Estimating a test's accuracy using tailored meta-analysis – How setting-specific data may aid study selection

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Estimating a test's accuracy using tailored meta-analysis - the potential of setting-specific data in aiding study selection

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Abstract

Objective

To determine a plausible estimate for a test's performance in a specific target setting using a new method for selecting diagnostic test accuracy studies which are applicable to the setting.

Study design

It is shown how routine data collected on the test positive rate and the prevalence of disease for the setting of interest may be used to derive a region of performance for the test in receiver operating characteristic (ROC) space. After qualitative appraisal, studies are selected based on the probability that their study accuracy estimates arose from parameters lying in this 'applicable region'. Three methods for calculating these probabilities are developed and used to tailor the selection of studies for meta-analysis. The Pap test applied to the UK NHS cervical screening programme provides a case example.

Results

The original meta-analysis for the Pap test included 68 studies but at most 17 studies were considered applicable to the NHS. For conventional meta-analysis the sensitivity and specificity (with 95% confidence intervals) were estimated to be 72.8% (65.8-78.8) and 75.4% (68.1-81.5) compared with 50.9% (35.8-66.0) and 98.0% (95.4-99.1) from tailored meta-analysis using a binomial method for selection. The effect of this is that for a prevalence for Cervical Intraepithelial Neoplasia (CIN) 1 of 2.2%, the post-test probability for CIN 1 increases from 6.2% to 36.6% between the two methods of meta-analysis.

Conclusion

Tailored meta-analysis provides a method for augmenting study selection based on the study's applicability to a setting. As such the summary estimate is more likely to be plausible for a setting and could improve diagnostic prediction in practice.

1. Introduction

Ensuring that study results are applicable in practice or in a particular clinical setting poses a challenge to clinicians and policy makers. Yet this may not always be readily appreciated particularly when applying the results of diagnostic or screening test studies in practice; we shall see in the methods developed here, it is possible for studies to provide estimates of a test's performance which are highly improbable in some settings.

To facilitate diagnosis, the performance of a test is most usefully reported in terms of either its sensitivity and specificity or its positive and negative likelihood ratio - the latter two being directly derived from the former two [1,2]. The difficulties arise from these being dependent on external factors that may change individually or multiply between different settings. Variations in the disease prevalence [3,4], the work up of patients with other tests [3], the patient spectrum [5,6], and the execution of the test [7,8] may all contribute to differences in a test's performance between different surroundings [9]. Hence, a study of a diagnostic test represents a snap shot of its performance within a particular setting, with its own set of external factors.

With the potential for these external factors to vary between different settings, it is not surprising that heterogeneity is so widespread in diagnostic test accuracy (DTA) reviews and meta-analyses [10]. Although meta-analysis has allowed the study of test characteristics across a wide range of environments, the summary estimates they provide represent the average performance across all studies [11-13] and may not be representative of an individual clinical setting. This may be the case even when study selection is confined to a particular setting, such as primary care; the resulting summary (average) estimate may still misrepresent some individual primary care settings due to heterogeneity in the true test performance across settings.

This creates a problem for the current paradigm of evidence-based medicine, which is broadly based on ensuring that the best evidence is applied to clinical practice [14]. This usually relies upon the existing methods of critical appraisal being effective at identifying those studies which are representative of the setting in question. But without details of the external factors from both the study and the end user's population, how can we be sure that this is the case?

Rather than wholly relying on the effectiveness of critical appraisal to assess representativeness of studies, here an alternative method is proposed. For the purpose of meta-analysis, it will be demonstrated how basic data collection from the setting where the test is being applied may be used to tailor the selection of studies.

2. Method

The objective is to determine a plausible estimate for a test's performance in a specific setting given the combination of routine data from the setting and evidence from the literature. Broadly, the method relies upon first collecting actual data on the test positive rate and prevalence from the setting in question and using this to deduce a region of plausible values for the sensitivity and false positive rate for the test in the setting. This is then used to aid study selection for meta-analysis by comparing the sensitivities and false positive rates of studies with this region. This is now discussed more fully below.

2.1Defining a plausible region of performance for the setting
Although the true performance of a test within a setting may not be known there are quantities which may be measured in the practice setting which allow us to define a plausible region of performance – called the *applicable region* for the test from hereon.

(i) Using the test positive rate as a constraint
Normally, within practice the test results are unverified since the true diagnosis, established by applying a reference standard, is not known at the time of testing [15]. Consequently, the numbers of true positives, false positives, false negatives and true negatives are unknown. However, these quantities must be non-negative.

In some settings the unverified results of all patients tested in a clinical population are known; for instance, the total number of positive test results and the negative test results for a particular test threshold may be counted. Importantly these may be used to constrain the possible values that the test's sensitivity, s and false positive rate, f, may take within the practice setting.

If we define the test positive rate, r, as the proportion of all those tested who test positive for a particular threshold, then from these observations, the following condition may be deduced

$$\text{if} \quad f \leq s \text{ this implies } f \leq r \text{ and } s \geq r \qquad (1)$$

Thus, providing the test is able to classify subjects better than a random process, we can define the range of possible values that the false positive rate (FPR) and sensitivity may take in the (*f, s*) plane or ROC space (after Receiver Operating Characteristic curve) [16].

If our estimate of *r* is unbiased and precise (zero standard error), since these are mathematical constraints, the effect of imposing them is to make large areas of ROC space mathematically impossible. Although such accuracy and precision is unlikely in practice, these inequalities still serve to define the applicable region in ROC space representing the feasible values for the test's performance within the setting in question.

The size of the applicable region is determined in part by the precision of our estimate for *r*, since it affects the width of the confidence interval. Figure 1 demonstrates the effect an interval estimate for $0.15 \leq r \leq 0.3$ (bold boundary) has on the shape of the applicable region for a point estimate $r = 0.225$. The locations of the boundaries are defined by the upper and lower limits of the interval.

To summarise, the test positive rate may be derived by counting the number of patients testing positive as a proportion of the total number of patients tested within the target setting and a confidence interval estimate may be obtained readily from this. As a result, clinicians who frequently apply a particular test in practice could feasibly collect their own data to help define their own applicable region for the test.

The applicable region for the test may be refined further by incorporating knowledge of the prevalence of the target disorder in clinical practice.

(ii) Incorporating knowledge of the local prevalence
Suppose the prevalence of the target disorder for the setting of interest, *p* may be estimated, then, it follows from the definitions of the prevalence and sensitivity, *s* (see appendix 1) that

$$s = \frac{r}{p} - \frac{(1-p)f}{p} \qquad (2)$$

5

If it was possible to have perfect knowledge for *r* and *p* this would constrain the sensitivity and false positive rate for the test in clinical practice to a straight line. Although including uncertainty in the estimates for *r* and *p* widens the applicable region from a straight line to a polygonal area, the area is still narrower than when information on the prevalence is not included.

Unlike *r*, it is more difficult to estimate *p* with both accuracy and precision. The best estimate is obtained from verifying (applying the reference standard to) all the patients in the setting, and is therefore unavailable. Accurate estimates of *p* may be obtained from verifying a small sub-sample of patients in the setting as a form of calibration, but with an obvious loss in precision; such as, taking a swab (reference standard) from a sub-sample of patients when the test is a prediction rule for infection.

More usually, estimates of the prevalence are derived from sources outside of the setting and so risk being inaccurate for the setting in question. For example, local laboratories may have estimates of disease prevalence for the locality. A Bayesian argument could be used where the interval estimate is based on belief either from previous test results or where the empirical estimate for the prevalence is believed to be potentially biased. Thus, in a Bayesian framework, any summary estimate for the test (see 2.3) is conditioned on this interval estimate for the prevalence.

In figure 2, the applicable region shown in figure 1 is refined using an interval estimate for the prevalence, for $0.05 \leq p \leq 0.12$. For each (*r, p*) pair a straight line constraint (labelled 1 to 4) is generated and these are illustrated for (*r*=0.15, *p*=0.12), (*r*=0.15, *p*=0.05), (*r*=0.30, *p*=0.12), (*r*=0.30, *p*=0.05), respectively.

The dotted lines for constraints 2 and 3 are used to demonstrate the fact that these constraints are surplus or 'dominated' by the other two constraints (1, 4). This follows since if the 'true' sensitivity and FPR for the test is located to the right of 2 it will always lie to the right of 1, but not vice versa. Similarly, 3 is surplus when compared with 4.

2.2 Study selection based on the applicable region

In contrast to conventional meta-analysis, where studies are selected on the basis of qualitative criteria alone, here we propose to augment this process by selecting only those studies which report performances which are compatible with the setting in question. To do this requires an appropriate test procedure which incorporates the constraints defining the applicable region.

We are interested in only those studies whose 'true' sensitivity and FPR are likely to lie in the applicable region, so we may 'tailor' the selection of studies for meta-analysis to the setting in question. The test procedure used for selecting studies is dependent on whether we have knowledge of the test positive rate only or knowledge of both the test positive rate and prevalence where deriving the applicable region. The two cases are discussed below.

(i) Knowledge of the test positive rate only

Suppose r is estimated by some confidence interval with a level of significance, α, then we know within a classical framework that the parameter ('true' value) for the test positive rate, μ_r, will be present in the interval $100(1-\alpha)\%$ of the time in the long run [17]. We will assume μ_r is contained in the interval. This is reasonable if we choose α so there is a high coverage probability, and suggest α is no more than 0.01. This will lead to a loss of precision in the estimate for r which may be mitigated by ensuring a large sample size.

Let μ_f, and μ_s be the parameters for the FPR and sensitivity, respectively for the test in the setting of interest. From (2) we have $\mu_f \leq \mu_r$ and $\mu_s \geq \mu_r$ whenever $\mu_f \leq \mu_s$. Since $r_{lcl} \leq \mu_r \leq r_{ucl}$, where r_{lcl} and r_{ucl} are the lower and upper confidence limits for r, the most extreme value for μ_f lies on the boundary when $\mu_f = r_{ucl}$.

Similarly, for a study i to be compatible with the setting of interest its parameter $\mu_{f,i}$ must lie in the applicable region. Its maximum permitted value is when it lies on the boundary when $\mu_{f,i} = r_{ucl}$. Thus, for studies lying to the right of this boundary we test whether the study estimate for the FPR, $\hat{f}_i$, arises from a distribution whose parameter $\mu_{f,i}$ lies on the boundary of the applicable region. Since the FPR, f_i has a binomial distribution we may calculate the probability of f_i being equal to or more extreme than the study estimate $\hat{f}_i$ given that $\mu_{f,i} = r_{ucl}$.

The FPR is constant along the vertical boundary (see figure 1) so we do not need to consider the sensitivity of the study when testing hypotheses.

Hence, we suggest the following test procedure (referred to here as the '*B1 method*') for selecting studies: for study i, the null hypothesis H_0: $\mu_{f,i} = r_{ucl}$ is rejected in favour of the alternative hypothesis, H_1: $\mu_{f,i} > r_{ucl}$ if the tail area binomial probability $P(f_i \geq \hat{f_i}) < \beta$ for level of significance β. Studies are excluded if H_0 is rejected. This provides an exact approach given the assumption that μ_r lies in the confidence interval for r.

Note it is possible for studies lying outside of the applicable region to lie closer to the horizontal boundary, $s = r_{lcl}$ than the vertical boundary $f = r_{ucl}$. On such occasions we proceed as above but test the null hypothesis of H_0: $\mu_{s,i} = r_{lcl}$ versus the alternative H_1: $\mu_{s,i} < r_{lcl}$.

(ii) *Knowledge of test positive rate and prevalence*

Although knowledge of the prevalence within a setting does not allow us to make any assertions on the sensitivity and FPR for the setting (see appendix 1), in combination with the test positive rate we may refine the size of the applicable region for the setting.

Again we know that the parameters μ_p and μ_r for the prevalence and test positive rate respectively will lie in their 100 $(1- \alpha)$% confidence intervals, with a coverage probability of $1- \alpha$. If we assume p and r to be independent then the coverage probability for both μ_p and μ_r being in their respective 95% confidence intervals at the same time is approximately 0.9. However, this probability is likely to be higher, since (1) may be derived from assuming p and r to be positively correlated [18]. Clearly, this coverage probability is dependent on the value of α chosen, but we will assume that μ_r and μ_p for the setting actually lie in their respective intervals by always choosing $\alpha \leq 0.01$.

Our aim is to select only those studies which have parameters for the sensitivity and FPR, $(\mu_{f,i}, \mu_{s,i})$ that lie in the applicable region. Other studies, which have $(\mu_{f,i}, \mu_{s,i})$ outside the applicable region, are considered implausible for the setting. Consistent with other models we will assume that for a single observation from each study i, the sensitivity, s_i and FPR, f_i are independent [11,12] and that both have binomial distributions [12].

If a study reports an estimate $(\hat{f}_i, \hat{s}_i)$ which lies in the applicable region we have no grounds for excluding it, since based on a single observation the maximum likelihood estimate (MLE) [19] for $(\mu_{f,i}, \mu_{s,i})$ must equal $(\hat{f}_i, \hat{s}_i)$. For studies which report estimates which lie outside of the applicable region we derive the MLE $(\mu_{max,f,i}, \mu_{max,s,i})$ for potential $(\mu_{f,i}, \mu_{s,i})$ pairs which are constrained to lie in the applicable region, (see Appendix 2).

Once $(\mu_{max,f,i}, \mu_{max,s,i})$ has been found, we may calculate the tail area probability, P_i of the study i producing an estimate $(f_i \geq \hat{f}_i, s_i \geq \hat{s}_i)$ given a parameter pair $(\mu_{max,f,i}, \mu_{max,s,i})$. Hence we have the following test procedure, ('*the B2 method*'): if we denote the applicable region by A, we reject the null hypothesis H_0: $(\mu_{f,i}, \mu_{s,i}) \in A$ in favour of H_1: $(\mu_{f,i}, \mu_{s,i}) \in A^c$ if $P_i < \beta$, where A^c is the complement of A (i.e. all points outside of the applicable region), and β is the level of significance. The study is excluded if H_0 is rejected and this method provides an exact approach given the assumptions on μ_r and μ_p lying in the respective intervals for r and p.

There are other approaches for estimating $\mu_{max,f,i}$ and $\mu_{max,s,i}$ based on assuming that the FPR and sensitivity for each study have independent but normal distributions. The estimate for $\mu_{max,f,i}$ and $\mu_{max,s,i}$ corresponds to the point on the boundary which minimises the 'statistical distance' called the Mahalanobis distance, D_i^2 between the boundary and the study estimate $(\hat{f}_i, \hat{s}_i)$ [20]. Here D_i^2 has a $\chi^2_{(2)}$ distribution [21] and so the critical value for $\beta = 0.025$ is 7.38. Thus, the 'D^2 *method*' consists of rejecting H_0 if $D_i^2 > 7.38$ for a particular study. This approach has the intuitive appeal of studies being selected on the basis of how 'close' they are to the applicable region. It also has the advantage that a good approximate estimate for D_i^2 may be calculated directly without recourse to sampling the applicable region (and therefore needing to write de novo software) as in the case of the *B2* approach. However, more refined estimates require an iterative approach which is best achieved computationally (see appendix 2).

Thus following qualitative appraisal, the process of study selection has two parts, this is summarised by the following algorithm (for the B2 method):

9

1. Define region in ROC space for the test in the setting by collecting data from the setting.

    (i). Collect data on test positives and prevalence (if available) to calculate interval estimates for r and p.

    (ii). Use upper and lower confidence limits for r and p to define region in ROC space according to relations (1) and (2) (see figure 2).

    (iii). Assume the parameters μ_r and μ_p are contained in their interval estimates, then the parameters for the sensitivity, μ_s and FPR, μ_f for the test in the setting are also contained in the region – the 'applicable region'.

2. Exclude those studies which report a sensitivity and FPR that is improbable for the setting.

    (i) For each primary study derive the maximum likelihood estimate (MLE) from all potential parameter pairs for the FPR and sensitivity that are constrained to lie in the applicable region – in practice the MLE will be on one of the boundaries.

    (ii). Calculate the tail probability of the study estimate for the FPR and sensitivity given the MLE of the parameter pair lying on the boundary.

    (iii). Exclude study if tail probability less than level of significance.

Similarly, study selection based on the 'minimum distance' (D^2) method follows readily with few changes to the second part of the algorithm.

2.3 Statistical methods for aggregating the relevant studies

Once the applicable studies have been identified, they may be aggregated using a bivariate random effects model (BRM) as previously described [12]. In effect a 'tailored' meta-analysis is conducted in which the summary estimate of the sensitivity and specificity is derived only from studies compatible with the applicable region.

The method is now illustrated by applying it to the Pap test to estimate its sensitivity and specificity when used in the NHS. All analyses were made using the statistical software R and STATA.

3. Results

3.1 Case example - Screening for Cervical cancer

Until 2003 the NHS Cervical Screening programme used the Pap test exclusively for screening women for cervical pre-cancerous changes [22]. The target group is women between the ages of 25 to 65 years, who between 25 and 49 are invited on a three yearly basis for a smear, and five yearly thereafter [23]. Negative smears result in routine recall, whereas abnormal smears lead to further investigation [24].

In 1999-2000, the NHS Cervical Screening programme reported that 169,946 smears were classed as mild dyskaryosis or worse [25]. Excluding inadequate smears, 3,675,297 smears were classed as negative or borderline [25]. To satisfy (2), the sensitivity of the Pap test in the NHS programme must be greater than $r = 169,946 / 3,845,244 = 4.4\%$. Table 1 shows that within the NHS, r has remained relatively constant across all thresholds for a number of years [25], suggesting that the Pap test had a consistent level of performance within the programme during this period.

We would like to maximise the coverage probability for the parameter, μ_r without a significant loss of precision. In this instance we may vastly exceed the 2.57 standard errors for a 99% confidence interval and provide an interval estimate of (4.437-4.447%) to 5 standard errors with minimal loss of precision. Essentially in the long run with repeated sampling, μ_r would lie outside such a confidence interval only once in 3.5 million [26]. We set $4.437\% \leq r \leq 4.447\%$.

The applicable region is refined by estimating the disease prevalence at a threshold of CIN 1. The prevalence of CIN 1 or greater in the UK may be estimated to be 2.2% (99% CI 2.19-2.22%) [27]. This is likely to be an underestimate as it based on those who are referred to colposcopy clinic and does not include those with negative smears. We will set a conservative range for p to be $0.5\% \leq p \leq 10\%$.

One meta-analysis [28] which evaluated the accuracy of the Pap test included 68 studies at a test threshold of Low grade Squamous Intraepithelial Lesion (mild dyskaryosis in the UK system) and a reference standard threshold of CIN 1 [28]. The qualitative criteria used for selecting studies were: the study evaluated cervical cytology as a screening test; used histology or colposcopy as a reference standard; there was less than 3 months between the

cytology and the reference standard being applied; and the 2 x 2 table could be completed [28].

Overall in the review, verification bias was a potential issue with 69% of primary studies reporting verification of only a selected (non-random) sample of test negatives. Further only a quarter of studies reported blinding of the reference standard. Other factors such as patient spectrum were also poorly reported [28]. However, it is unclear what the combined effect of these was on individual study estimates.

The results of applying the different methods B1, B2 and D^2 are summarised in table 2. The level of significance, β =0.025. As expected when the applicable region is defined by r only (B1 method) more studies (17) are included for tailored meta-analysis than when both r and p define the region. The D^2 method excludes one of these studies (16) and the B2 method excludes a further four. The difference between D^2 and B2 is that the former relies upon a normal approximation which may not be valid for some studies of small sample size.

Figure 3 illustrate the effects of applying the B2 method to meta-analysis. The dotted lines define the applicable region. The bold squares represent 12 studies reporting FPRs which are most likely to be compatible with the NHS programme; there was agreement across the three methods on these studies. The transparent triangles lying outside of the applicable region are those studies which are incompatible with the NHS. Out of 17 UK-based studies only 3 were in the applicable region. It is clear from figure 3 that conventional meta-analysis provides an estimate which would be highly improbable in the NHS given the location of the applicable region.

The median sample size for the included set of studies was 105, that is, 50% (6/12) of studies had a sample size, n ≤ 105. To put this in context, the studies varied in sample size across ROC space: 44% (7/16) of studies had a sample size, n ≤ 105 in the region FPR ≤ 0.1, compared with 19% (10/52) of studies in the region FPR >0.1. Thus, the sample sizes of the included studies did not vary significantly (*p=0.39,* Fisher's exact test) from the FPR ≤ 0.1 region which contains the applicable region.

Confining the meta-analysis to those studies which are in the applicable region has a profound effect on the summary estimates of performance for the Pap test. From conventional

meta-analysis the sensitivity and specificity are estimated to be 72.8% (95% CI: 65.8-78.8) and 75.4% (95% CI: 68.1-81.5) compared with 50.9% (35.8-66.0) and 98.0% (95% CI: 95.4-99.1) from tailored meta-analysis using the B2 method for selection. The increased specificity also accounts for the eight-fold increase in the positive likelihood ratio from 3.0 (95% CI: 2.4-3.7) to 25.6 (95% 10.1- 65.0) between the conventional and tailored meta-analysis. The effect of this is that, for a background prevalence of CIN 1 of 2.2%, the post-test probability for CIN 1 increases from 6.2% to 36.6%.

This example provides empirical evidence that basic information on the target setting may be required before applying the results of diagnostic test studies to clinical practice.

4. Discussion

It is the observation that a test's performance may vary between settings that makes determining when performance statistics are actually applicable to a particular setting, important. Within the traditional paradigm, if the diagnostic process is to truly become evidence-based, then this is probably one of the most important questions to answer; especially, as it affects both primary and secondary research.

When selecting primary studies for a meta-analysis the usual approach is to use qualitative criteria to decide on which studies to include. However, if meta-analyses are to produce results that are relevant to clinical practice, choosing studies based on qualitative criteria alone may be insufficient. In particular, if there is a wide variation in performances across different clinical settings, being clear on the target setting seems equally important. While this is usually made clear in the review question, the problem in defining the target setting qualitatively is that it may not accurately represent which studies are likely to be applicable.

Here, the possibility of using data collected from the target setting has been highlighted and how they may be used to introduce greater objectivity to ascertaining a test's performance in a particular setting. As a result it represents a departure from the usual methodology in meta-analysis by selecting studies on the basis of their results and not on qualitative criteria alone.

However, this should be considered in context. In general, when conducting a meta-analysis no assumption is made on where the true performance lies and therefore, there is no justification in selecting studies based on their individual results. Nonetheless the studies are still constrained by mathematical plausibility.

Similar to conventional meta-analysis potentially some of the included studies may report estimates which are either biased due to flaws in the primary study design or subject to sampling error. Whereas sampling error is largely accommodated by the models, a number of study design biases such as verification bias, participant selection bias, incorporation bias and reference standard bias are recognised and may lead to both the overstating and understating of test accuracy [29, 30, 31]. In principle part of the critical appraisal process should be aimed at mitigating these but it is not always possible.

Other setting-specific factors such as differences in patient spectrum, the positioning of the test threshold and the way the test is executed by the clinician may also explain some of the variation in the reported test accuracies. Changes in patient spectrum may manifest as a change in prevalence [5,6], whilst the latter two may be precipitated by changes in prevalence between settings [4, 32].

The difficultly is in being able to distinguish unbiased estimates from biased estimates and there seems to be no straight forward way of achieving this. Usually any differences between studies are investigated as part of a general exploration of heterogeneity and since this gives some indication of the sources of between-study variation, it should always be carried out.

Ideally, if all the relevant sources of variation were known and their individual and combined effects quantifiable, the estimate provided by each study could be modified accordingly to provide us with an unbiased estimate of the study parameter. Unfortunately, there are often multiple drivers to the accuracy of a test reported in a study and due to a lack of study-level data and the potential challenges of modelling multiple covariates, their overall combined effect on the reported accuracy is, in general, unknown.

Thus, the method developed here represents a pragmatic approach which considers the reported estimate at face-value in terms of its compatibility with the intended target setting. Providing a meta-analysis for the test in question exists and test data may be collected from

the practice setting, decisions on the applicability of the primary studies to the setting may be made. This allows us to produce a summary estimate which is at least plausible for the setting, something which conventional meta-analysis is not always able to.

There are two obvious roles for tailored meta-analysis in practice. For those diagnostic tests that are being applied in routine practice and where meta-analyses are available, there is the potential to use tailored meta-analysis to provide plausible estimates for the performance within the setting. This could improve diagnostic prediction and management decision-making.

Another use may be to aid the decision process of whether a particular test should be used at all in practice. Before a new diagnostic technology is introduced into practice, there is often substantial uncertainty on how it will actually perform in the intended setting and such decisions to implement the technology are most often based on appraisals of the literature and economic considerations. However, post-implementation there is the opportunity to re-appraise the decision to introduce the technology. By collecting setting-specific data and defining an applicable region, tailored-meta analysis could be used to re-assess the performance of the test and see if it is compatible with those estimates made prior to implementation. Ultimately this may lead to a decision on disinvestment.

The apparent theoretical advantage of constraining studies to an applicable region, to calculate summary estimates, needs to be validated empirically. This could take the form of comparing the results of a primary study in the target setting with the results of a tailored meta-analysis based on the available studies or alternatively could be done by way of a simulation study. The latter has the advantage of allowing other statistical properties of the method to be explored.

Limitations of the analysis and potential areas of research
The foregoing analysis has demonstrated that the summary estimate derived using only those studies which lie in the applicable region is at least feasible for the target setting which is not always the case for those estimates derived from conventional meta-analysis. Although, this follows from the mathematical constraints, uncertainty in the estimates of the test positive rate and the prevalence may result in inaccurate boundaries being drawn for the applicable region. However, this is minimised by using interval estimates with a high coverage

probability. In the case example, our estimate of the test positive rate in the NHS was to five standard errors - the sort of significance demanded by particle physicists when confirming the existence of the Higgs Boson [26]!

In tailored-meta-analysis studies are included if they are either inside or 'close enough' to the applicable region that they cannot be confidently excluded. Although it was not the case with the Pap test example used earlier, potentially, some studies of small sample sizes which are close to the applicable region could be included because uncertainty in the estimate does not allow them to be confidently excluded. However, such studies will have less influence on the summary estimate which is weighted towards studies with larger sample sizes.

A potential consequence of selecting only those studies lying in the applicable region for meta-analysis is that it is feasible there will be none to aggregate. In such instances, it is worth considering whether the data used to define r and p for the setting are reliable. If they are then it must be concluded that none of the studies accurately represents how the test performs within the target setting.

In summary, the foregoing analysis demonstrates the possibility of using quantitative data collected from clinical practice to augment the process of study selection by determining quantitatively which studies may be applicable to a setting. Such an approach suggests tailoring the meta-analysis to include only the applicable studies before deriving summary estimates.

Conflicts of interest

None.

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Appendix 1. Derivation of the applicable region

1.1 Using the test positive rate to define the test performances feasible in practice

In the unverified population, all that may be known are the test results without the corresponding reference standard results. This is represented by the 2 by 2 below, where x (the total number tested positive) and y (the total number tested negative) are known and a, b, c and d are unknown. We do know that $a,b,c,d \geq 0$, otherwise negative numbers of subjects are possible.

		DISEASE		
		Positive	Negative	Totals
TEST	Positive	a	b	x
	Negative	c	d	y
	Totals	$a + c$	$b + d$	$x + y$

From definitions of sensitivity, s and FPR, f

$$c = \frac{a(1-s)}{s} \quad \text{and} \quad d = \frac{b(1-f)}{f}$$

Also

$$c + d = y \quad \text{and} \quad x - a = b$$

Hence we have

$$y = \frac{a(1-s)}{s} + \frac{(x-a)(1-f)}{f}$$

From re-arranging we have for $f \neq s$

$$a = \frac{sfy - s(1-f)x}{(f-s)}$$

Now for $a \geq 0$ consider the 2 possibilities $a = 0$ and $a > 0$. Trivially if $a = 0$ we have $s = 0$

For $a > 0$

either $f > s$ and $sfy - s(1-f)x > 0 \Rightarrow f > \dfrac{x}{(x+y)}$

or $f < s$ and $sfy - s(1-f)x < 0 \Rightarrow f < \dfrac{x}{(x+y)}$

$$\text{for} \quad f = s \qquad f = \frac{x}{(x+y)}$$

Similarly, solving for b, c and d then setting them all >0 we get the following 2 inequalities.

For $f \geq s$ we have $s \leq \dfrac{x}{(x+y)}$ and for $f < s$ we have $s > \dfrac{x}{(x+y)}$

Thus we have the results

$$f < r \text{ and } s > r \text{ whenever } f < s \qquad\qquad (1)$$

$$f \geq r \text{ and } s \leq r \text{ whenever } f \geq s \qquad\qquad (2)$$

$$\text{where} \quad r = \frac{x}{(x+y)}$$

An alternative derivation of (1) may be obtained from assuming that the probability of a test positive and the presence of disease are correlated. This approach was used by Kraemer [18] to derive (1). Kraemer's use of the inequality was confined to single primary studies and not used to select studies for meta-analysis.

1.2 Incorporating the prevalence of the target disorder

Suppose the prevalence of the target disorder, p may be estimated, then, from the definition of prevalence, p, sensitivity, s and false positive rate f we have

$$p(x+y) = \frac{a}{s} \qquad \text{and} \qquad (1-p)(x+y) = \frac{b}{f}$$

Since $a + b = x$ $\qquad sp + f(1-p) = \dfrac{x}{(x+y)} = r$

Hence, we have $\qquad s = \dfrac{r}{p} - \dfrac{(1-p)}{p} f \qquad\qquad (3)$

Comparing (1) and (3) it can be seen that the size of the applicable region is most dependent on having precise knowledge of r. Thus, if p is known perfectly and r is not known, (ie $0 \leq r$

≤ 1) then all values for f and s in ROC space are still possible. It follows from (3) that for a fixed value of p, allowing r to vary between 0 and 1 changes only the intercept. This produces a plane of parallel lines which covers all values of ROC space. To appreciate this, consider the extreme values of f. For $f = 0$, s has a value r/p, and since $0 \leq r \leq 1$ this implies that $0 \leq s \leq (1/p)$. Hence, s can take on all values between 0 and 1 since $(1/p) \geq 1$.

Similarly, for $f = 1$, s has a value of $(r/p) - (1-p)/p$. For values of $0 \leq r \leq 1$, this implies $-(1-p)/p \leq s \leq 1$. Hence s takes on values between zero and 1 since $-(1-p)/p \leq 0$. For $f=1$, s again covers all values between 0 and 1 in ROC space. Thus, without knowledge of r, even perfect knowledge of p is unhelpful.

Appendix 2 - Selection of studies based on the applicable region

2.1 Binomial B2 method

In all three methods we make the assumption that the parameters μ_r and μ_p for the test positive rate, r and prevalence, p, respectively, lie in their corresponding interval estimates. This is only reasonable if the level of significance is chosen so that there is a high coverage probability.

For a study i, (f_i, s_i) are the FPR and sensitivity, $(\hat{f}_i, \hat{s}_i)$ are the study estimates and $(\mu_{f,i}, \mu_{s,i})$ are the study parameters. Also $n_{f,i}$ and $n_{s,i}$ are the total number without and with the target disorder. We are interested only in studies which have $(\mu_{f,i}, \mu_{s,i})$ pairs in the applicable region. For a study estimate $(\hat{f}_i, \hat{s}_i)$ lying outside of the applicable region, the maximum likelihood estimate (MLE) for a $(\mu_{f,i}, \mu_{s,i})$ pair which actually lies in the applicable region must be located on the boundary closest to $(\hat{f}_i, \hat{s}_i)$. Since s_i and f_i are independent with $s_i \sim Bin(n_{s,i}, \mu_{s,i})$ and $f_i \sim Bin(n_{f,i}, \mu_{f,i})$, respectively, the likelihood function, $L(\mu_{f,i}, \mu_{s,i} \mid \hat{f}_i, \hat{s}_i)$ for a study i is given by

$$L(\mu_{f,i}, \mu_{s,i} \mid f_i = \hat{f}_i, s_i = \hat{s}_i) = Bin(b_i \mid n_{f,i}, \mu_{f,i}) Bin(a_i \mid n_{s,i}, \mu_{s,i})$$

where b_i and a_i are the number of false positives and true positives for study i respectively. This is maximised for $(\mu_{f,i}, \mu_{s,i})$ pairs lying on the closest boundary to $(\hat{f}_i, \hat{s}_i)$ and provides $(\mu_{max,f,i}, \mu_{max,s,i})$. If this is written in terms of Log $(L(\mu_{f,i}, \mu_{s,i} \mid \hat{f}_i, \hat{s}_i))$, the maximum likelihood estimate may be obtained by finding the real root to a cubic equation. Alternatively, it may be found by sampling points on the boundary closest to $(\hat{f}_i, \hat{s}_i)$ and finding the pair $(\mu_{f,i}, \mu_{s,i})$ which yields the maximum value for $L(\mu_{f,i}, \mu_{s,i} \mid \hat{f}_i, \hat{s}_i)$. The latter method was used here.

The tail area probability, $P(f_i \geq \hat{f}_i, s_i \geq \hat{s}_i \mid \mu_{f,i} = \mu_{max,f,i}, \mu_{s,i} = \mu_{max,s,i})$ is given by

$$P_i = \left(\sum_{b=b_i}^{n_{f,i}} Bin(\, b \,/\, n_{f,i}\,, \mu_{max,f,i}\,) \right) \left(\sum_{a=a_i}^{n_{s,i}} Bin(\, a \,/\, n_{s,i}\,, \mu_{max,s,i}\,) \right)$$

Studies are rejected if $P_i < \beta$ for level of significance β, where β was set to 0.025.

2.2 Mahalanobis distance, D^2 method

If we assume s_i and f_i to have independent normal distributions such

that, $s_i \sim N(\,\mu_{s,i}\,,\sigma_{s,i}^2\,)$ and $f_i \sim N(\,\mu_{f,i}\,,\sigma_{f,i}^2\,)$ then the *Mahalanobis distance*, D_i^2 for a study

i, may be written as

$$D_i^2 = \frac{(\,\hat{f}_i - \mu_{f,i}\,)^2}{\sigma_{f,i}^2} + \frac{(\,\hat{s}_i - \mu_{s,i}\,)^2}{\sigma_{s,i}^2}$$

Unlike the Euclidean distance between points this allows us to weight the variates according to the inverse of their individual variances. As such it represents a 'statistical' distance between points. The optimum $(\mu_{f,i}\,,\,\mu_{s,i})$ point on the boundary, that is, the point which maximises the probability of a study estimate for a given $(\mu_{f,i}\,,\,\mu_{s,i})$, is that which minimises D_i^2. It is straight forward to show that this corresponds to the MLE for $(\mu_{f,i}\,,\,\mu_{s,i})$ since s_i and f_i are assumed to have independent normal distributions.

It may be shown that D_i^2 is minimised for a point with $\mu_{f,i}$ on the boundary when it is given by

$$\mu_{f,i} = \frac{\sigma_{s,i}^2 p^2 \hat{f}_i + r(1-p)\sigma_{f,i}^2 - p(1-p)\sigma_{f,i}^2 \hat{s}_i}{\sigma_{s,i}^2 p^2 + (1-p)^2 \sigma_{f,i}^2}$$

Similarly, $\mu_{s,i}$ is given by substituting $\mu_{f,i}$ into

$$\mu_{s,i} = \frac{r}{p} - \frac{(1-p)\mu_{f,i}}{p}$$

Where (r,p) correspond to either (r_{ucl}, p_{lcl}) or (r_{lcl}, p_{ucl}) depending on which boundary we are considering. The parameter $\mu_{f,i}$ is obtained iteratively by first making initial estimates for the

variances $\sigma^2_{f,i} = \dfrac{\hat{f}_i(1-\hat{f}_i)}{n_{f,i}}$ and $\sigma^2_{s,i} = \dfrac{\hat{s}_i(1-\hat{s}_i)}{n_{s,i}}$.

Once we have our first estimates $\mu_{s,i}$ and $\mu_{f,i}$ these are then substituted into the variances instead of $\hat{f}_i$ and $\hat{s}_i$ and the process continued until we have convergence.

Since D_i^2 here is the sum of two squared standardised normal variables it has an approximate $\chi^2_{(2)}$ distribution. Thus, for level of significance, $\beta = 0.025$, the critical value is 7.38. Studies are excluded if $D_i^2 > 7.38$.

Appendix 3 Results of inclusion/ exclusion decisions using the applicable region.

Name	Year	Sens	FPR	Binomial (B1) AR (r only)		Binomial (B2) AR (r and p)		Mahalanobis (D^2) AR (r and p)	
				Probability	Decision	Probability	Decision	D^2	Decision
Chomet	1987	33.3	20.0	0.20439	Include	0.0059	Exclude	2.97	Include
Cox	1995	38.0	4.2	0.62166	Include	1.0	Include	0.00	Include
Davis	1981	69.5	0.0	1.0	Include	1.0	Include	0.00	Include
Davison	1994	53.3	0.0	1.0	Include	1.0	Include	0.00	Include
DiBonito	1993	61.0	4.3	0.59327	Include	0.1777	Include	0.04	Include
Fung	1997	86.6	9.5	0.03428	Include	0.0033	Exclude	6.45	Include
Giles	1989	81.3	0.0	1.0	Include	1.0	Include	0.00	Include
Glenthoj	1988	81.6	0.0	1.0	Include	1.0	Include	0.00	Include
Gonzalez	1996	38.1	12.2	0.03512	Include	0.0030	Exclude	6.20	Include
Gundersen	1988	15.4	10.0	0.14879	Include	0.0152	Exclude	2.22	Include
Jones	1987	17.2	2.2	0.95960	Include	0.2166	Include	0.26	Include
Morrison	1992	83.3	0.0	1.0	Include	1.0	Include	0.00	Include
Spitzer	1987	18.2	4.8	0.56556	Include	0.1161	Include	0.01	Include
Stafl	1981	43.8	10.0	0.36701	Include	0.0257	Include	0.80	Include
Tay	1987	33.3	0.0	1.0	Include	0.5026	Include	0.13	Include
Wright	1994b	26.7	1.5	0.9993	Include	0.2987	Include	0.08	Include
Skehan	1990	82.4	82.8	0	Exclude	0	Exclude	0.00	Exclude
Cox	1992	43.8	7.8	0.0039	Exclude	0.0005	Exclude	10.64	Exclude
Coibion	1994	22.0	15.0	0.0083	Exclude	0.0007	Exclude	10.76	Exclude
Naslund	1986	100.0	23.1	0.0182	Exclude	0.0000	Exclude	12.38	Exclude
Jones	1992	36.6	13.1	0.0057	Exclude	0.0005	Exclude	11.47	Exclude
Korn	1994	62.9	15.8	0.0064	Exclude	0.0004	Exclude	12.80	Exclude
Hellberg	1987	88.9	33.3	0.0266	Include	0.0005	Exclude	13.26	Exclude
Frisch	1994	35.0	27.3	0.0112	Exclude	0.0004	Exclude	14.03	Exclude
MacCormac	1988	84.6	5.4	0.0024	Exclude	10^{-06}	Exclude	19.60	Exclude
Korn	1994	63.6	26.3	0.0012	Exclude	10^{-05}	Exclude	23.30	Exclude
Garutti	1994	41.7	14.1	10^{-05}	Exclude	10^{-06}	Exclude	29.84	Exclude
Kealy	1986	86.0	12.1	10^{-06}	Exclude	10^{-07}	Exclude	34.14	Exclude
Del Priore	1995	80.0	25.0	10^{-05}	Exclude	10^{-06}	Exclude	35.64	Exclude
Andrews	1989	26.3	12.3	10^{-06}	Exclude	10^{-08}	Exclude	35.86	Exclude
Herrington	1995	68.8	38.5	0.0002	Exclude	10^{-06}	Exclude	38.51	Exclude
Tait	1988	74.5	18.4	10^{-06}	Exclude	10^{-07}	Exclude	39.36	Exclude
Ferris	1998	37.0	14.5	10^{-07}	Exclude	10^{-09}	Exclude	45.32	Exclude
Giles	1988	53.1	14.9	10^{-07}	Exclude	10^{-09}	Exclude	47.03	Exclude
Mayeaux	1995	43.8	19.2	10^{-08}	Exclude	10^{-09}	Exclude	53.87	Exclude
Singh	1985	75.2	66.7	10^{-05}	Exclude	10^{-07}	Exclude	59.51	Exclude
Herrington	1995	68.8	29.7	10^{-07}	Exclude	10^{-09}	Exclude	60.91	Exclude
Wheelock	1989	48.1	18.6	10^{-10}	Exclude	10^{-11}	Exclude	70.51	Exclude
Parker	1986	74.5	15.4	10^{-10}	Exclude	10^{-12}	Exclude	72.81	Exclude
Oyer	1986	75.1	21.0	10^{-09}	Exclude	10^{-11}	Exclude	75.43	Exclude
Johansen	1979	90.2	28.3	10^{-10}	Exclude	10^{-12}	Exclude	91.35	Exclude
Syrjanen	1987	72.8	17.9	10^{-14}	Exclude	10^{-16}	Exclude	107	Exclude
Koonings	1992	79.5	29.0	10^{-11}	Exclude	10^{-13}	Exclude	109	Exclude
Chomet	1987	67.0	38.9	10^{-10}	Exclude	10^{-12}	Exclude	109	Exclude
Haddad	1988	86.7	56.3	10^{-09}	Exclude	10^{-11}	Exclude	112	Exclude
Smith	1987	78.0	41.9	10^{-10}	Exclude	10^{-12}	Exclude	113	Exclude
Young	1993	72.0	27.4	10^{-12}	Exclude	10^{-14}	Exclude	115	Exclude
Nyirjesy	1972	60.0	50.0	10^{-11}	Exclude	10^{-13}	Exclude	136	Exclude
Koonings	1992	69.3	36.4	10^{-13}	Exclude	10^{-16}	Exclude	144	Exclude

Name	Year	Sens	FPR	Binomial (B1) AR (r only) Probability	Decision	Binomial (B2) AR (r and p) Probability	Decision	Mahalanobis (D^2) AR (r and p) D^2	Decision
Walker	1986	76.9	46.9	10^{-12}	Exclude	10^{-14}	Exclude	149	Exclude
Bolick	1998	85.1	63.6	10^{-14}	Exclude	10^{-16}	Exclude	200	Exclude
Lozowski	1982	93.0	50.0	0	Exclude	0	Exclude	219	Exclude
Germain	1994	66.7	21.0	0	Exclude	0	Exclude	220	Exclude
Beeby	1993	65.7	21.9	0	Exclude	0	Exclude	288	Exclude
Baldauf	1995	92.9	68.8	0	Exclude	0	Exclude	347	Exclude
Maggi	1989	76.9	47.8	0	Exclude	0	Exclude	436	Exclude
Soutter	1986	83.2	56.9	0	Exclude	0	Exclude	464	Exclude
Bigrigg	1990	96.4	66.0	0	Exclude	0	Exclude	469	Exclude
Kwikkel	1986	98.0	91.9	0	Exclude	0	Exclude	744	Exclude
Rasbridge	1995	86.6	49.7	0	Exclude	0	Exclude	872	Exclude
Wetrich	1986	81.2	33.1	0	Exclude	0	Exclude	928	Exclude
Upadhyay	1984	99.6	77.9	0	Exclude	0	Exclude	970	Exclude
Fahim	1991	85.1	38.0	0	Exclude	0	Exclude	1283	Exclude
Melnikow	1997	88.6	88.5	0	Exclude	0	Exclude	2075	Exclude
Melnikow	1997	98.7	88.5	0	Exclude	0	Exclude	2103	Exclude
Parham	1991	98.5	82.2	0	Exclude	0	Exclude	2500	Exclude
Soost	1991	86.6	65.3	0	Exclude	0	Exclude	6701	Exclude
Jones	1996	74.5	25.3	0	Exclude	0	Exclude	6871	Exclude

Data from McCrory et al [28]

Notes:
Probability = probability of study estimate given parameter pair on the boundary
Decision = decision to include or exclude study from tailored meta-analysis
AR = applicable region defined by either *r* only, or *r* and *p*.

A study was excluded if the probability was <0.025. Using the Mahalanobis distance this corresponded to a critical value of 7.38
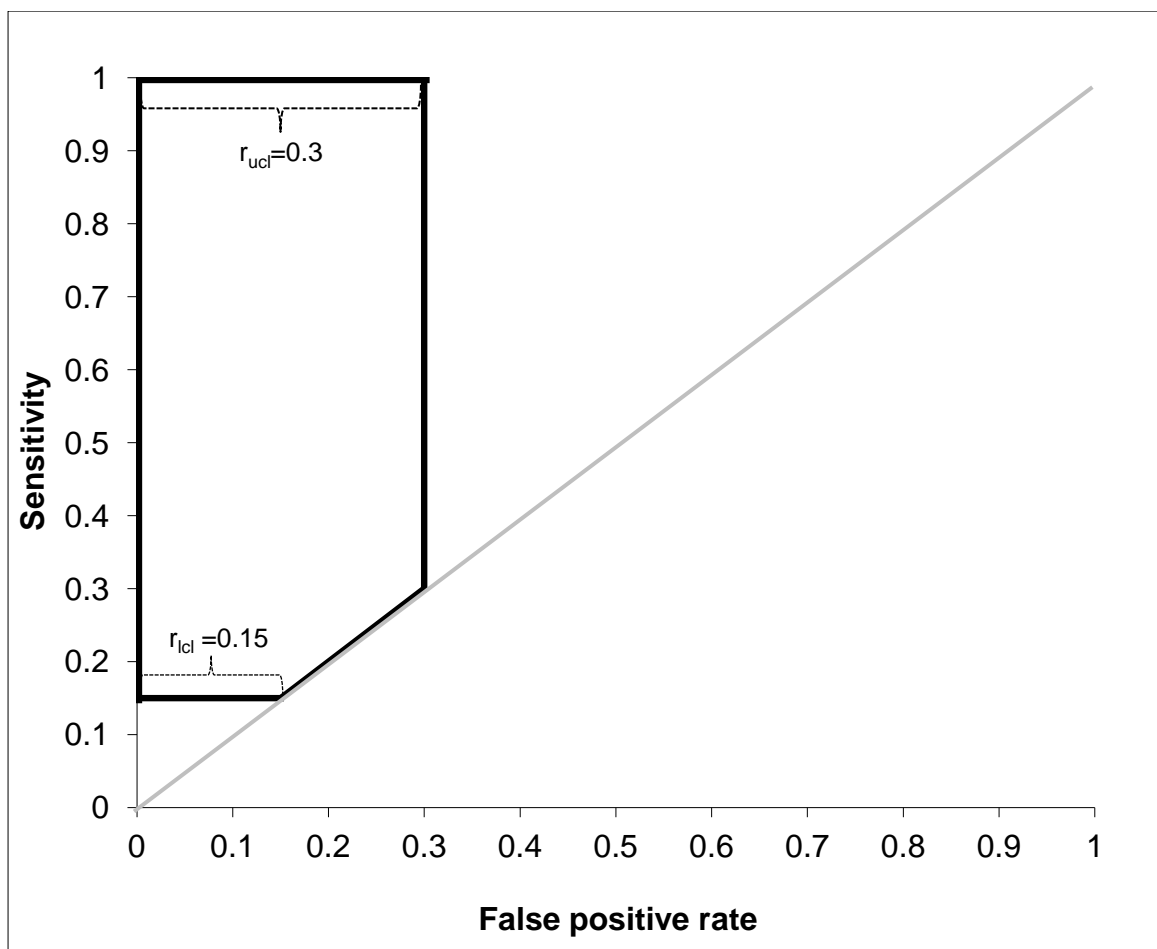
Figure 1. Hypothetical example demonstrating how the constraints define the applicable region (the bold continuous line).

The bold lines represent the constraint imposed by $r_{lcl} \leq r \leq r_{ucl}$, on s and f (inequality (1) in text), where r_{lcl} and r_{ucl} correspond to the lower and upper confidence limits for r. Here $r_{lcl} = 0.15$ and $r_{ucl} = 0.30$.
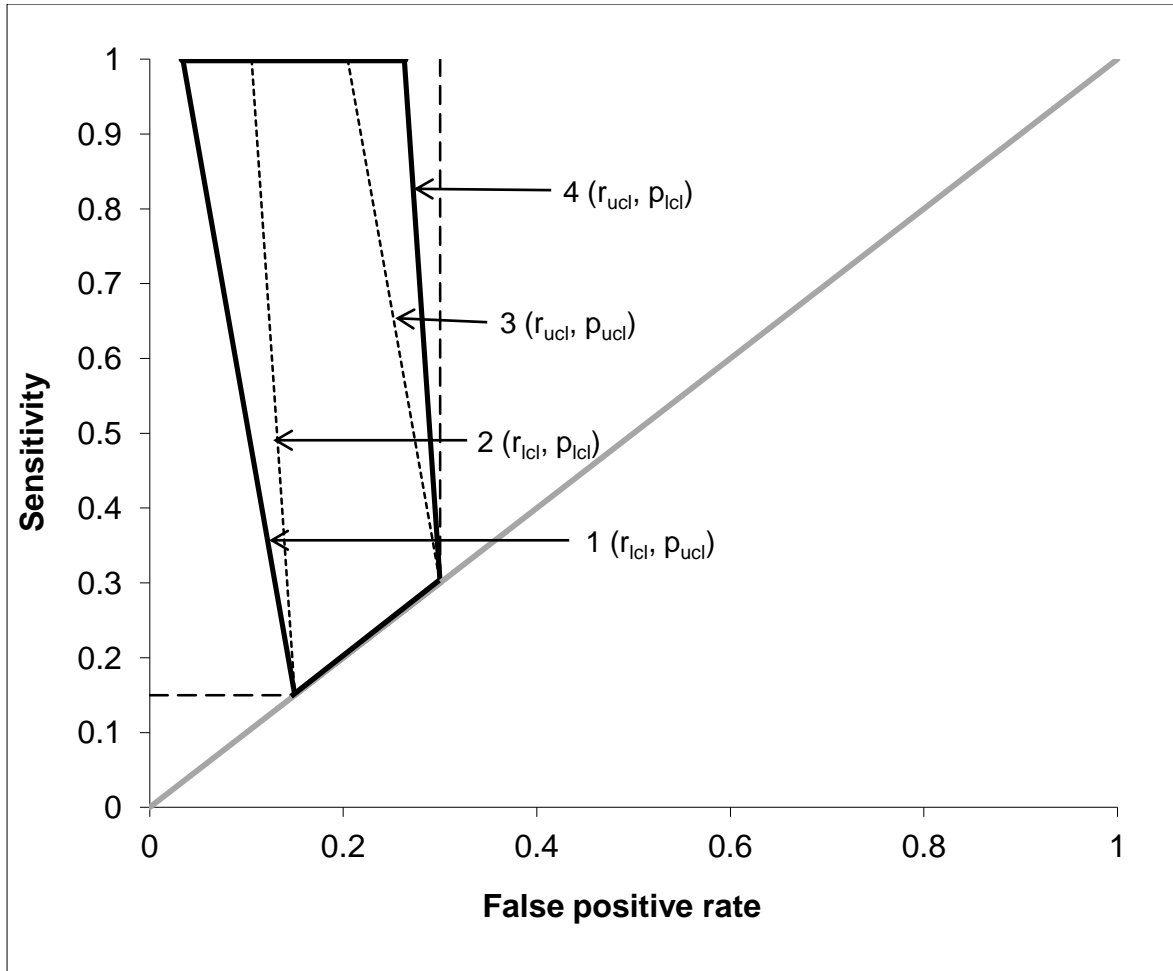
1

Figure 2. Hypothetical example demonstrating how the constraints define the applicable region (the bold continuous trapezium) after including estimates of the test positive rate, r and prevalence, p. The outer dashed lines represent the constraint imposed by $0.15 \le r \le 0.3$ on s and f. The lines represented by 1-4 are the result of imposing equation (2) in addition to (1) for $0.05 \le p \le 0.12$ and $0.15 \le r \le 0.3$. For example line 1 combines $s= (r/p) -((1-p)f/p)$ for ($r =r_{lcl}= 0.15$, $p=p_{ucl} = 0.12$) and ($s \ge r$ and $f \le r$) for ($r= r_{lcl}= 0.15$). Lines 2 and 3 are dominated by 1 and 4 and are therefore surplus (see text for explanation).

Threshold	1999-2000	2000-01	2001-02	2002-03
borderline	0.0919	0.0900	0.0861	0.0851
mild	0.0442	0.0431	0.0406	0.0406
moderate	0.0173	0.0166	0.0158	0.0156
severe	0.0076	0.0075	0.0071	0.0071

Table 1. The test positive rate, r, for each of the cytology thresholds in the NHS Cervical screening programmes over 4 years

	All	AR (*r* only) Binomial (B1)	AR (both *r* and *p*) Mahalanobis, (D^2)	Binomial (B2)
Included studies (n)	68	17	16	12
sensitivity	72.8% (65.8-78.8)	52.6% (37.9-66.9)	49.6% (35.4-63.8)	50.9% (35.8-66.0)
specificity	75.4% (68.1-81.5)	96.0% (93.0-97.8)	96.6% (93.8-98.1)	98.0% (95.4-99.1)
LR+	2.96 (2.37-3.68)	13.21 (7.22-24.17)	14.4 (7.4-28.2)	25.6 (10.1-65.0)
LR-	0.36 (0.30-0.44)	0.49 (0.36-0.67)	0.52 (0.39-0.70)	0.50 (0.36-0.69)

Table 2. Performance characteristics of the Pap test using conventional meta-analysis, the B1 method, D^2 method and the B2 method. Note AR = applicable region. 95% confidence intervals in brackets.
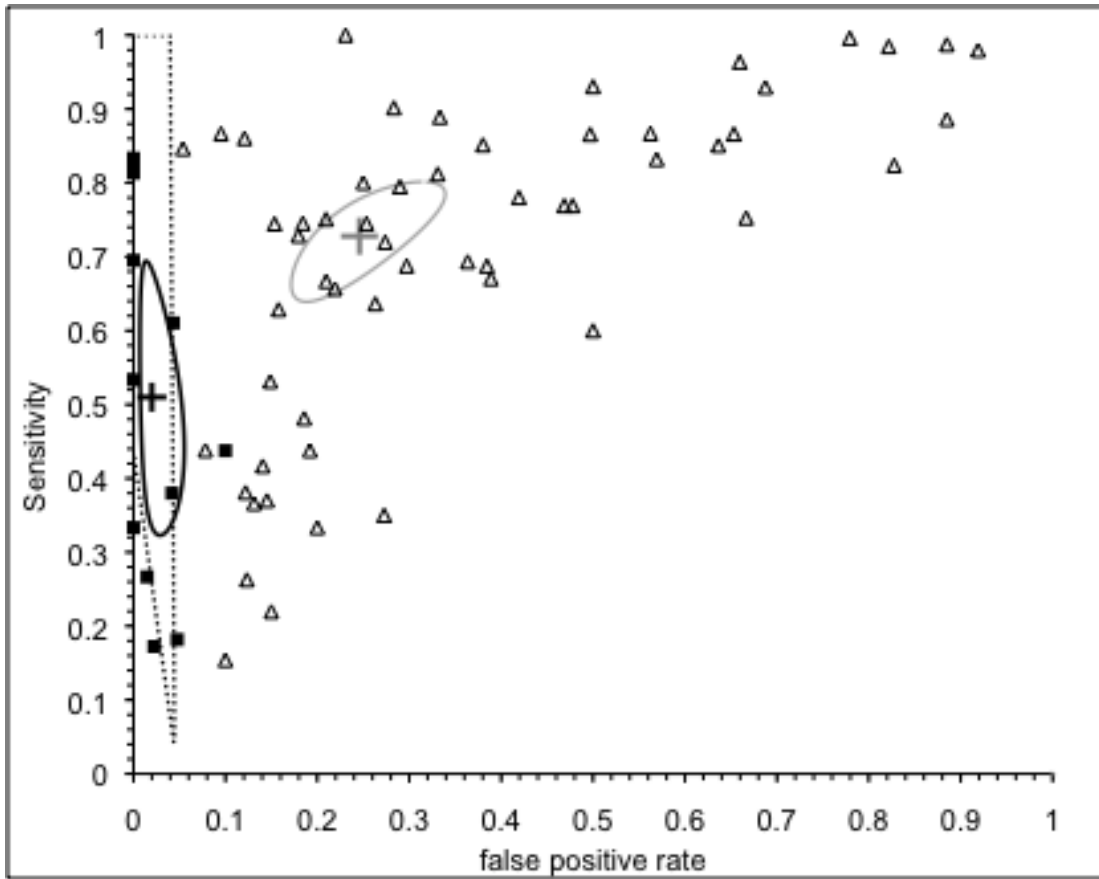
Figure 3. Tailored meta-analysis of the Pap test in the NHS using the B2 method.
The dotted line represents the applicable region using interval estimates for the test positive
rate *r* and prevalence *p*. The bold squares are the included studies under the B2 method and
the unfilled triangles are the excluded studies. The grey 'elliptical region' represents the
confidence region (point estimate in centre) using conventional meta-analysis. The black
ellipse is the associated confidence region enclosing the point estimate for tailored meta-
analysis.

*Conflict of Interest/Financial Disclosure

Conflicts of interest: None

Conflicts of interest: None