Diagnostic test accuracy evidence

In this guideline, diagnostic test accuracy (DTA) data are classified as any data in which a feature – be it a symptom, a risk factor, a test result or the output of some algorithm that combines many such features – is observed in some people who have the condition of interest at the time of the test and some people who do not.. Diagnostic accuracy data can be summarised in a number of ways. Those that were used for decision making in this guideline are as follows:

- **Positive likelihood ratios** describe how many times more likely positive features are in people with the condition compared to people without the condition. Values greater than 1 indicate that a positive result makes the condition more likely.
  - LR^+ = (TP/[TP+FN])/(FP/[FP+TN])
- **Negative likelihood ratios** describe how many times less likely negative features are in people with the condition compared to people without the condition. Values less than 1 indicate that a negative result makes the condition less likely.
  - LR^- = (FN/[TP+FN])/(TN/[FP+TN])
- **Sensitivity** is the probability that the feature will be positive in a person with the condition.
  - sensitivity = TP/(TP+FN)
- **Specificity** is the probability that the feature will be negative in a person without the condition.
  - specificity = TN/(FP+TN)
- P values refer to the percentage of participants with a continuous index test value sufficiently close to their score on the reference standard. In this review P values below P50 were deemed useful for decision making and data were found for P10, P15 and P30 (referring to the percentage of the total sample who had an index test score within 10%, 15% and 30% of their reference standard score, respectively).

Interpretation of diagnostic accuracy measures

Clinical decision thresholds were chosen by the committee to correspond to the likelihood ratio above (for positive likelihood ratios) or below (for negative likelihood ratios) which a diagnostic test was accurate enough to be recommended. The following schema, adapted from the suggestions of Jaeschke et al. (1994), was used inform these discussions.

Table 5: Interpretation of likelihood ratios

Value of the likelihood ratios	Interpretation
LR ≤ 0.1	**Very large** decrease in probability of disease
0.1 < LR ≤ 0.2	**Large** decrease in probability of disease
0.2 < LR ≤ 0.5	**Moderate** decrease in probability of disease
0.5 < LR ≤ 1.0	**Slight** decrease in probability of disease
1.0 < LR < 2.0	**Slight** increase in probability of disease
2.0 ≤ LR < 5.0	**Moderate** increase in probability of disease
5.0 ≤ LR < 10.0	**Large** increase in probability of disease
LR ≥ 10.0	**Very large** increase in probability of disease

The schema above has the effect of setting a minimal important difference for positive likelihoods ratio at 2, and a corresponding minimal important difference for negative

likelihood ratios at 0.5. Likelihood ratios (whether positive or negative) falling between these thresholds were judged to indicate no meaningful change in the probability of disease.

Quality assessment

Individual studies were quality assessed using the QUADAS-2 tool, which contains four domains: patient selection, index test, reference standard, and flow and timing. Each individual study was classified into one of the following two groups:

- Low risk of bias – Evidence of non-serious bias in zero or one domain.
- Moderate risk of bias – Evidence of non-serious bias in two domains only, or serious bias in one domain only.
- High risk of bias – Evidence of bias in at least three domains, or of serious bias in at least two domains.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, index features and/or reference standard in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, index feature and/or reference standard.
- Partially indirect – Important deviations from the protocol in one of the population, index feature and/or reference standard.
- Indirect – Important deviations from the protocol in at least two of the population, index feature and/or reference standard.

Methods for combining diagnostic test accuracy evidence

Meta-analysis of diagnostic test accuracy data was conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

Where applicable, diagnostic syntheses were stratified by:

- Presenting symptomatology (features shared by all participants in the study, but not all people who could be considered for a diagnosis in clinical practice).
- The reference standard used for true diagnosis.

Where five or more studies were available for all included strata, a bivariate model was fitted using the mada package in R v3.4.0, which accounts for the correlations between positive and negative likelihood ratios, and between sensitivities and specificities. Where sufficient data were not available (2-4 studies), separate independent pooling was performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity, using Microsoft Excel. This approach is conservative as it is likely to somewhat underestimate test accuracy, due to failing to account for the correlation and trade-off between sensitivity and specificity (see Deeks 2010).

Random-effects models (der Simonian and Laird) were fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results

from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Modified GRADE for diagnostic test accuracy evidence

GRADE has not been developed for use with diagnostic studies; therefore a modified approach was applied using the GRADE framework. GRADE assessments were only undertaken for positive and negative likelihood ratios, as the MIDs used to assess imprecision were based on these outcomes, but results for sensitivity and specificity are also presented alongside those data.

Cross-sectional and cohort studies (retrospective and prospective cohort studies) were initially rated as high-quality evidence if well conducted, and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness) as detailed in Table X below. All retrospective cohort studies were judged to be at moderate or high risk of bias.

Table 6: Rationale for downgrading quality of evidence for diagnostic questions

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.

GRADE criteria	Reasons for downgrading quality
Imprecision	If the 95% confidence interval for positive or negative likelihood ratios crossed the decision threshold for recommending a test the outcome was downgraded 1 level. If the 95% confidence interval crossed 1 (the likelihood ratio corresponding to no diagnostic utility), the outcome was downgraded 1 level. If the 95% confidence interval crossed 1 and the decision threshold for recommending a test the outcome was downgraded 2 levels as suffering from very serious imprecision. For information on how decision thresholds were determined, see the section on interpretation of diagnostic accuracy measures. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.