and investigations findings, although references were made to previous studies which may have given some guidance on this. Standardisation of the disease categorisation process and threshold for disease positivity are recognised to be problems with heart failure. It is not clear if domination by a specific person or persons in the consensus panel was an issue, as this is certainly plausible when the panel has generalists and specialists with varying levels of expertise in cardiology. Despite these weaknesses, this study is an excellent example of the use of a consensus panel as a reference standard.

Latent class analysis

This group contains many variations, but all methods have in common the use of a statistical model to combine different pieces of information (test results) from each patient to construct a reference standard. These methods acknowledge that there is no gold standard and that the available tests are all related to the unknown true status: target condition present or absent.[64,83–89]

The problem that the outcome of interest cannot be measured directly occurs in many research situations. Examples include constructs such as intelligence, personality traits or, as in our case, the true diagnosis. These unobservable outcomes are named latent variables. These latent variables can only be measured indirectly by eliciting responses that are related to the construct of interest. These measurable responses are called indicators or manifest variables. Latent variable models are a group of methods that use the information from the manifest variables to identify subtypes of cases defined by the latent variable.

The problem of evaluating an index test in the absence of a gold standard can be viewed as a latent variable problem. In our case we have dichotomous latent variable, namely whether or not patients have the target condition. When the latent variable is categorical (dichotomous being a special case within this group), the latent models are referred to as latent class models, whereas when the latent variable is continuous they are named latent trait models. Results of the index test and other imperfect tests are then the observable (manifest) variables that can be used to estimate the parameters that are linked to true diseases status, like sensitivity, specificity and prevalence. Maximum likelihood methods can be used to estimate these parameters of the latent model.

The latent class approach has similarities with the panel or consensus diagnosis methods, which also uses multiple pieces of information to construct a reference standard. In the panel method, experts determine whether each patient has the target condition given a set of test results, whereas a formal statistical model is used to obtain the statistics of interest in the latent class approach.

Basic model

The statistical framework underlying latent class models can be illustrated using the following basic example. In this example we have three different tests being applied in all patients with each test producing a dichotomous test result (e.g the test is either positive or negative). All three tests relate to the same target condition, but none of them is error free. For a single test, the probability of obtaining a positive test result can be written as the sum of finding a positive test in a patient who has the target condition (true positive result) or a positive test result in a patient without the target condition (false positive result). These probabilities (Prob) can be written as a function of the following unknown measures: prevalence (prev), sensitivity of test 1 ($sens_1$) and specificity of test 1 ($spec_1$). The probability of finding a true positive result for test 1 (TP_1) can be written as

$$\text{Prob}(TP_1) = \text{prev} \times \text{sens}_1$$

and the probability for obtaining a false positive result (FP) as

$$\text{Prob}(FP_1) = (1 - \text{prev}) \times (1 - \text{spec}_1)$$

Therefore, the probability of a positive test results for test 1 is the sum of these two probabilities

$$\text{Prob}(+) = \text{Prob}(TP_1) + \text{Prob}(FP_1) = \text{prev} \times \text{sens}_1 + (1 - \text{prev}) \times (1 - \text{spec}_1) \quad (1)$$

In the same way, we can write the probability for obtaining a true negative (TN) result as

$$\text{Prob}(TN_1) = (1 - \text{prev}) \times \text{spec}_1$$

and for a false negative (FN) test result as

$$\text{Prob}(FN_1) = \text{prev} \times (1 - \text{sens}_1)$$

and the probability of a negative test result as

$$\text{Prob}(-) = \text{Prob}(TN_1) + \text{Prob}(FN_1) = (1 - \text{prev}) \times \text{spec}_1 + \text{prev} \times (1 - \text{sens}_1) \quad (2)$$

Of course, the probabilities of the other tests are defined in the same way, but then using the sensitivity and specificity of that specific test. This means that there are seven unknown parameters in this example: one prevalence parameter and the sensitivity and specificity for each of the three tests (1 + 6 = 7).

With three different dichotomous tests, there are eight possible combinations of test results: all tests being positive, three variations where two tests are positive and one negative, three situations where one test is positive and two negative, and the situation where all tests are negative. By using the probabilities for a positive [equation (1)] or negative test result [equation (2)] for each test, we can write down the likelihood of observing each pattern of test results. Under the assumption of statistical independence, the likelihood of observing a specific pattern can be written as the probability of observing that pattern in patients who have the target condition plus the probability of observing the same pattern in patients without the target condition.

For instance, the probability of observing the pattern ++– is

$$\text{Prob}(++-) = \text{sens}_1 \times \text{sens}_2 \times (1 - \text{sens}_3) \times \text{prev} + (1 - \text{spec}_1) \times (1 - \text{spec}_2) \times \text{spec}_3) \times (1 - \text{prev})$$

When we carry out such a study, we would observe the number of patients for each of the eight patterns of test results. The sum of these numbers has to be equal to the total number of patients in the study, which means that we have 8 – 1 = 7 degrees of freedom. If the degrees of freedom are equal to or greater than the number of parameters to be estimated, standard maximum likelihood methods can be used to obtain a (unique) solution. More mathematical details can be found elsewhere.[85,90]

Extensions of the basic latent class model

Several extensions to this basic model (dichotomous latent variable, three dichotomous tests assuming uncorrelated errors) have been formulated. Here we discuss the main extensions relevant for diagnostic research.

The number and type of tests

Latent class models are flexible and can incorporate dichotomous results, but also ordinal test results or continuous test results.[90] The model can easily be extended to incorporate the results of more than three tests. Including additional tests is beneficial from a modelling point of view as it increases the available degrees of freedom (more tests lead to more test results combinations). More degrees of freedom mean that more parameters can be estimated, for instance a correlation parameter to acknowledge that errors between tests might be correlated (see also the section below on conditional dependence). The extra degrees of freedom can also be used for additional checks of the fit of the model.

Much attention has been given to estimating the accuracy of a test when only one other additional test (e.g. imperfect reference standard) is available.[91,92] In this case, the number of parameters to estimate (1 prevalence + 2 sensitivities + 2 specificities = 5 unknown parameters) is larger than the available degrees of freedom (4 test results combinations: ++, +–, –+, –– minus 1 = 3 degrees of freedom). This means that no optimal maximum likelihood solution can be identified: different combinations of values of prevalence, sensitivities and specificities fit the data equally well. Only through restrictions can we estimate the parameters of the model, for instance assuming that the sensitivities and specificities of the two tests are equal. Another option is to incorporate prior information about the parameters into the model by using a Bayesian approach to estimate their values (see the section 'Bayesian framework', p. 28).

Conditional dependence

The basic model assumed that the results of the three available tests were independent conditional

on the true disease status, also known as local independence. Independence in this context means that the errors of the test are not correlated, e.g. if a diseased patient is misclassified by one test, it does not increase the likelihood that this patient will be misclassified by another test. In other words, there is no group of 'difficult' patients in whom several tests perform less than expected. This assumption might hold if tests measure different manifestations of the target condition and/or use different clinical methods. In the detection of *Chlamydia*, for example, when antigen detection with EIA, cell culture and DNA amplification with PCR is used, it is less likely that these tests make the same type of errors than if two of the three tests were DNA amplication tests. An example where the assumption of conditional independence is likely to be violated is in the detection of lumbar herniation if all three available tests are imaging tests, such as magnetic resonance imaging (MRI), CT and radiography, all focusing at the detection of visible abnormalities of the discus.

For many situations, the independence assumption is unlikely to be true. Ignoring the correlation of errors between tests can seriously affect the estimates of accuracy.[26,64] To solve this problem, we can incorporate the correlation of errors between tests into the model.[26,88] This requires the estimation of additional parameters and therefore more degrees of freedom to estimate them. Additional degrees of freedom can be obtained by including more tests, repeating the study in another population with a different prevalence of the condition (but unchanged accuracy estimates) or incorporating prior information using a Bayesian framework (see the next section).

Bayesian framework

The parameters of a latent class model can also be estimated through a Bayesian approach instead of the more traditional maximum likelihood estimation (frequentist approach). The Bayesian framework estimates the same latent model and parameters, but it explicitly incorporates prior information to the model.[54,91,93–95] In the Bayesian approach, the unknown parameters are all treated as random variables having a probability distribution. Information available on each parameter prior to collecting the data is summarised in the prior probability distribution, which is then combined with information from the observed data to obtain a posterior probability distribution for each parameter. The posterior distribution can be used to obtain point estimates for the mean and median sensitivity and specificity with credibility intervals, which can be loosely interpreted as Bayesian CIs.

Prior distributions typically are uninformative or determined from the published literature or in consultation with experts. The Bayesian approach is sensitive to the chosen prior distribution used: using different priors can lead to differences in estimates of diagnostic accuracy.

The Bayesian approach can be particular helpful in ill-defined situations, such as situations where the number of parameters to be estimated is large relative to the available degrees of freedom. The use of prior information in combination with simulations means that the Bayesian approach can obtain estimates where traditional methods fail.[96] Bayesian modelling is more complicated as it requires programming, simulations and validations of the results.

Strengths and weaknesses

The latent class analysis methods are well documented, statistically sound and have been applied in many areas of research.[90] The characteristics of this method have been extensively studied, including in simulations studies[64,85,88] and in studies that compare latent class estimates of accuracy with the estimates derived from a classic design where a gold standard was available.[97] The model provides estimates of sensitivity and specificity for all tests incorporated in the model, which are the indexes most commonly used in test evaluation research. Latent class analysis is a flexible approach that can incorporate different types of test results (dichotomous, ordinal and continuous).

The drawbacks of latent class analysis are well described in the literature.[64,85,89] The greatest concern is not related to statistical issues but to a more basic principle. In a latent class analysis, the target condition is not defined in a clinical sense. Because we make no clinical definition of disease in latent class analysis, clinicians can feel uncomfortable about what the results represent.[24,64,85]

Latent class analysis does not fully comply with a basic principle of test evaluation research. When evaluating the performance of an index test, it needs to be compared with a standard that is independent of the index test itself. In latent class analysis, however, this principle is partly violated because the index test results are often used to construct the reference standard. Considerations similar to those mentioned in the panel diagnosis

methods apply (see the section 'Panel or consensus diagnosis', p. 24). This problem lies more in the panel method because experts may overestimate the capabilities of the index test, whereas in the latent class setting a formal statistical model is applied, which is not sensitive like humans to the reputation of any test.

Like any statistical model, the validity of the results of a latent class model depends on whether the underlying assumptions are met. Whether or not a latent class model assumes conditional independence is a critical issue. Simulation studies have shown that violation of conditional independence biases the estimates of diagnostic accuracy.[26,64] If tests are positively related to diseased and/or not diseased patients, latent class analysis will yield accuracy estimates which are too high, especially for the more accurate test. A problem is that the conditional independence assumption cannot be fully tested in a model with three dichotomous tests. Additional or repeated testing to increase the degrees of freedom might not be feasible for ethical or economic reasons.

These observations have led to caution against the use of latent class analysis in practice when only three tests are available. Some even extrapolate this view to all latent class models, as even when it is possible to incorporate more information in the model, unverifiable assumptions about dependence are still required.[64,85]

Field of application

Latent class analysis can be applied in those situations where multiple pieces of information are available for each patient.

Software

Several more advanced statistical packages have implemented latent class analysis, such as Splus and R. In addition, there are programs specially developed for latent variable models such as Latent Gold and LEM. Free software to perform Bayesian latent class analysis is available, requiring only a user registration (WinBugs).

Clinical example

In the detection of *Chlamydia trachomatis*, culture, DNA amplification methods such as PCR and antigen detection methods such as EIA have been modelled with latent class analysis (the same example is also used in discrepant analysis and latent class analysis). Culture is believed to have nearly perfect specificity. PCR and EIA are believed to be more sensitive than culture to detect *Chlamydia trachomatis*. In *Table 10*, we present the observed test results of these tests in a group of 324 persons, as reported by Alonzo and Pepe.[64] The frequency of occurrence for each pattern of test results is given. Latent class analysis uses the information displayed in the table to determine associations between the diagnostic tests. More detail on the analytical expressions for estimates can be found in the paper by Pepe and Janes.[85] Referring to the detection of *Chlamydia trachomatis* with cell culture as the imperfect reference standard, specificity is assumed to be close to 100%, whereas a wide range of values have been reported for its sensitivity.[93,98,99] Different priors can be incorporated in the Bayesian approach, for instance an optimistic prior (using a uniform distribution in the range 80–90%) and a pessimistic prior (in the range 55–65%) for the sensitivity of culture. If nothing is known about the index test, a prior distribution for sensitivity and specificity allowing equal weighting in the 0–100% range can be used.

TABLE 10 *Pattern of tests results and their frequency of occurrence*

Pattern	PCR	EIA	Culture	Observed frequency
1	+	+	+	19
2	+	+	–	4
3	+	–	+	3
4	–	+	+	1
5	+	–	–	2
6	–	+	–	3
7	–	–	+	0
8	–	–	–	292

Parameter estimates derived from latent class analysis are as follows:

Prevalence:	0.081
Sensitivity and specificity of EIA:	0.909 and 0.990
Sensitivity and specificity of culture:	0.834 and 0.997
Sensitivity and specificity of PCR:	1.000 and 0.995

Validate index test results

In all previous methods, the focus was on correcting imperfect reference standards, or constructing a new or better reference standard, to calculate the classical indexes of diagnostic test accuracy such as sensitivity and specificity. In this section, we discuss approaches to evaluate index

test results that go beyond the diagnostic accuracy paradigm. Validation is an alternative process to evaluate a medical test in the absence of an unproblematic and equivocal reference standard. In this context, validity refers to how well the index test measures what it is supposed to be measuring.[100–102]

Many instruments in the social sciences and elsewhere in science rely on a validation process to determine whether or not the instrument can serve its purpose. In these cases, the diagnostic accuracy paradigm often cannot be used because the 'truth' cannot be observed. The latter applies to many hypothetical or conceptual constructs. We cannot observe a construct, or any latent variable (see the section 'Latent class analysis', p. 26). What we can do is to observe associated attributes, as, for instance, sweating, moaning and asking for pain medication in the evaluation of pain.[101,103] In a similar way, we can evaluate associations between the index test and these attributes.

Three different forms of validity have traditionally been distinguished: content validity, criterion-related validity and construct validity.[101] In this context the classical diagnostic accuracy design (*Figure 1*, p. 2) refers to criterion-related validity where the reference standard provides the criterion against which the index test is validated. Several other definitions have been provided, including intrinsic validity, logical and empirical validity, factorial validity and face validity. This proliferation is in part based on a misinterpretation of the classical paper by Cronbach and Meehl, who pointed to the quintessential nature of **construct validation** in all areas where criterion-oriented definitions cannot be used.[104]

Approaches towards the validation of medical tests explore meaningful relations between index test results and other test results or clinical characteristics, none of which can be uplifted to the status of a reference standard, either isolated or in combination. Relevant items can come from the patients' history, clinical examination, imaging, laboratory or function tests, severity scores and prognostic information.

Construct validity is not determined by a single statistic, but by a body of research that demonstrates the relationship between the test and the target condition that it is intended to identify or characterise. Validating a test can then be understood as a gradual process whereby we determine the degree of confidence we can place on inferences about the target condition in tested patients, based on their index test results. That degree of confidence is based on a network of associations between the test results and other pieces of information in tested patients.

One important way to validate an index test is to use dedicated follow-up to capture clinical events of interest in relation to index test results. If the index test will be used for predicting future events, such a prognostic study can be seen as an evaluation of the predictive validity of the test.[101] The question of whether it is safe to withhold further testing in patients with low probability of pulmonary embolism and a negative D-dimer result has been studied by looking at the 3-month incidence of venous thromboembolism, and reported as such.[61]

One step further is the evaluation of a test within randomised clinical trials of therapy. One aim of the test is to identify patients who are more likely to benefit from the new, active treatment.[105,106] A possible design corresponding to that study question is displayed in *Figure 5*.

Note that all patients receive the index test, but that none of them receives a reference standard. After testing, patients are randomly allocated to either treatment or clinical follow-up. At the end of follow-up, the data collected can be displayed in four 2-by-2 tables (*Figure 5*). Different study objectives can be answered by these tables. In Tables A and B in *Figure 5*, a conclusion can be drawn as to whether treatment is beneficial compared with clinical follow-up in index test positive patients and test negative patients, respectively. Odds ratios and CIs can be calculated to underpin the conclusions. In Tables C and D, conclusions can be drawn concerning the prognostic value of the test within the context of subsequent clinical decision-making. Table C refers to the ability of the index test to identify patients who are likely to benefit from therapy. The test properties can be either expressed as event rates (of, for example, poor events) or odds ratios. Table D refers to the ability to discriminate between different risk categories for a specific event. Several modifications of the basic randomised controlled trial (RCT) model to evaluate tests have been described by Lijmer and Bossuyt.[105]

Basic design

No single basic design exists for construct validation studies. There are many possible designs to evaluate the validity of an index, as there are many different predictions possible based on our theory or construct.

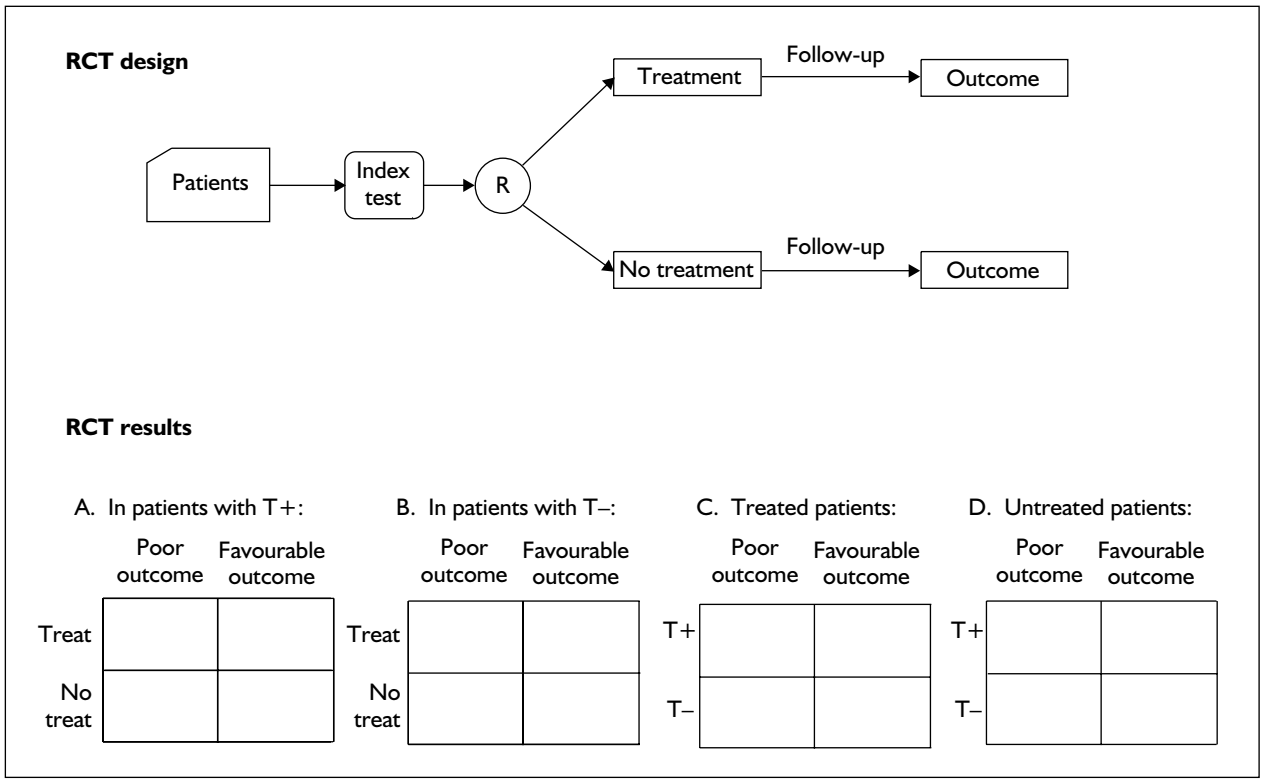

FIGURE 5 *Randomised controlled trial (RCT) using index test results as a prognostic marker (T = test)*

As an example, we look at the evaluation of a new questionnaire to evaluate psychological stress. Many hypotheses may be generated, including that level of stress increases heart frequency, and also blood values of cortisol. An association study could be conducted to evaluate the correlation between the score, heart frequency, blood levels of cortisol and past exposure to psychological stress, such as surviving a Tsunami. An additional approach would be to perform a factor analysis, to evaluate whether the elements of the questionnaire belong to one or more dimensions (factors), and to match if the identified factors correspond with the theory of psychological stress. Still another theory could point out that stress is artificially induced by an intervention, such as showing pictures of tortured persons. If so, participants should have higher scores on the questionnaire after such an intervention. Stated alternatively: if patients with high scores are given a tranquilliser, then their scores should drop. Here an intervention study would be conducted. If scores drop after tranquilliser intake in those with initially high scores, whereas those with low scores remain at approximately the same level, then the new questionnaire can be considered to have construct validity. Additional studies would have to be conducted. Gradually, our confidence in the construct validity and the inferences we can draw from measuring that construct will grow.

Several ways exist to express associations between the measured attribute and other attributes, events or subgroups, including correlation indexes, odds and risk ratios and absolute and relative differences.

Strengths and weaknesses

In situations where no reference standard is available, association studies may be the only type of study that can be performed. The validation of the index test will depend on the underlying theories about the target condition, as the latter provides us with hypotheses about the kind of associations between index test and attributes that have to be evaluated. If the theory is wrong, totally or in part, any quantitative expression of the strength of the association may be misleading.

Whenever the index test results fail to show the hypothesised network of associations between the target condition and other observations, more than one conclusion is possible: the index test has low validity, the theory about the target condition is not correct or both the index test and the theory are inadequate.

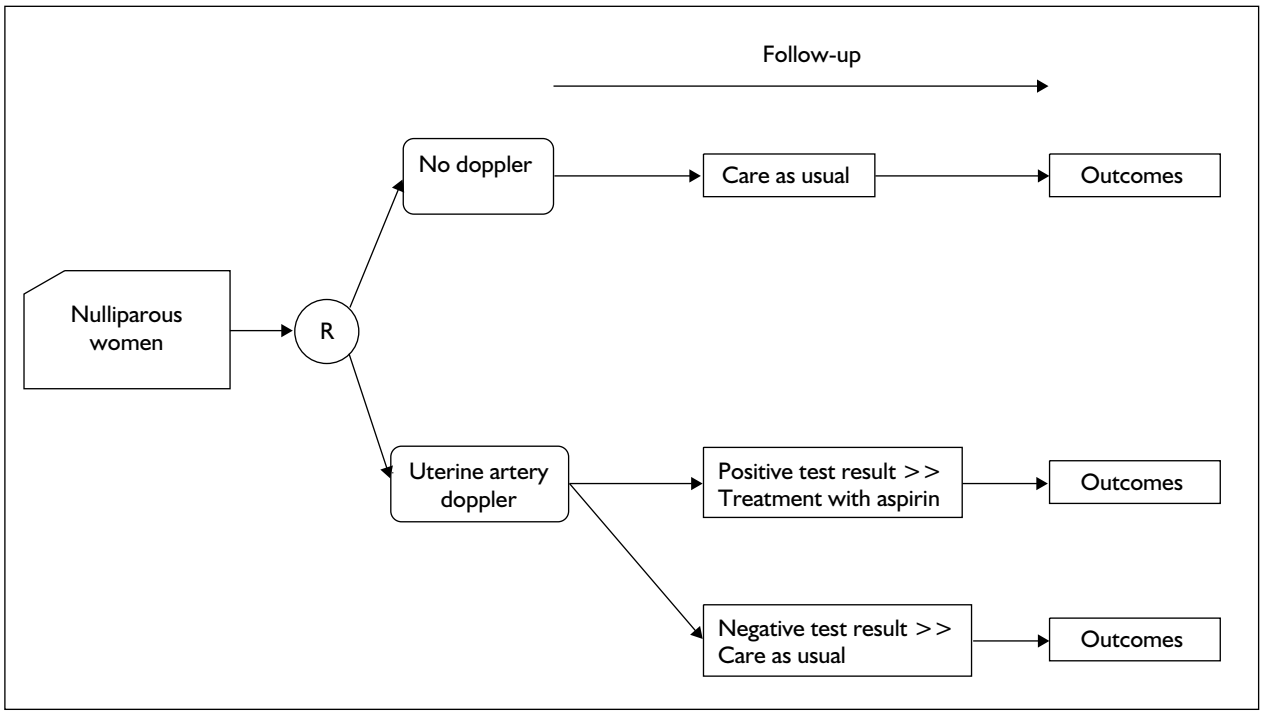

FIGURE 6 *Design of the uterine artery Doppler trial*

Specific problems related to clinical follow-up have been identified. The nature of the target condition may change during clinical follow-up. Even when present, the target condition is not guaranteed to produce detectable events or complaints. The length of follow-up has to be chosen judiciously for each specific target condition.

An additional problem arises when an intervention is used. If the intervention is chosen badly, and does not achieve what it was intended to achieve, the construct validity of the index test will be masked. If the outcome is favourable, any chance cannot be attributed exclusively to the discriminatory characteristics of the index test. Hence test evaluation and management consequences cannot be disentangled in this type of test evaluation.

A major drawback of construct validity is that there is no single type of study that can be prescribed, as in diagnostic accuracy studies. Several studies have to be performed, before enough confidence in the validity of the index test can be achieved.[107]

Field of application

We hypothesise that this type of test evaluation can be done in all areas of medicine where an accepted reference standard, or any other criterion to determine the diagnostic accuracy of a test, is absent. In the discussion (Chapter 5), we will argue that validation is a more universal way of appraising the value of medical tests.

Clinical example 1: randomised controlled trial

We will use a study by Subtil and colleagues titled 'Randomised comparison of uterine artery Doppler and aspirin (100 mg) with placebo in nulliparous women' to explain some of the design and efficiency issues that play a role when using an RCT to evaluate a test.[108]

The objective of this study was to assess the effectiveness of a strategy of pre-eclampsia prevention based on routine uterine artery Doppler examination during the second trimester of pregnancy, followed by a prescription of 100 mg of aspirin in those with abnormal Doppler, versus no Doppler strategy. The population were nulliparous women (no previous delivery before ⩾22 weeks) between 14 and 20 weeks' gestation, with no history of hypertension. Randomisation was used to determine whether women would receive uterine artery Doppler testing between 22 and 24 weeks or not. Women in the no testing arm of the trial would receive usual care, as would the women in the testing arm with a negative test result (for the design, see *Figure 6*). The outcomes of the trial were the development of pre-eclampsia, having a baby small for gestational age and perinatal deaths. The trial did not find a difference

in outcomes between the tested (Doppler group) and the non-tested group (no Doppler).

This design offers an assessment of the Doppler test and aspirin therapy combination, as women are randomised to Doppler or no Doppler groups, with treatment of the Doppler positive women in the Doppler arm. It addresses the question: does testing with Doppler (plus aspirin for test positive cases) prevent pre-eclampsia? In this design, if testing and treatment were shown not to be effective, it could be because the test is inaccurate or because aspirin is ineffective. This design, therefore, addresses two questions in one, but unfortunately, it is not often possible to segregate the accuracy of the test from the effectiveness of the treatment.

This design has various weaknesses. First, the design is not efficient and requires large samples to achieve satisfactory power. This is because the only women contributing to the expected difference in outcome in the two trial arms are those who belong to a small subgroup of those with abnormal Doppler result in the Doppler arm. In this study, 2491 women were randomised in a 2:1 ratio to Doppler and control arms, and of these 2491 women, an abnormal Doppler result was found in 239 (10%) women and these received aspirin. Even with a 2:1 ratio of randomisation to improve the numbers of women who had abnormal Doppler result (and, therefore, received the active treatment, aspirin), the total number of women who contributed to the difference between the Doppler and control arms was just 239, suggesting an under-powered study.

Even if this trial recruited many more thousands of women, and became adequately powered, and a benefit is subsequently shown for the Doppler arm, this may not be a vindication of benefit for the combination of Doppler test and aspirin therapy. This is because more women in the Doppler arm would have received aspirin compared with the no Doppler arm, and as aspirin has been shown to be generally effective in reducing pre-eclampsia,[109] then it is possible that the Doppler arm would have shown benefit regardless of whether the Doppler test was a good predictor of pre-eclampsia or not or, indeed, whether the Doppler test was done or not. This is because about 10% of women would have received aspirin in the Doppler group compared with none or few in the control group.

This design is, therefore, of limited use in assessing the role of uterine Doppler testing for aspirin therapy.

Clinical example 2 and 3: validation studies other than trials

An example of a validation approach can be found in a series of studies that evaluated the use of troponin to identify acute coronary syndrome in chest pain patients. Initial studies have evaluated cardiac troponin in an accuracy framework, using the original WHO definition of acute myocardial infarction. The latter invites the use of a composite reference standard, looking at characteristic ECG changes – either ST segment elevation or the development of new Q waves – confirmed by significant changes in serial cardiac enzymes.[110] Other studies have looked at 30-day outcomes in patients admitted without ST segment elevation on the initial ECG. They found that cardiac events increased significantly with increasing cardiac troponin values, suggesting that the degree of troponin elevation, and also clinical variables such as previous myocardial infarction and an ischaemic ECG, should be considered when deciding treatment.[111] These and other studies have led to the recommendation that cardiac troponins should be the preferred markers for the diagnosis of myocardial injury.[112] More recent investigations have indicated that increases in biomarkers upstream from markers of necrosis, such as inflammatory cytokines, cellular adhesion molecules, acute-phase reactants, plaque destabilisation and rupture biomarkers, biomarkers of ischaemia and biomarkers of myocardial stretch may provide an even earlier assessment of overall patient risk. The studies to support this claim are all closer to the validation framework than to the accuracy paradigm.[113]

Another example of association studies for test validation includes the evaluation of new tests for latent tuberculosis infection (LTBI), a condition for which no gold standard exists. The tuberculin skin test (TST) has been the standard test to detect LTBI, although it is known to have false results, particularly in people with previous Bacillus Calmette–Guérin (BCG) vaccination. Interferon-gamma assays (e.g. Quantiferon and Elispot) have recently been developed for use as new tests for LTBI. Tuberculosis infection evokes a strong T-helper 1 (Th1) type cell-mediated immune response with release of interferon-gamma. *In vitro* assessment of interferon-gamma production in response to mycobacterial antigens can be used to detect latent infection with *Mycobacterium tuberculosis*. Blood infected with *M. tuberculosis* contains a specific clone of T-lymphocytes stimulated by exposure to the ESAT-6 or CFP-10 antigen. The Elispot assay is based on the detection of interferon-gamma, which these

ESAT-6 and CFP-10 specific T lymphocytes secrete. As there is no gold standard or a suitable reference standard for LTBI against which the comparative accuracy of the TST and Elispot could be assessed, a validation study described below provides a good alternative to the classical diagnostic accuracy paradigm. The risk of infection is greatest among those contacts who share a room with the index case for the greatest length of time. This means that airborne transmission increases with length of exposure and proximity to an infectious case of tuberculosis. Hence results of tests for LTBI should correlate with level of exposure, and the test with the strongest association with exposure would be likely to be the most accurate. This issue can be evaluated in observational studies that ascertain exposure to tuberculosis in a relevant population and setting (e.g. outbreak investigation), perform various index tests of interest in all eligible subjects and compare test results with exposure status.[114] TST and Elispot response to ESAT-6 and CFP-10 were evaluated in this manner in 535 subjects during a school outbreak.[114] In this outbreak investigation, four exposure groups based on proximity and shared activities with an infected case were established following detailed interviews undertaken by a school nurse. The association of index test with exposure status was examined using the gradient of dose–response relating test results to degree of tuberculosis exposure. Comparison of these gradients showed that Elispot test was statistically significantly better than TST. Elispot correlated significantly more closely with *M. tuberculosis* exposure than did TST on the basis of measures of proximity ($p = 0.03$) and duration of exposure ($p = 0.007$) to the infected case. TST was significantly more likely to be positive in BCG-vaccinated than in non-vaccinated students ($p = 0.002$), whereas Elispot results were not associated with BCG vaccination ($p = 0.44$). The authors concluded that Elispot offers a more accurate approach than TST for identification of individuals who have LTBI. Further validation may come from observational studies evaluating whether new test results are predictive of development of active tuberculosis in the future.

Chapter 5

Guidance and discussion

In this report, we have summarised a number of methods that can be used to evaluate tests in the absence of a gold standard, an error-free method to establish with certainty the presence or absence of the target condition in tested patients. In this chapter we present our conclusions as guidance to researchers and emphasise the need to enrich or enlarge the accuracy paradigm in the evaluation of medical tests.

Guidance for researchers

The guidance we have distilled from the existing evidence and the recommendations from researchers can be summarised as follows (*Figure 7*). Readers should be aware that this flowchart can only provide general guidance because many factors have to be balanced when choosing one method over another.

The first question to be answered is whether the uncertainty about the test can be satisfactorily answered by knowing its accuracy. The diagnostic accuracy of a test is an expression of how well the test is able to identify tested persons with the target condition. The limits of this report do not allow us to discuss at length the various other ways in which a test can be evaluated, including randomised trials of test–treatment combinations that can document whether the use of a test will lead to improved patient outcomes.[106] We also omitted from consideration many of the lower-level evaluations that usually precede evaluations of diagnostic accuracy, including studies examining the reproducibility and intra- and inter-observer variability of tests.

We found that in situations that deviate only marginally from the classical diagnostic accuracy paradigm, for example, where there are few missing values on an otherwise acceptable reference standard or where the magnitude and type of imperfection in a reference standard is well documented, the methods we summarised may be valuable. However, in situations where an acceptable reference standard does not exist, holding on to the accuracy paradigm may be fruitless. In these situations, applying the concept of clinical test validation can provide a significant methodological advance (see also the next section of this chapter).

A different class of test evaluation methods focuses on changes in patient outcome from using tests. This class includes randomised clinical trials of tests: comparisons of testing versus not testing, or of one index test compared with another. As the number of testing strategies usually exceeds the number that can be adequately dealt with in an RCT, many researchers turn to modelling to explore the health consequences of testing. In decision analysis, data on test characteristics are combined with estimates of the effectiveness, risks and side-effects of treatment. A test's accuracy is not carved in stone, but will depend on the target condition that is to be detected. In talking about a test's accuracy, we will assume that the corresponding target condition has been defined.

If knowing a test's accuracy is important, the next question to ask is whether there is a reference standard providing adequate classification. This would be a reference standard about which there is consensus that it is the best available method for establishing the presence or absence of the target condition. In addition, researchers and readers should have confidence in the classification provided by reference standard, although misclassification should be considered in every accuracy study.

If the outcome of the reference standard cannot or has not been obtained in all study participants, statistical methods can be used to correct for the incomplete verification. The STARD statement encourages researchers to be explicit about missing information.[115] With small rates of missing information on reference standard outcome, these methods can be effectively used. For large volumes of missing data on the reference standard, the soundness of the approach depends on whether the mechanisms that led to the missing data are known. A general problem for these methods is that the general level of acceptance for correction techniques and for imputation methods is still fairly low.

If the pattern of missingness is not random, researchers could consider using a second

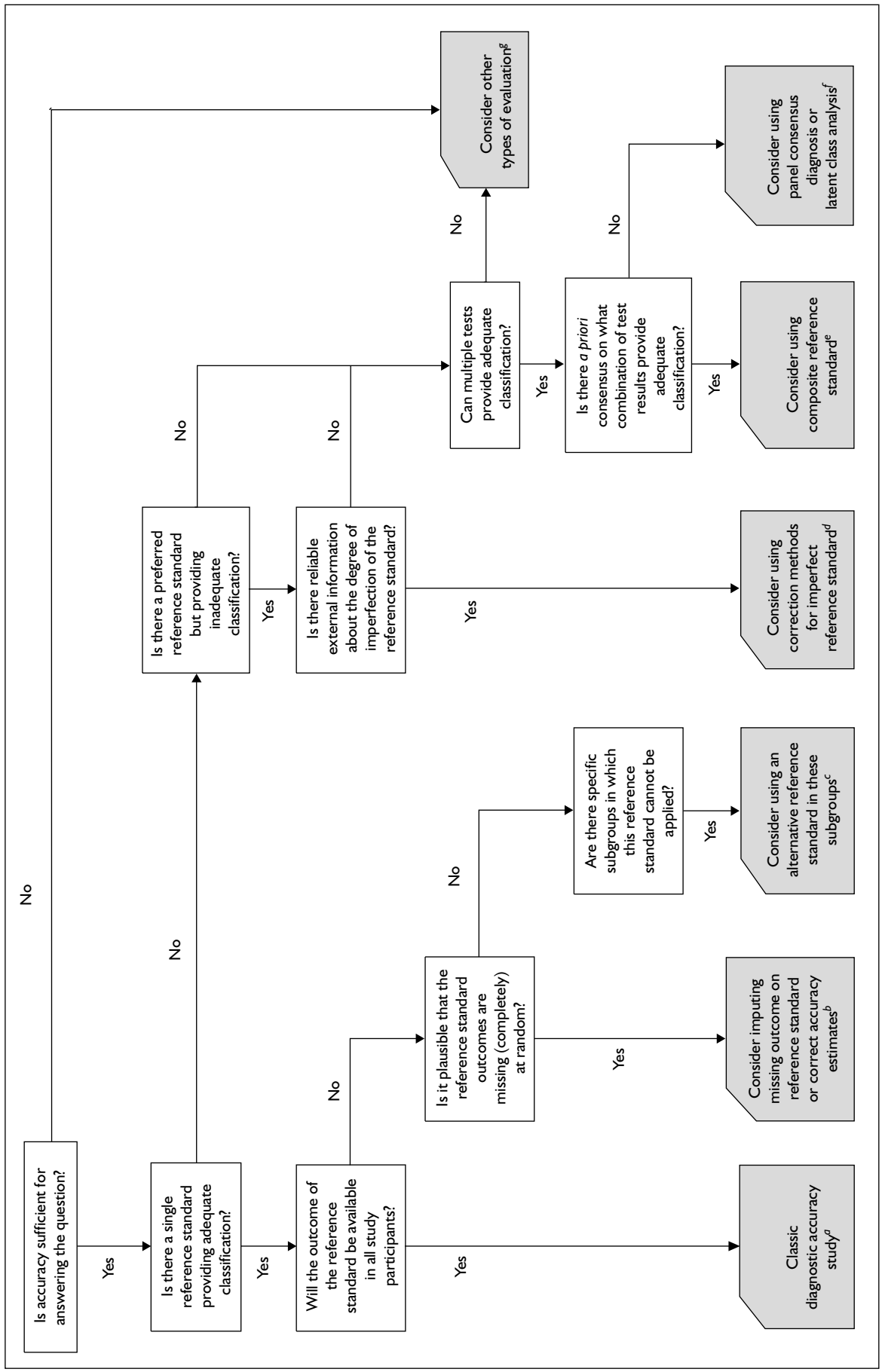

FIGURE 7 *Guidance for researchers when faced with no gold standard diagnostic research situations.*[a] *See Chapter 1.* [b] *See 'Impute or adjust for missing data on reference standard' (p. 13).* [c] *See 'Differential verification' (p.18).* [d] *See 'Correct imperfect reference standard' (p. 16).* [e] *See 'Composite reference standard' (p. 21).* [f] *See 'Panel or consensus diagnosis' (p. 24) and 'Latent data analysis' (p. 26).* [g] *See Chapter 5.*

reference standard in patients in whom the result of the first, intended reference standard is not available. The use of that second reference standard should preferably be stipulated in the protocol and reported as such. With differential verification, as in the use of one reference standard in test positive patients and a second one in test negative patients, the results should be reported for each reference standard to prevent bias.

If there is a reference standard but one that is known to be prone to error, statistical methods could be used to obtain estimates that are corrected for these reference standard errors. When there is an identified target condition but no available reference standard, the researcher may aim to construct one, based on two or more other tests. If these are used in a rule-based way to obtain information about the target condition, a composite reference standard has been constructed. If such a rule cannot be made explicit, it is possible to use a panel method, by inviting experts. An alternative method is the use of statistical techniques to obtain the most likely classification. By selecting one of these methods, the researchers – or the panel members – use their knowledge of the clinical target condition to identify variables or features that allow the identification of patients with that particular target condition.

With these techniques, there is an implicit assumption that they can be used to classify patients in previously unknown categories: the latent classes. This means that in latent class analysis the target condition is not defined in a clinical sense, but is a mathematically defined entity. The classification that comes out of the analysis may not fully coincide with pre-existing knowledge of the patients and the conditions that are amenable to treatment.

If none of these methods seem appropriate, the researchers have to turn to alternative methods for evaluation. Several proposals for a staged evaluation of tests have been made in the literature. A number of these focus on the added value or diagnostic gain of tests.[116] This includes studies that determine the added discriminatory power of tests, relative to pre-existing data from history, physical or previous tests. Multivariable logistic regression modelling is often used for this purpose, with the change in area under the curve as one of the statistics. The subjective side of the 'diagnostic gain' invites clinicians to express the reduction in experience they feel after having received the index test result. These reductions are elicited using visual analogue or quantitative scales. An additional step in these subjective approaches is to look at changes in management, either explicitly or in intended decisions.

Several authors have claimed that the accuracy paradigm is insufficient for evaluating the clinical usefulness of tests. The methods just mentioned can all be used, although most require an appropriate reference standard (diagnostic gain) or a clear link with management consequences (RCTs, decision analysis). We feel that there is both a need and a place for additional methods for exploring the likely clinical usefulness of tests. In the final section, below, we introduce the concept of test validation, a progressive exploration and testing of the tests results with other features, as a more general and more productive way of evaluating tests.

Limits to accuracy: towards a validation paradigm

In clinical medicine, tests are not only ordered for knowing the results for their own sake. A physician at the emergency department (ED) not only wants to know the concentration of cardiac troponin of the patient with chest pain, but also wants to know the likelihood of a diagnosis of acute coronary syndrome. In addition, he or she wants to know where to locate the patient in the risk spectrum of acute coronary syndrome.[77,117] The ED physician will probably rely on the troponin results and also on other findings in trying to find out what to do with the patient. Can this patient be safely sent home? Does the patient have to be admitted to the coronary care unit? Does the patient qualify for primary angioplasty? An umbrella question for these issues is: are patients with chest pain at the ED better off if they are routinely tested for troponin? In the answers to these questions, the exact value of the troponin concentration is an essential but insufficient element. It is not the attribute that is measured (troponin), but the level of confidence by which that attribute can be used to classify the patient in the risk spectrum of the acute coronary syndrome.

For decades, the diagnostic accuracy paradigm has been used to obtain answers to this type of question. It is difficult to pinpoint its origins exactly, but they go back well to – and beyond – Ledley and Lusted's seminal 1959 paper.[18] In its most classical sense, as can be found in all textbooks, the accuracy paradigm requires a gold standard, a technique used to identify with certainty patients with the disease of interest.

Pathophysiology and histology present the prototypical form of a gold standard: a method to determine unequivocally the presence or absence of disease in the human body. Sensitivity and specificity are the two best known statistics to express the results of the comparison of the test results with those of the gold standard.

The accuracy paradigm has proven to be a very valuable one. Its ubiquity has provided a focal point for the clinical evaluation of tests. The need for knowing the diagnostic accuracy of a test has prompted many useful evaluations. Reports of the poor sensitivity or specificity of a test are likely to inhibit the premature dissemination of tests in modern medicine.

The limited time frame of this report did not allow us to explore, analyse and speculate why the gold standard and the diagnostic accuracy paradigm have become so dominant in the evaluation of medical tests. We can only hint at the prevailing power of the classical view of clinical medicine, and its classical triad aetiognosis–diagnosis–prognosis. One can also point to the appealing simplicity of the basic accuracy design, which allows study results to be summarised in a very simple two-by-two table, or a slanted curve in two-dimensional ROC space. However, things should only be made as simple as possible and no simpler. Beyond any doubt, the prevailing accuracy paradigm is far from sufficient to cover all issues in the evaluation of the clinical evaluation of tests. We will summarise only a few of these issues here.

To start, many tests are not used for making a diagnosis at all. They are used for a variety of other purposes, such as guiding treatment decisions, monitoring treatment in chronic patients, informing patients and documenting changes in their condition, or for clinical or basic research. Many problems in present-day healthcare do not rely on issues of diagnosis, definitely not in chronic conditions, where patients are known to have diabetes, cardiovascular disease or COPD. The diagnostic accuracy paradigm cannot be simply applied in situations where tests are used for purposes other than diagnosis.

The second issue is the problematic relation between pathophysiology and diagnosis, and that between pathology and subsequent actions. Furthermore, the definition or the concept of a disease can change over time as new insights become available. The classical diagnosis of 'acute myocardial infarction' is now embedded in the spectrum of conditions known as 'acute coronary syndrome'. New management options and advances in testing can change the concept of disease, as in ectopic pregnancy. This diagnosis, once attached to a life-threatening condition, now covers subclinical conditions, such as 'throphoblast in regression'.[118] Advances in imaging allow the detection of even smaller, subsegmental pulmonary emboli or micro-metastases in patients with cancer. The current 'diagnoses' do not coincide with the older categories.

To some extent, this problem can be remedied by replacing the term 'disease' with 'target condition', as has been done in this report and elsewhere.[5] The target condition is a much broader concept, covering any particular disease, a disease stage or just any other identifiable condition that may prompt clinical action, such as further diagnostic testing or the initiation, modification or termination of treatment.

Another – and more widely documented – problem is the absence of a true gold standard to classify with certainty and without errors patients as having the target condition or not. In more cases than many imagine, such a gold standard simply does not exist. It definitely does not exist for many of the most prevalent chronic conditions, including diabetes, migraine and cardiovascular disease. For these problems, the term 'reference standard' has been introduced. This term acknowledges the absence of a 'gold standard' and refers to the best available method for classifying patients as having the target condition.

The term reference standard may seem like a solution, but in accordance with the Law of Frankenstein – 'the monster you create is yours, forever' – it also introduces ineradicable subjectivity. What should the reference standard be for appendicitis, or for deep venous thrombosis? Is it an image, or is it follow-up? The two methods will not yield identical results, and whereas one may be closer to pathophysiology, the other may be closer to patient outcome, the penultimate criterion for decisions in healthcare. A number of authors have suggested that these problems can be circumvented by jumping to the cornerstone of evaluations of interventions: the RCT. As summarised earlier in the report, RCTs cannot act as a panacea.[105,106] To allow meaningful interpretations of their results, such trials presume that the links between test results and subsequent clinical actions have been well established. That may not always be the case.

In our view, a move towards a test validation paradigm is justified. This means that scientists and

practitioners examine, using a number of different methods, whether the results of an index test are meaningful in practice. Validation will always be a gradual process. It will involve the scientific and clinical community defining a threshold, a point in the validation process, where the information gathered would be considered sufficient to allow clinical use of the test with confidence.

Validating a test is a process through which scientists and practitioners can find out whether the results of a test are meaningful. The process of validation will come after initial evaluations of the basic properties of the test: its reliability, consistency, trueness. Once these hurdles have been overcome, we can try to find out how and to what extent the test results fit in our understanding of a patient's condition, its likely causes and course.

To validate a test, we will have to build a conceptual framework, defining how the test results relate to other features. These features may be derived from history, from physical examination, from other test results, from follow-up or from response to treatment.

The concept of test validation encompasses the traditional notion of diagnostic accuracy. If there is an accepted pathophysiological gold standard, one that can be used to detect the presence of absence of disease with certainty, we can validate a test by comparing its results with the findings of the gold standard (criterion validity). Test validation also allows the option for evaluating test results of tests that are not used, or not used exclusively, in making a diagnosis.

Test validation is probably the way to go in case there is a test that is proclaimed to be 'better than the existing reference standard'. In these cases also, we have to show that the differences between that test and the reference standard are 'meaningful', by demonstrating reliable associations with other findings and test results.

The results of a validation process cannot be captured in simple statistics. The associations with other variables can and must be expressed in a quantitative sense, but they will never be reduced to a simple pair of numbers, as a test's sensitivity and specificity.

Discovering or demonstrating that test results are meaningful does not justify the use of that test in daily practice. In the end, the use of tests has to be justified by demonstrating that it leads to better healthcare, by improving outcome, reducing costs, or both.

Validation offers a way out of the dilemma introduced by the multiple fixes that are needed in order to cling to the diagnostic accuracy paradigm in the absence of an accepted gold standard. Replacing the gold standard by the reference standard, and the pathophysiological detection of disease by the identification of the target condition is not enough. Like all humans, we value simplicity, and the alluring attraction of two simple statistics makes it hard to give up the notion of fixed test characteristics. In some cases these fixes are feasible and reasonable, as has been summarised in this report. In others, we may well abandon the accuracy paradigm and replace it by a new one: the concept of the validation of medical tests.

Recommendations for further research

Diagnostic research with partial verification is common, this includes research based on routinely collected clinical data. There is a need to increase awareness that naïve estimates of accuracy by leaving out unverified patients from the calculation can lead to serious bias.

There is a need to perform empirical and simulation studies that will determine the potential and limitations of multiple imputation methods to reduce the bias caused by missing data on the reference standard.

In setting up consensus-based diagnosis, there are many practical choices to be made. These include the number of experts, the way patient information is presented, and how to obtain a final classification. There is a need to perform more methodological studies to provide guidance in this area.

There is a need to design studies that compare the results based on a consensus procedure with the results of latent class models when multiple pieces of information will be combined to construct a reference standard. Also there is a need to examine approaches that combine both procedures.

There is a need to develop more elaborate schemes outwith the accuracy paradigm for the validation of tests targeted at diseases or conditions for which there is no acceptable reference standard.

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Contribution of authors

Anna Rutjes (Research Fellow) was a co-applicant on the project grant application and worked on the development of the protocol, acted as a reviewer, and was involved in the drafting of methods and results. Johannes Reitsma (Senior Clinical Epidemiologist) was a co-applicant on the project grant application and carried out work on the development of the protocol, project management, supervision of review work, as well as drafting and editing of the final report. Arri Coomarasamy (Honorary Lecturer in Epidemiology) was a co-applicant on the project grant application and worked on the development of the protocol and on drafting the results. Khalid Khan (Professor of Obstetrics-Gynaecology and Clinical Epidemiology) was a main applicant on the project grant application and also carried out development of the protocol, project management, drafting of results and editing of the final report. Patrick Bossuyt (Professor and Chair of Department of Clinical Epidemiology) was a main applicant on the project grant application and worked on the development of the protocol, on drafting the results and contributed to discussion, as well as to editing the final report.

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Appendix 1

Search terms in databases

MEDLINE
Searched 6 October 2005 via OVID
Date coverage: 1966–September 2005
1. reference.ti.
2. gold.ti.
3. golden.ti.
4. test.ti.
5. standard.ti.
6. 1 or 2 or 3
7. 4 or 5
8. 6 and 7
9. absen$.ti.
10. reference test.ti.
11. 9 and 10
12. 9 and 1
13. 9 and 2
14. 9 and 3
15. 10 and 5
16. 8 or 11 or 12 or 13 or 14 or 15

Cochrane databases
(DARE, CENTRAL, CMR, NHS)
Searched 13 October 2005
1. reference.ti.
2. gold.ti.
3. golden.ti.
4. test.ti.
5. standard.ti.
6. 1 or 2 or 3
7. 4 or 5
8. 6 and 7
9. absen*.ti.
10. reference test.ti.
11. 9 and 10
12. 10 and 1
13. 9 and 2
14 9 and 3
15 9 and 5
16 8 or 11 or 12 or 13 or 14 or 15

Medion
Searched 24 November 2005 via www.mediondatabase.nl
Filter used: 'Methodological Studies on Systematic Reviews of Diagnostic Tests'
1. MKD (quality assessment)
2. MBD (bias in meta-analysis)
3. MH (heterogeneity)
4. MAD (several/methods)

EMBASE
Searched 6 October 2005 via OVID
Date coverage: 1980–September 2005
1. reference.ti.
2. gold.ti.
3. golden.ti.
4. test.ti.
5. standard.ti.
6. 1 or 2 or 3
7. 4 or 5
8. 6 and 7
9. absen$.ti.
10. reference test.ti.
11. 9 and 11
12. 9 and 1
13. 9 and 2
14. 9 and 3
15. 10 and 5
16. 8 or 11 or 12 or 13 or 14 or 15

Pubmed
Searched 6 October 2005 via www.pubmed.gov
Date coverage: 1966–October 2005
((("reference"[ti] OR "gold"[ti] OR "golden"[ti]) AND("test"[ti] OR "standard"[ti])) OR ((absen*[ti] AND gold*[ti]) OR ("no gold*"[ti]) OR (absen*[ti] AND referen*[ti]) OR (absen*[ti] AND standard[ti]) OR (absen*[ti] AND "reference test"[ti])))

Appendix 2

Experts in peer review process

We assembled a list of topic-specific experts outside our research team to review each method. In addition, several general experts reviewed the whole report.

Topic-specific experts

'Impute missing data on reference standard' and 'Correct imperfect reference standard'

Professor Aeilko H Zwinderman
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'Construct reference standard'

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'Validate index test results'

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General experts reviewing the full report

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The HTA Programme and the authors would like to know your views about this report.

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We look forward to hearing from you.

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