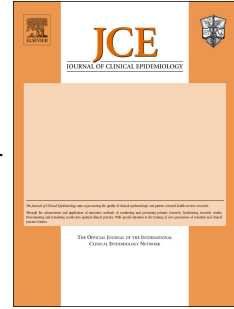


# Accepted Manuscript



Defining ranges for certainty ratings of diagnostic accuracy: A GRADE concept paper

Monica Hultcrantz, Reem A. Mustafa, Mariska M.G. Leeflang, Valéry Lavergne, Kelly Estrada-Orozco, Mohammed T. Ansari, Ariel Izcovich, Jasvinder Singh, Lee Yee Chong, Anne Rutjes, Karen Steingart, Airton Stein, Nigar Sekercioglu, Ingrid Arévalo Rodriguez, Rebecca L. Morgan, Gordon Guyatt, Patrick Bossuyt, Miranda W. Langendam, Holger J. Schünemann

PII: S0895-4356(18)31069-2

DOI: <https://doi.org/10.1016/j.jclinepi.2019.05.002>

Reference: JCE 9877

To appear in: *Journal of Clinical Epidemiology*

Received Date: 6 December 2018

Revised Date: 7 April 2019

Accepted Date: 14 May 2019

Please cite this article as: Hultcrantz M, Mustafa RA, Leeflang MMG, Lavergne V, Estrada-Orozco K, Ansari MT, Izcovich A, Singh J, Chong LY, Rutjes A, Steingart K, Stein A, Sekercioglu N, Rodriguez IA, Morgan RL, Guyatt G, Bossuyt P, Langendam MW, Schünemann HJ, Defining ranges for certainty ratings of diagnostic accuracy: A GRADE concept paper, *Journal of Clinical Epidemiology* (2019), doi: <https://doi.org/10.1016/j.jclinepi.2019.05.002>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

## Defining ranges for certainty ratings of diagnostic accuracy: A GRADE concept paper

Monica Hultcrantz<sup>a</sup>, Reem A Mustafa<sup>b,c</sup>, Mariska M.G. Leeflang<sup>d</sup>, Valéry Lavergne<sup>e,f</sup>, Kelly Estrada-Orozco<sup>g,h</sup>, Mohammed T Ansari<sup>i</sup>, Ariel Izcovich<sup>j</sup>, Jasvinder Singh<sup>k,l,m</sup>, Lee Yee Chong<sup>n</sup>, Anne Rutjes<sup>o</sup>, Karen Steingart<sup>p</sup>, Airton Stein<sup>q,r</sup>, Nigar Sekercioglu<sup>s,c</sup>, Ingrid Arévalo Rodriguez<sup>u</sup>, Rebecca L Morgan<sup>c</sup>, Gordon Guyatt<sup>c</sup>, Patrick Bossuyt<sup>d</sup>, Miranda W Langendam<sup>d</sup>, Holger J. Schünemann<sup>c,v</sup>

<sup>a</sup> Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU), S:t Eriksgatan 117, SE-102 33, Stockholm, Sweden

<sup>b</sup> Department of Medicine, Division of Nephrology and Hypertension, University of Kansas Medical Center, 3901 Rainbow Blvd, MS3002, Kansas City, KS 66160, USA

<sup>c</sup> Department of Health Research Methods, Evidence, and Impact, McMaster University, 1280 Main Street West, Hamilton, Ontario L8S 4K1, Canada

<sup>d</sup> Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam Public Health research institute, Amsterdam University Medical Centers, Meibergdreef 9, Amsterdam, Netherlands

<sup>e</sup> Department of Medicine, Sacré-Coeur Hospital, University of Montreal, Montreal, Canada

<sup>f</sup> Department of Clinical Affairs & Practice Guidelines, Infectious Disease Society of America, Arlington, VA, USA

<sup>g</sup> Clinical Research Institute, Faculty of Medicine, Universidad Nacional de Colombia, Bogotá, Colombia

<sup>h</sup> Research Unit, Faculty of Medicine, Fundación Universitaria Sanitas, Bogotá, Colombia

<sup>i</sup> School of Epidemiology, Public Health and Preventive Medicine, Faculty of Medicine, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Ontario K1G 5Z3, Canada

<sup>j</sup> Internal Medicine Service, German Hospital, Pueyrredón 1640, Buenos Aires C1118AAT, Argentina

<sup>k</sup> Medicine Service, VA Medical Center, 510, 20th street South, FOT 805B, Birmingham, AL, USA

<sup>l</sup> Department of Medicine at the School of Medicine, University of Alabama at Birmingham (UAB), 1720 Second Ave. South, Birmingham, AL 35294-0022, USA

<sup>m</sup> Department of Epidemiology at the UAB School of Public Health, 1665 University Blvd., Ryals Public Health Building, Room 220, Birmingham, AL 35294-0022, USA

<sup>n</sup> Ateimed Consulting Ltd. 3rd Floor 166 College Road, Harrow, Middlesex, HA1 1BH, United Kingdom

<sup>o</sup> Institute of Social and Preventive Medicine (ISPM), University of Bern, Mittelstrasse 43, 3012 Bern, Switzerland

<sup>p</sup> Department of Clinical Sciences, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, UK

<sup>q</sup> Programa de Ciências da Saúde - Universidade Federal de Ciências da Saúde de Porto Alegre (Ufcspa) Rua Sarmento Leite, 245 - CEP 90050-170 Porto Alegre, Brazil

<sup>r</sup> Teaching and Research Unit - Grupo Hospitalar Conceição (GHC) Rua Francisco Trein, 596 - CEP - 91.350-200, Porto Alegre, Brazil

<sup>s</sup> Division of Nephrology, Department of Medicine, University of Toronto, 585 University Avenue, Toronto ON M5G 2N2, Canada.

<sup>u</sup> Clinical Biostatistics Unit, Hospital Universitario Ramon y Cajal, CIBER Epidemiology and Public Health, Ctra. Colmenar Km. 9,100, 28034, Madrid, Spain

<sup>v</sup> Department of Medicine, Michael G DeGroot Cochrane Canada Centre and GRADE centre, McMaster University, 1280 Main Street West, Hamilton, Ontario L8S 4K1, Canada

**Abstract**

**Objective:** To clarify how the Grading of Recommendations Assessment, Development and Evaluation (GRADE) concept of certainty of evidence applies to certainty ratings of test accuracy.

**Study Design and Setting:** After initial brainstorming with GRADE Working Group members, we iteratively refined and clarified the approaches for defining ranges when assessing the certainty of evidence for test accuracy within a systematic review, health technology assessment, or guidelines.

**Results:** Ranges can be defined both for single test accuracy and for comparative accuracy of multiple tests. For systematic reviews and health technology assessments, approaches for defining ranges include some that do not require value judgments regarding downstream health outcomes. Key challenges arise in the context of a guideline that requires ranges for sensitivity and specificity that are set considering possible effects on all critical outcomes. We illustrate possible approaches and provide an example from a systematic review of a direct comparison between two test strategies.

**Conclusions:** This GRADE concept paper provides a framework for assessing, presenting, and making decisions based on the certainty of evidence for test accuracy. More empirical research is needed to support future GRADE guidance on how to best operationalize the candidate approaches.

**Keywords:** Certainty of evidence, test accuracy, GRADE, Guidelines, Systematic reviews, Health technology assessments

**Running title:** Defining ranges for certainty ratings of diagnostic accuracy

## Introduction

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) concept of certainty of evidence (also called quality of evidence) represents our confidence that the true effect lies above or below a threshold, or in a specified range (1). To assess the certainty of evidence for an individual outcome, authors of systematic reviews, health technology assessments or guidelines need to specify the thresholds or ranges they are using and the associated rationale. Several approaches exist for setting thresholds and ranges. For recommendations in clinical practice and public health guidelines, GRADE has suggested setting a threshold based on consideration of all critical outcomes. For systematic review authors, we have illustrated three different approaches: expressing certainty in the range set by the 95% confidence interval (CI), certainty in the direction of effect, or certainty in a particular magnitude of effect, e.g. small, medium or large.

Although GRADE has illustrated the concept of certainty using effects of treatment interventions, the guidance to specify ranges or thresholds also applies to questions of diagnostic tests. When diagnostic intervention studies comparing alternative diagnostic test strategies with direct assessment of patient-important outcomes are available (such as RCTs addressing the impact on survival after a screening strategy), the approaches for setting thresholds or ranges previously presented apply (1). In this paper, we will explore the concepts when there are no such studies.

If no studies have directly compared the effects of alternative test strategies on downstream health outcomes, modeling the impact of diagnostic accuracy on the health outcomes could inform management decisions (2, 3). For example, false negatives (FN) and false positive (FP) test results, by missing or delaying the diagnosis (FN) or through unnecessary treatment (FP), can adversely impact health outcomes (2, 3). GRADE previously described that to evaluate impact, one may, through formal or informal modeling, link different types of evidence: diagnostic test accuracy estimates (e.g. sensitivity and specificity), direct effects of the test(s) (e.g. complications of an invasive test), natural course of the condition, treatment effectiveness and the link between the test results and clinical management (2-5). Arriving at an overall rating of certainty of evidence requires rating every component.

This article explores possible ways of setting thresholds or ranges for rating certainty in diagnostic test accuracy, and what this would mean in the context of systematic reviews, health technology assessment and healthcare recommendations. GRADE has described approaches for setting thresholds or ranges in terms of levels of contextualization (1). Box 1 presents levels of

contextualization for diagnostic accuracy, concepts that this paper will further illustrate. The discussion is consistent with previous guidance on rating certainty in diagnostic accuracy (2-5).

#### **Box 1. Degree of contextualization when defining range**

**Non-contextualized (primarily for systematic reviews and health technology assessments).** The ranges used are independent of value judgments regarding – e.g. the relative importance of false negatives versus false positives.

**Partially contextualized (primarily for systematic reviews and health technology assessments).** The ranges depend on some value judgment – e.g. the importance of downstream health consequences of true and false positives and negatives. This approach to contextualization requires setting boundaries of ranges expressed in absolute terms for a given prevalence.

**Fully contextualized (primarily for guidelines and other decision making).** The boundaries are set considering the range of possible effects on all critical outcomes, bearing in mind the decision(s) that need to be made, and the associated values and preferences. This approach to contextualization requires setting boundaries of ranges expressed in absolute terms for a given prevalence.

#### **Definitions and scope**

In our previous work clarifying the construct of certainty of evidence, we used the term *threshold* as a set border (e.g. a threshold at which the benefits start outweighing the harms) and the term *range* when using two borders (e.g. the upper and lower limits of a small effect). Although one could use the same terminology for the borders set in test accuracy, to avoid confusion with the thresholds used to dichotomize the test results for a particular test, throughout this paper we will use *range* meaning *threshold or range*.

We use the term *test strategy* to denote a combination of tests (e.g. clinical test followed by MRI), not to be confused with test-treatment strategy that also includes the treatment that is guided by the test result (2). The test under consideration can have different roles within a test strategy: to replace an existing test, as triage test before an existing test, as an add-on to an existing test (6), or parallel to an existing test (7). When evaluating diagnostic accuracy of a test, it is important to define the role of the test to address the accuracy of the full test strategy. The approaches for setting ranges suggested in this paper apply to all types of test strategies. We will present the approaches for

comparisons between tests as well as for single tests, but our main focus will be on the comparative scenario which we will further explain below.

When addressing the certainty of evidence for test accuracy, we are presenting and rating ranges for sensitivity and specificity. However, when interpreting a test result in clinical practice, multilevel likelihood ratios or multivariable approaches may be more useful.

We refer to *non-contextualized* certainty ratings if authors make choices of ranges without value judgments, that do not involve modelling. The term *fully contextualized* refers to situations in which the entire health care question/context is considered when assessing the certainty of sensitivity and specificity, typically in the setting of a guideline (1). Less contextualized ratings are typically made in systematic reviews and health technology assessments (HTA). We will continue to make distinctions between certainty ratings that are fully contextualized (considering all critical outcomes with their associated values within a particular decisional context), partly contextualized (including some value judgment regarding the importance of the individual outcome), and non-contextualized (without value judgments). Non- or partially contextualized approaches refer only to the chosen ranges, and not to other decisions. For instance, authors of systematic reviews always need to consider the context of interest, for example in their eligibility criteria (e.g. only including studies with a certain prevalence or setting), or when assessing indirectness.

Currently, authors use decision models of varying complexity to inform decisions regarding test strategies: ranging from back of the envelope estimations of the possible consequences to advanced models estimating all benefits and harms to the patients as well as the uncertainty associated with the parameters in the model (3). We will exemplify the contextualized approaches using a simple model estimating the consequences of changes in the sensitivity and specificity of the test strategies. However, the concepts we present apply to any level of modelling, requiring only consideration of all critical direct and downstream outcomes.

### **Comparisons of test strategies**

If the goal is to evaluate two test strategies, one can compare the accuracy of the two tests using a study design in which one administers the tests in the same population comparing to the same reference standard (direct comparison) (8). In many cases, however, primary research has only studied the accuracy of single tests against a reference standard in separate populations and separate studies. In these cases, the comparison between the relevant tests will be indirect, leading to additional challenges beyond the scope of this paper.

Table 1 shows possible approaches for setting ranges in sensitivity and specificity and illustrates what the certainty ratings represent for a direct comparison versus a single test. We will start by presenting an overview of the suggested approaches and then continue with an example of applying the approaches to a direct comparison.

**Non-contextualized ratings of test accuracy (typically for systematic reviews and health technology assessments)**

We refer to the first two approaches presented in Table 1 as non-contextualized, meaning that the choice of the boundaries for the range of sensitivity and specificity does not involve value judgments (box 1). That is, the importance of the number of false negatives or false positives does not bear on the ranges chosen, and the downstream consequences of the test results have no influence on the certainty ratings of sensitivity and specificity. Analysts use these approaches when they wish to assess the certainty of the test accuracy without further interpreting the results or providing advice.

*Using the ranges of the confidence intervals*

The first approach assesses how certain we are that the true sensitivity and specificity lies within the observed confidence intervals. Using this approach, one omits the rating of imprecision, i.e. one could have high certainty that the true sensitivity or specificity lies within the range set by the confidence interval regardless of whether this range is wide or narrow. The ranges can be presented for sensitivity and specificity, or for the number of false positives and false negatives given a particular pre-test probability. In comparing two tests, one will rate the certainty of the difference in sensitivity and specificity, or false positives and negatives between the tests under consideration. This approach could potentially mean that we express high certainty in very imprecise results.

*Using the direction of effect*

The second approach assesses our certainty regarding whether a difference exists between the accuracy of two test strategies. In other words: How certain are we that Test A has a higher/lower sensitivity or specificity than Test B? In some cases, one would want to address the certainty that the true difference in test accuracy lies close to no difference. This requires a decision regarding what difference would be trivial and thus requires a partly contextualized judgment that we describe below.

**Partly contextualized ratings of certainty: Ranges of magnitude of accuracy (typically for systematic reviews and health technology assessments)**

The third option described in Table 1 is to rate our certainty in a specific accuracy. When applying this approach to a comparison between two tests, one could specify categories of no or trivial, small, moderate, or large difference in accuracy. Similarly, when evaluating the accuracy of a single test in comparison to the reference standard, one could specify trivial, low, moderate, or high accuracy. This approach requires setting boundaries of ranges expressed in absolute terms for a given prevalence – boundaries that likely will depend on the value placed on the direct effects (i.e. burdens/adverse effects) of the test as well as the downstream health consequences of the true and false positives and negatives.

For example, consider a situation in which the downstream health consequences of a management decision are serious, such as recurrence of disease. In such situations, ranges of false positives and negatives will have a lower value than if the downstream consequences are less serious such as minor adverse events or length of hospital stay.

#### **Fully contextualized ratings (typically for guidelines) of test accuracy**

When we make fully contextualized ratings, we are simultaneously weighing the benefits and harms of every critical or important health outcome or even all desirable and undesirable consequences (1) (box 1). In the absence of studies comparing the health consequences of tests, one would ideally use a fully developed model for assessing the effects of the test strategies on patient important outcomes. If such models can generate estimated effects with confidence intervals, one can make fully contextualized ratings of the patient important outcomes in the same way as we have previously described (1). The accuracy data would in this case be one of several pieces of data feeding into the model.

Currently guideline panels seldom have access to advanced models. As a result they will inevitably focus on diagnostic accuracy (9-11). Here we discuss how one can, in these cases, make fully contextualized ratings of sensitivity and specificity, i.e. address whether one would make a different decision at either end of the certainty ranges. One can then use models or explicit considerations to decide what sensitivity and specificity one would require to recommend a particular test. That is, what levels of sensitivity and specificity would be required to ensure that the desirable health effects will outweigh the undesirable. In some cases, it is also possible to set ranges for sensitivity and specificity by inferring decision thresholds from other recommendations and decisions about testing (12).



When all else is judged exactly equal between the two test strategies (e.g. side effects, invasiveness, resources considerations, timing of test, location of test in the care pathway, feasibility, availability), the fully contextualized range would be the same as the non-contextual no-effect range. Although it is unlikely to occur, one could then base a decision solely on knowledge of whether the test accuracy increases or decreases with one test-strategy compared with another (9, 13, 14).

Fully contextualized ranges are often decided on through discussions in guideline panels, based on what is known about the direct and downstream health outcomes of the test strategies. In some cases, panels conduct formal surveys of their members to establish test and treatment thresholds (15). In some situations, considering downstream health outcomes can be sufficient and no formal modeling is needed - for example if it is obvious that the health consequences of using the test would be negative.

We will now illustrate how simple models of health outcomes can inform the choice of fully contextualized ranges for sensitivity and specificity. If the values are very uncertain, or the results will be used in several different contexts, one can provide several certainty ratings, each for a specific set of values.

**Table 1.** Possible ways of setting ranges for sensitivity and specificity, and what the certainty expressed will represent for a comparison between tests vs single test

Degree of contextualization	Range	How it is set	What the certainty rating represents	
			For a comparison between tests	For a single test
Non-contextualized  (primarily for systematic reviews and health technology assessment)	Range: 95% Confidence Interval	Using existing limits of the 95% CIs, which implies precision is not routinely part of the rating	Certainty that the true difference in accuracy lies within the confidence region of the tests compared or the true difference in sensitivity and specificity lies within their respective confidence intervals	Certainty that the true sensitivity and specificity lies within their respective confidence intervals
	Difference $\neq$ 0	Using the threshold of null effect	Certainty that the sensitivity or specificity of one test strategy differs from that of another	Not applicable
Partially contextualized  (primarily for systematic reviews and health technology assessment)	Specified magnitude (set in natural frequencies for a given prevalence)	E.g. a small difference in sensitivity or specificity can be defined as a difference small enough that one might consider not using the test if adverse effects or costs are appreciable	Certainty in a specified magnitude of difference between the sensitivity or specificity of two tests (e.g. no or trivial, small, medium or large difference)	Certainty in a specified magnitude of sensitivity or specificity (e.g. low, moderate or high accuracy)*
Fully contextualized  (primarily for guidelines)	Threshold determined with considerations of all critical outcomes (set in natural	Considering the range of possible effects on all critical outcomes (3), bearing in mind the decision(s) that need to be made, and the associated values	For each outcome (in this case sensitivity and specificity), ratings represent our confidence that the overall balance between net benefit and net harm will not differ	For each outcome (in this case sensitivity and specificity), ratings represent our confidence that the overall balance between net benefit and net harm will not differ

	frequencies for a given prevalence)	and preferences	from one end of the certainty range** to the other.	from one end of the certainty range** to the other.
--	-------------------------------------	-----------------	---	---

\*This will have to be specific to the test, condition and setting. Sensitivity of 97% may be considered extremely accurate for some conditions/test/setting while it may be considered low accuracy for a different scenario. This decision will be informed by the patient and population consequences based on the test results.

\*\*By *certainty range* we mean the range in which we anticipate that the true sensitivity or specificity may lie, after considering not only precision, but also risk of bias, inconsistency, indirectness and publication bias (1, 16).

### Applying ranges to direct comparisons of accuracy between test strategies

To make decisions about tests direct comparisons of the relevant test strategies are ideal. We will show what the approaches for setting ranges would mean in such a setting using the direct comparison of accuracy between two tests for cervical cancer screening, the Human Papilloma Virus (HPV) test (HPV DNA-PCR testing) and unaided visual inspection of the cervix with acetic acid (VIA) (17).

Cervical intraepithelial neoplasia (CIN) is a premalignant lesion diagnosed by histology, in 3 stages: CIN 1, CIN 2, and CIN 3. If left untreated, CIN 2 or 3 (CIN2-3) can progress to cervical cancer. HPV causes virtually all cancer of the cervix and is the most common sexually transmitted disease (18). The setting for this example is a screen-treat strategy in low- and middle-income countries, in which treatment is provided to all with a positive screening test.

We used this example in prior GRADE articles (2, 3, 5). It is based on a systematic review of five studies assessing the accuracy of HPV and VIA against a common reference standard (a combination colposcopy with or without biopsy and in some instances clinical follow up as well) (17). For the HPV test, the pooled sensitivity was 95% (95% CI: 84 to 98) and the pooled specificity 84% (95% CI: 72 to 91), and for VIA the pooled sensitivity was 69% (95% CI: 54 to 81) and the pooled specificity 87% (95% CI: 79 to 92). The diagnostic sensitivity is 26% points higher with HPV compared to VIA (95% CI: 11-41% higher) while the specificity is 3% lower (95% CI: 15% lower to 8% higher) (method in appendix 1). At the estimated prevalence in the general population of 2%, based on WHO data (18), if 1000 women are screened with the HPV test instead of VIA, 5 more true positives will be found (2

to 8 more) while there will be 34 more false positives (147 more to 78 fewer), who would receive treatment.

No serious concerns regarding risk of bias, indirectness or publication bias for this comparison of test accuracy were identified. Whether there are serious problems with inconsistency (the estimated differences in sensitivity with HPV vs VIA in the included five studies ranged from an increase of 1% to an increase in 56%, and the estimated difference in specificity ranged from a decrease of 22% to an increase in 9%) and imprecision will depend on the ranges used; those judgments are described below.

*Non-contextualized approaches (primarily for systematic reviews or health technology assessments)  
Using the ranges of the confidence intervals*

The first non-contextualized approach listed in Table 1 is to assess our certainty in the ranges defined by the 95% confidence intervals. In this case we would be rating how certain we are that the sensitivity of the HPV test is 11% to 41% higher than VIA and the specificity is somewhere between 15% lower to 8% higher. Since the estimated difference of the test accuracy results in individual studies are outside of these ranges, we might rate down for inconsistency in both sensitivity and specificity. With this approach, we do not judge the width of the intervals, i.e. precision is omitted from the ratings, and since no serious concerns were identified for the other domains, we would end up with moderate ratings of certainty for the ranges set by the 95% CIs (Table 2). Different target audiences can use these ranges with certainty ratings for their particular goals, for example as input into a model for estimating downstream consequences.

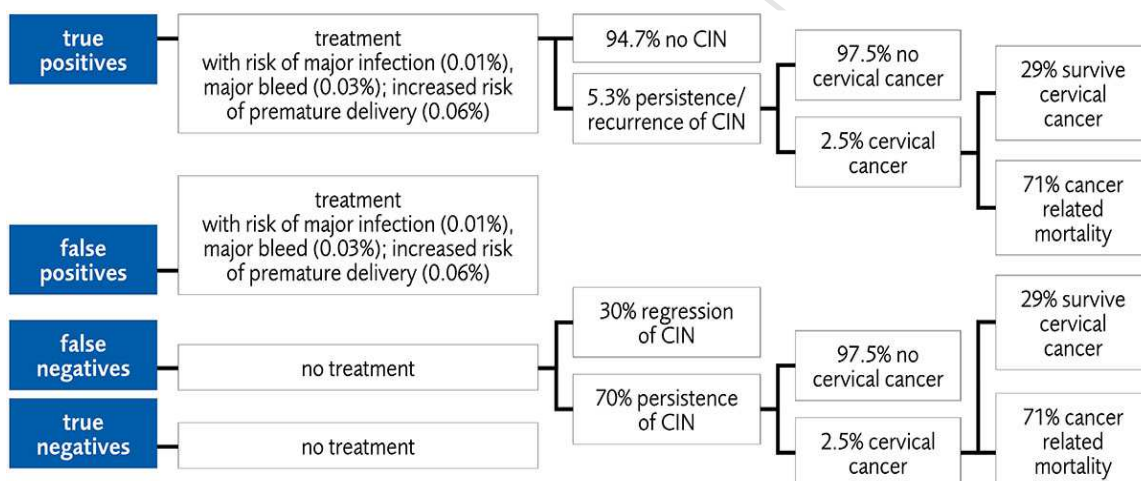
*Using the direction of effect*

The second non-contextualized approach for defining ranges is to use the boundary of no difference in sensitivity or specificity. When doing so, we are addressing our certainty in the direction (increase or decrease) of sensitivity and specificity, neglecting the magnitude of the difference. In this case, we would be rating how certain we are that by using the HPV test rather than VIA we would increase the sensitivity and decrease the specificity. Since the entire confidence interval for the difference in sensitivity lies on one side of no effect, as well as the estimated differences in all the included studies, we would not rate down for imprecision or inconsistency and we would have high certainty that the HPV test indeed increases the sensitivity for detecting CIN 2-3. On the other hand, there is a serious problem with imprecision for specificity since the confidence interval reaches from a decrease of 15% to an increase of 8%. Furthermore, individual studies have estimated differences in

specificity between an increase in 9% and a decrease in 22%, and we would therefore rate down for both imprecision and inconsistency (Table 2).

*Partly contextualized ratings of certainty: Ranges of magnitude of accuracy (primarily for systematic reviews and health technology assessments)*

Using this approach, one would define ranges for a trivial, small, moderate or large difference in sensitivity and specificity. Since these judgments are based on the downstream health consequences, reviewers must address these clearly in the beginning of the review process. In our example, a simple model was used based on five outcomes: cervical cancer, cervical cancer related mortality, major bleeds, premature delivery and major infections (Figure 1, and detailed explanation in appendix 1). Cervical cancer and cervical cancer related mortality due to false negative test results could be reduced using a test with a higher sensitivity. Major bleeds, premature delivery and major infections due to false positive test results can be reduced using a test with a higher specificity.



**Figure 1.** Estimated consequences of the four possible test results for CIN. The setting for this example is a screen-treat strategy in low- and middle-income countries, in which treatment is provided to all with a positive screening test.

The model provides approximations regarding how differences in sensitivity and specificity will affect the outcomes of interest. At a prevalence of 2% (18), increasing sensitivity by 1% would result in approximately 2 fewer cervical cancer related deaths and 3 fewer cases of cervical cancer per million women screened. A 1% increase in specificity will result in approximately 3 fewer major bleeds, 6 fewer premature births and 1 less major infection per million women screened. One can use this information to guide the choice of ranges for no or trivial, small, moderate, or large difference in

sensitivity or specificity. As previously noted, the choices of ranges will likely differ depending on the value placed on the outcomes. In contrast to a range set directly on a patient-important outcome, the ranges for sensitivity and specificity can be affected by several downstream health outcomes. This is illustrated in Table 3, in which examples of ranges for the difference in sensitivity and specificity for HPV versus VIA are presented.

For this example, the point estimate for sensitivity was within the presented range of a large increase. As the CI crosses the border of a moderate increase, and individual studies have estimated differences that can be considered trivial or small, the certainty rating is low due to imprecision and inconsistency. For specificity, the point estimate is within the range defined as a no or trivial difference. Since the CI crosses the border to a small decrease, one would rate down for imprecision. Also, one of the included studies has an estimated decrease of 22% in specificity (considered a medium-large difference), which might warrant rating down for inconsistency, in which case the certainty rating would be low (Table 2).

**Table 2.** Examples of certainty ratings for the difference in sensitivity and specificity between HPV and VIA. The partially and fully contextualized ranges are set considering a prevalence of 2%.

Approaches	Examples of set ranges	Certainty
<b>Range: 95% Confidence Interval</b>	<p>Sensitivity: The 95% CI, in this case an increase by 11-41% (at a pre-test probability of 2%, 2-8 more true positives per 1000 women screened.)</p> <p>Specificity: The 95% CI, in this case a decrease by 15% to increase by 8% (at a pre-test probability of 2%, 147 more to 78 fewer false positives per 1000 women screened)</p>	<p>We have <b>moderate certainty</b> that the true increase in sensitivity is between 11 and 41% (rating down for inconsistency)</p> <p>We have <b>moderate certainty</b> that the true difference in specificity is between an 15 % decrease to an 8% increase (rating down for inconsistency)</p>
<b>rsens ≠ 1, rspec ≠ 1</b>	Direction of effect	We have <b>high certainty</b> that the sensitivity of HPV testing is higher than

		<p>VIA for detecting CIN 2-3</p> <p>We have <b>low certainty</b> that the specificity of HPV testing is lower than VIA for detecting CIN 2-3 compared to VIA (rating down for imprecision and inconsistency)</p>
<p><b>Specified magnitude of difference in sensitivity and specificity</b></p>	<p>The set range for a large effect on sensitivity was a difference in more than 4 TP per 1000 screened (corresponds to mortality of more than 50 and cervical cancer cases of more than 60, per million screened)</p> <p>The set range for a no or trivial effect on specificity was a difference in up to 200 FP per 1000 screened (corresponds to a difference of up to approx.33 major bleeds, 120 premature births, 13 major infections per million women screened)</p>	<p>We have <b>low certainty</b> that HPV has a large increase in sensitivity compared to VIA (rating down for imprecision and inconsistency)</p> <p>We have <b>low certainty</b> that there is no or trivial difference in specificity between HPV and VIA (rating down for imprecision and inconsistency)</p>
<p><b>Range determined with considerations of all critical direct and downstream health outcomes or all desirable and undesirable consequences</b></p>	<p>Thresholds based on the values we place on mortality and cervical cancer vs major bleeds, premature delivery and major infections.</p>	<p>Considering downstream health outcomes, we have <b>low certainty in the sensitivity</b> outcome, i.e. this outcome may not shift the overall balance between net benefit and net harm (rating down for imprecision and inconsistency).</p>

		Considering downstream health outcomes, we have <b>low certainty in the specificity outcome</b> , i.e. this outcome may not shift the overall balance between net benefit and net harm (rating down for imprecision and inconsistency).
--	--	---

ACCEPTED MANUSCRIPT



**Table 3.** Example of ranges set for different magnitudes of difference in sensitivity and specificity for HPV vs VIA\*. The boundaries of the ranges represent a hypothetical group consensus based on the importance placed on cervical cancer and cervical cancer related mortality (for sensitivity), and major bleeds, premature births and major infections (for specificity).

Sensitivity	Specificity
No or trivial difference in sensitivity: 0-4% Difference in 0-1 TP found per 1000 screened (corresponds to a difference in mortality of up to 10, and cervical cancer cases of up to 12, per million screened)	No or trivial difference in specificity: 0-10% Difference in 0-100 FP per 1000 screened (corresponds to a difference of up to approx.33 major bleeds, 60 premature births, 13 major infections per million women screened)
Small difference in sensitivity: 4-10% 1-2 TP per 1000 screened (corresponds to a difference in mortality of around 10-25, and cervical cancer cases of around 12-30, per million screened)	Small difference in specificity: 10-20% 100-200 FP per 1000 screened (corresponds to a difference of approx.33-66 major bleeds, 60-120 premature births, 13-26 major infections per million women screened)
Moderate difference in sensitivity: 10-20% 2-4 TP per 1000 screened (corresponds to a difference in mortality of around 25-50, and cervical cancer cases of around 30-60, per million screened)	Moderate difference in specificity: 20-30% 200-300 FP per 1000 screened (corresponds to a difference of approx.66-100 major bleeds, 120-180 premature births, 26-39 major infections per million women screened)
Large difference in sensitivity: more than 20% >4 TP per 1000 screened (corresponds to mortality of more than 50 and cervical cancer cases of more than 60, per million screened)	Large difference in specificity: more than 30% >400 FP per 1000 screened (corresponds to a difference of approx. 100 or more major bleeds, 240 or more premature births, 39 or more major infections per million women screened)

\* The values for sensitivity and specificity represent the absolute ranges at a prevalence of 2%

*Fully contextualized ratings (primarily for guidelines or other decisions) of test accuracy*

When making fully contextualized ratings of the difference in sensitivity and specificity, we start by considering the downstream health outcomes (Figure 1). Moreover, just as for treatment interventions, we will have to specify values for all critical health outcomes. The values should be

those of the patients, and the process for obtaining them can include a systematic review of the relevant literature, the experience of the topic experts in conducting shared decision-making, consultation with patients and patient groups, and conduct of targeted surveys (19-21).

In the present example, the guideline panel might infer that women eligible for screening would value major infections and major bleeds equally, premature delivery twice as high, and would place an appreciably greater value on cervical cancer and cervical cancer related mortality, say seven and 20 times higher, respectively. Such an inference may be informed by, for example, reported utility estimates from similar clinical contexts (22-24).

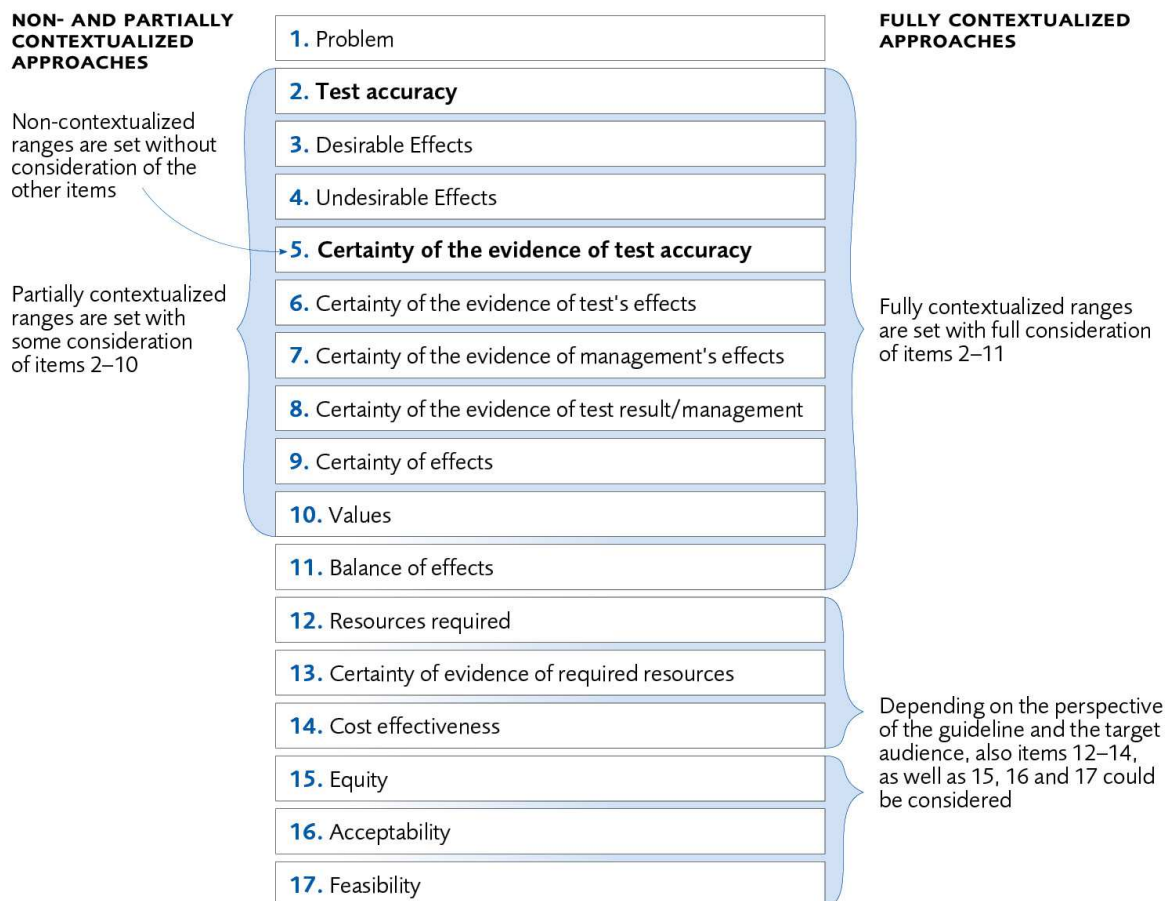
The question will be how much harm we are willing to accept given a certain benefit, or the other way around. For this particular example, the guideline panel will consider how certain they are that the increase in sensitivity is high enough to outweigh the potential decrease in specificity. At a prevalence of 2%, the estimated effect of increasing sensitivity with 1% is 2.5 fewer cervical cancer related deaths and 3 fewer cervical cancer cases per million women screened. Correspondingly, the estimated effect of increasing specificity with 1% would be 6 fewer premature deliveries, 1.3 fewer major infections and 3.3 fewer major bleeds per million women screened.

Using the estimated effects on downstream health outcomes and the values suggested above, the guideline development group decided to accept a 4.5% decrease in specificity for every percentage increase in sensitivity (calculation in Appendix Table 1). This means that even if the lower limit of the CI of sensitivity (11% increase) were true, we would accept an increase in specificity of 50%. Since the entire CI of specificity is within this range, one would not rate down for imprecision in the specificity outcome. For the same reason, we would not rate down for imprecision in the sensitivity outcome. One should, however, also consider the uncertainty of the estimated downstream health outcomes on which we are basing the chosen range. Is it, for example, possible that the increased risk of premature delivery in treated women is 0.4% instead of the estimated 0.06%? If this is plausible, we would only accept an increase in specificity of 0.9% for every percentage increase in sensitivity (calculation in Appendix Table 2), and rating down for both imprecision and inconsistency for sensitivity and specificity would be warranted.

Just as for intervention effects, the fully contextualized ratings represent a sensitivity analysis addressing whether the test outcomes being considered (in this case sensitivity and specificity) are influential in altering the overall net benefit or harm.

### Certainty ratings in the Evidence to Decision framework (EtD)

As illustrated above, the ranges with different levels of contextualization will take into account one or several of the criteria in the EtD (figure 2, (2)). For the non-contextualized ranges, only test accuracy is considered, whereas some level of consideration of the positive and negative health outcomes and values of these will be needed to set the partially contextualized ranges. For the fully contextualized ranges, all direct and downstream health outcomes are considered, as well as the balance of effects based on patient values. Depending on the perspective taken in the guideline one could choose to also incorporate resource use, as well as issues of equity, acceptability and feasibility when setting the fully contextualized ranges for sensitivity and specificity. For example, from a policy makers' perspective, one might want to include resources, such as further expensive testing in false positives, or more expensive treatments due to delayed diagnosis in false negatives.



**Figure 2.** The 17 items in the Evidence to Decision framework (2) and how the illustrated non-, partially- and fully contextualized approaches for setting ranges relate to them.

### DISCUSSION

This paper illustrates the concepts of certainty of evidence applied to test accuracy. We show that defining ranges for the certainty ratings is important, since the ranges chosen will affect the interpretation of the result and the degree of certainty presented. More empirical data is needed to inform approaches for defining ranges that would be most useful, and to what degree different levels of modeling will affect the decisions being made.

Situations also exist that are complicated by issues related to research on tests. For example, primary research on test accuracy is historically seldom performed with direct comparisons between tests. Therefore, most often systematic review authors, health technology assessors and guideline developers will not have access to primary studies directly comparing the accuracy of the relevant test strategies. Although this is starting to change, currently many decisions will have to be made based on indirect comparisons. Future studies are needed to inform how best to deal with these specific challenges.

Modelling of downstream health outcomes will inevitably include assumptions, which some review authors might feel reluctant to make. However, making decisions about tests will always require judgments regarding the importance of outcomes, though guideline panels or decision-makers may not make their judgments explicit. An advantage of the fully contextualized approach for guideline development presented in this paper, is the transparency of all assumptions made.

### **Conclusions**

Previous work has shown that the certainty of evidence is a rating of our certainty that the true effect lies in a particular range. Although the examples related to intervention effects, previous guidance suggested that review authors specify the relevant thresholds underlying the certainty judgments. This guidance also applies to questions of diagnosis. In this conceptual paper, we have illustrated what the suggested approaches for defining ranges would mean when rating sensitivity and specificity in the context of systematic reviews, health technology assessments or guidelines.

### **Acknowledgments**

The authors would like to thank colleagues who have contributed to the article during group discussions at GRADE Working Group meetings, or discussions at the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU). The authors also thank Dr Emelie Heintz for input on health economic modeling and Graphic Designer Elin Rye-Danjensen for assisting with the figures, both at SBU.

## References

1. Hultcrantz M, Rind D, Akl EA, Treweek S, Mustafa RA, Iorio A, et al. The GRADE Working Group clarifies the construct of certainty of evidence. *J Clin Epidemiol.* 2017;87:4-13.
2. Schunemann HJ, Mustafa R, Brozek J, Santesso N, Alonso-Coello P, Guyatt G, et al. GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. *J Clin Epidemiol.* 2016;76:89-98.
3. Schunemann HJ, et al. GRADE Guidelines: 22. The GRADE approach for tests and strategies - from test accuracy to patient important outcomes and recommendations. Accepted pending revision.
4. Schunemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ.* 2008;336(7653):1106-10.
5. Schunemann HJ, et al. Manuscript in preparation.
6. Bossuyt PM, Irwig L, Craig J, and Glasziou P. Comparative accuracy: assessing new tests against existing diagnostic pathways. *BMJ.* 2006;332(7549):1089-92.
7. Mustafa RA, Wiercioch W, Cheung A, Prediger B, Brozek J, Bossuyt P, et al. Decision making about healthcare-related tests and diagnostic test strategies. Paper 2: a review of methodological and practical challenges. *J Clin Epidemiol.* 2017;92:18-28.
8. Takwoingi Y, Leeflang MM, and Deeks JJ. Empirical evidence of the importance of comparative studies of diagnostic test accuracy. *Ann Intern Med.* 2013;158(7):544-54.
9. Mustafa RA, Wiercioch W, Ventresca M, Brozek J, Schunemann HJ, and group DU-De. Decision making about healthcare-related tests and diagnostic test strategies. Paper 5: a qualitative study with experts suggests that test accuracy data alone is rarely sufficient for decision making. *J Clin Epidemiol.* 2017;92:47-57.
10. Mustafa RA, Wiercioch W, Santesso N, Cheung A, Prediger B, Baldeh T, et al. Decision-Making about Healthcare Related Tests and Diagnostic Strategies: User Testing of GRADE Evidence Tables. *PLoS One.* 2015;10(10):e0134553.
11. Mustafa RA, Wiercioch W, Arevalo-Rodriguez I, Cheung A, Prediger B, Ivanova L, et al. Decision making about healthcare-related tests and diagnostic test strategies. Paper 4: International guidelines show variability in their approaches. *J Clin Epidemiol.* 2017;92:38-46.
12. Pepe MS, Janes H, Li CI, Bossuyt PM, Feng Z, and Hilden J. Early-Phase Studies of Biomarkers: What Target Sensitivity and Specificity Values Might Confer Clinical Utility? *Clin Chem.* 2016;62(5):737-42.
13. Lord SJ, Irwig L, and Bossuyt PM. Using the principles of randomized controlled trial design to guide test evaluation. *Med Decis Making.* 2009;29(5):E1-E12.
14. Lord SJ, Staub LP, Bossuyt PM, and Irwig LM. Target practice: choosing target conditions for test accuracy studies that are relevant to clinical practice. *BMJ.* 2011;343:d4684.
15. Hsu J, Brozek JL, Terracciano L, Kreis J, Compalati E, Stein AT, et al. Application of GRADE: making evidence-based recommendations about diagnostic tests in clinical practice guidelines. *Implement Sci.* 2011;6:62.
16. Schunemann HJ. Interpreting GRADE's levels of certainty or quality of the evidence: GRADE for statisticians, considering review information size or less emphasis on imprecision? *J Clin Epidemiol.* 2016;75:6-15.
17. Mustafa RA, Santesso N, Khatib R, Mustafa AA, Wiercioch W, Kehar R, et al. Systematic reviews and meta-analyses of the accuracy of HPV tests, visual inspection with acetic acid, cytology, and colposcopy. *Int J Gynaecol Obstet.* 2016;132(3):259-65.
18. Santesso N, Mustafa RA, Schunemann HJ, Arbyn M, Blumenthal PD, Cain J, et al. World Health Organization Guidelines for treatment of cervical intraepithelial neoplasia 2-3 and

- screen-and-treat strategies to prevent cervical cancer. *Int J Gynaecol Obstet*. 2016;132(3):252-8.
19. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol*. 2013;66(7):726-35.
  20. Zhang Y, Alonso-Coello P, Guyatt GH, Yepes-Nunez JJ, Akl EA, Hazlewood G, et al. GRADE Guidelines: 19. Assessing the certainty of evidence in the importance of outcomes or values and preferences-Risk of bias and indirectness. *J Clin Epidemiol*. 2018.
  21. Zhang Y, Coello PA, Guyatt GH, Yepes-Nunez JJ, Akl EA, Hazlewood G, et al. GRADE guidelines: 20. Assessing the certainty of evidence in the importance of outcomes or values and preferences-inconsistency, imprecision, and other domains. *J Clin Epidemiol*. 2018.
  22. Kuppermann M, Melnikow J, Slee C, Tancredi DJ, Kulasingam S, Birch S, et al. Preferences for surveillance strategies for women treated for high-grade precancerous cervical lesions. *Gynecol Oncol*. 2010;118(2):108-15.
  23. Soergel P, Makowski L, Schippert C, Staboulidou I, Hille U, and Hillemanns P. The cost efficiency of HPV vaccines is significantly underestimated due to omission of conisation-associated prematurity with neonatal mortality and morbidity. *Hum Vaccin Immunother*. 2012;8(2):243-51.
  24. Wang K, Li H, Kwong WJ, Antman EM, Ruff CT, Giugliano RP, et al. Impact of Spontaneous Extracranial Bleeding Events on Health State Utility in Patients with Atrial Fibrillation: Results from the ENGAGE AF-TIMI 48 Trial. *J Am Heart Assoc*. 2017;6(8).

## APPENDIX – background to HPV example, methods and model

### Background

Cervical intraepithelial neoplasia (CIN) is a premalignant lesion that is diagnosed by histology, in 3 stages: CIN 1, CIN 2, and CIN 3. If left untreated, CIN 2 or 3 (CIN2-3) can progress to cervical cancer. Standard practice for diagnosing CIN is to perform a colposcopy, biopsy suspicious lesions, and then treat only when CIN2-3 has been histologically confirmed. Additionally, it is known that persistent viral infection with carcinogenic Human Papilloma Virus (HPV) genotypes causes virtually all cancer of the cervix. HPV is the most common sexually transmitted disease known. Most HPV infections, including carcinogenic HPV genotypes, typically resolve within 6 to 12 months. However, women with persistent carcinogenic HPV infections are at risk of developing precancerous lesions, although not all persistent infections progress. Treatment is typically surgical and there are three principal interventions available in low- and middle-income countries to treat CIN: cryotherapy (freezing the lesion), large loop excision (cutting using electrocautery) of the transformation zone (LEEP/LLETZ), and cold knife (cutting without electrocautery) conisation (CKC) (1).

An alternative approach to diagnose and treat CIN is to 'screen and treat' in which treatment decisions are based on a screening test, instead of histologically confirmation of CIN 2-3, and treatment is provided soon, or ideally, immediately after a positive screening test. The goal of a screen and treat program for cervical cancer is to reduce cervical cancer and related mortality with relatively few adverse events. Common screening tests that are widely used are tests for the Human Papillomavirus (HPV), cytology (PAP) and unaided visual inspection with acetic acid (VIA). Countries currently providing or considering screen and treat strategies may be uncertain about whether or not to provide one test (or strategy) over another.

For the rest of this example, we will be interested in a screen-treat strategy assessing HPV compared to VIA as a screening test for women who are at risk for CIN 2-3 and then followed by cryotherapy as the treatment of choice.

### METHODS - Summary estimates of sensitivity and specificity

We used the bivariate random-effects model (2, 3) to estimate the summary sensitivity and specificity of both HPV and VIA. This approach allowed us to calculate summary estimates of the mean sensitivity and specificity while dealing with potential sources of variation caused by: (1) imprecision of sensitivity and specificity estimates within individual studies; (2) correlation between sensitivity and specificity across studies; and (3) variation in sensitivity and specificity between studies. All five available studies were included in the model twice: once for HPV and once for VIA. A

covariate for test-type was added to the model, so that we could assess the association between test-type and sensitivity or specificity, or both. We included separate variance terms for each test. Based on the summary estimates of sensitivity and specificity, we estimated the difference in estimated sensitivity and specificity between the two tests.

## **METHODS – Outcomes of the simple model for HPV vs VIA**

### **Prevalence of CIN**

The overall prevalence of CIN2-3 is estimated to 2% in the general population (4).

### **Mortality from cervical cancer**

In our simple model, we assumed that mortality from cervical cancer is a consequence of having CIN which means that mortality from cervical cancer can happen in any patients who have CIN. However, mortality from cervical cancer will happen at a different rate in those who are treated (TP) and in those who are missed and not treated (FN). We also assumed that there will be no mortality from cervical cancer in those who do not have CIN including both TN and FP.

To calculate the mortality from cervical cancer, we assumed 250 deaths per 350 women with cervical cancer. These numbers are based on Eastern Africa age standardized rates of cervical cancer and mortality provided by WHO at <http://globocan.iarc.fr>

Mortality is 250/350 in the group with cervical cancer = 0.7142

To calculate cervical cancer incidence in women with persistent CIN 2/3, we assumed 350 cervical cancers per 14000 women who have persistent CIN 2/3 (i.e. FN). This incidence is based on Eastern Africa age standardized rate of cervical cancer of 350 cervical cancers per 1000000 women, of whom 2% have CIN 2/3 (20000 women with CIN 2/3, and a subsequent 30% regression for a total of 14000 with persistent CIN 2/3). This data is available from WHO at <http://globocan.iarc.fr/>.

Incidence of cervical cancer in woman with persistent CIN2/3 = 350/14000 = 0.025

From the above, we calculated the mortality in women with persistent CIN2/3 as: **(0.7142 \* 0.025) = 0.0178**

Our calculations in the model are based on 70% natural persistence of CIN 2/3 with no treatment (30% regression) in FN.

(Persistence of CIN2/3 in FN group = (FN\*0.7)



Mortality in FN group will be **(FN\*0.7) \* 0.0178**

We assumed all TP are treated. Based on systematic reviews of treatment, we established that persistence/recurrence rates of CIN 2/3 are 5.3% in cryotherapy, and this was the value used in the model.

Mortality in TP group was **(TP\* 0.053) \* 0.0178**

In this example, the sensitivity of the test is a major determinant of the effect on mortality. This happens because:

- The outcome evaluated (mortality), depend on progression of CIN 2/3 in patients who have it whether treated (TP) or not (FN).
- Mortality occurs in a different proportion in TP and FN (less in TP because they receive effective treatment).
- All patients correctly identified as having the condition (TP) will be treated with cryotherapy that has proven useful in reducing development of cervical cancer and hence mortality from it.
- All patients mislabeled as not having the disease (FN) will not be treated. 30% of them will naturally regress and no longer have CIN2/3 and 70% of them will persist to have CIN 2/3.
- The FN group is the biggest contributor to mortality.
- A higher value of sensitivity, will maximize the number of the patients in the TP group and decrease the number in the FN group and will decrease the number of patients whom will not receive treatment.
- Specificity does not affect the numbers of patients who will die from cervical cancer.

From our simple modeling HPV Vs VIA test on mortality outcomes, we concluded that for each one point increase the sensitivity for HPV or VIA, mortality (deaths) will decrease by 2 to 3 per million in a population with 2% prevalence of CIN. We also conclude that change in specificity in this example does not affect mortality and that is simply related to our assumption that mortality from cervical cancer happens in TP and FN.

**Cervical cancer incidence CCI**

In our simple model, we assumed that cervical cancer is a consequence of having CIN which means that cervical cancer can happen in any patients who have CIN (TP and FN). However, cervical cancer will happen at a different rate in those who are treated (TP) and in those who are missed and not treated (FN). We also assumed that there will be no cervical cancer incidence in those who do not have CIN including both TN and FP.

To calculate cervical cancer incidence in women with persistent CIN 2/3, we assumed 350 cervical cancers per 14000 women who have persistent CIN 2/3 (i.e. FN). This incidence is based on Eastern Africa age standardized rate of cervical cancer of 350 cervical cancers per 1000000 women, of whom 2% have CIN 2/3 (20000 women with CIN 2/3, and a subsequent 30% regression for a total of 14000 with persistent CIN 2/3). This data is available from WHO at <http://globocan.iarc.fr/>.

Incidence of cervical cancer in woman with persistent CIN2/3 =  $350/14000 = 0.025$

Our calculations in the model are based on 70% natural persistence of CIN 2/3 with no treatment (30% regression) in FN.

(Persistence of CIN2/3 in FN group =  $FN * 0.7$ )

Incidence of cervical cancer in FN =  $(FN * 0.7) * 0.025 = FN * 0.0175$

We assumed all TP are treated. Based on systematic reviews of treatment, we established that persistence/recurrence rates of CIN 2/3 are 5.3% in cryotherapy, and this was the value used in the model.

If Incidence of cervical cancer in woman with persistent CIN2/3 =  $350/14000 = 0.025$

Incidence of cervical cancer in TP group was  $(TP * 0.053) * 0.025 = TP * 0.001325$

In this example, the sensitivity of the test is a major determinant of the effect on cervical cancer incidence. This happens because:

- The outcome evaluated (cervical cancer incidence), depend on progression of CIN 2/3 in patients who have it whether treated (TP) or not (FN).
- Incidence of cervical cancer occurs in a different proportion in TP and FN (less in TP because they receive effective treatment).
- All patients correctly identified as having the condition (TP) will be treated with cryotherapy that has proven useful in reducing development of cervical cancer.

- All patients mislabeled as not having the disease (FN) will not be treated. 30% of them will naturally regress and no longer have CIN2/3 and 70% of them will persist to have CIN 2/3.
- The FN group is the biggest contributor to cervical cancer incidence because this group do not receive treatment.
- A higher value of sensitivity, will maximize the number of the patients in the TP group and decrease the number in the FN group and will decrease the number of patients whom will not receive treatment.
- Specificity does not affect the numbers of patients who will die from cervical cancer.

From our simple modeling of HPV versus VIA test on cervical cancer incidence outcomes, we concluded that for each one point increase the sensitivity for HPV or VIA, new cases (incidence) will decrease by 3 per million in a population with 2% prevalence of CIN. We also conclude that change in specificity in this example does not affect incidence of cervical cancer and that is simply related to our assumption that cervical cancer incidence happens in TP and FN.

### **Major bleeding**

In our simple model, we assumed that major bleeding is a complication of treatment which means that major bleeding can happen in any patients who receives treatment whether they have CIN or not that includes TP and FP.

Based on systematic reviews of treatment, we established that 0.000339 of the population treated with cryotherapy will have major bleeding (1).

In this example, the specificity of the test is a major determinant of the effect on major bleeding. This happens because:

- The example assesses a relatively rare disease CIN2/3 with a low prevalence of 2% which means that only 2% of the patients will be TP and FN and 98% of the patients will be TN or FP
- Major bleeding is a complication of treatment in patients identified as having CIN 2/3 (Test positive)
- All patients identified as having the condition will be treated and suffer from complications whether they are correctly or incorrectly identified (TP or FP)

The FP group is the main drive for the patients with major bleeding because due to the low prevalence, 98% of the patients will be TN or FP

- A higher value of specificity, will minimize the number of the patients with false positive test. On the other hand, a lower value of specificity, will increase the number of the patients with false positive test results which will impact the number of patients with major bleeding.

In this example, using the simple model explained above, we found that with any sensitivity value above a minimum of 50% for HPV or VIA we can reduce 10 major bleeds with every 3% increase in the specificity. This trend is maintained regardless of the specificity value of the test and with sensitivity values equal to or greater than 50%.

### **Premature delivery**

Premature delivery is a complication which occurs in pregnant women in a low proportion, however the risk is higher after a treatment with cryotherapy whether they have CIN or not, i.e. TP and FP. Based on systematic reviews of treatment, we established that 0.0005 of the general population will have premature delivery and 0.001125 of the population treated with cryotherapy will have premature delivery (1).

In this example, the specificity of the test is a major determinant of the effect on premature delivery. This happens because:

- The example assesses a relatively rare disease CIN2/3 with a low prevalence of 2% which means that only 2% of the patients will be TP and FN and 98% of the patients will be TN or FP
- Premature delivery is a complication more frequent in patients identified as having CIN 2/3 (Test positive) after the treatment
- All patients identified as having the condition will be treated and suffer from complications whether they are correctly or incorrectly identified (TP or FP)
- The FP group is the main drive for the patients with premature delivery because due to the low prevalence, 98% of the patients will be TN or FP
- A higher value of specificity, will minimize the number of the patients with false positive test. On the other hand, a lower value of specificity, will increase the number of the patients with false positive test results which will impact the number of patients with major bleeding.

In this example, using the simple model explained above, we found that with any sensitivity value above a minimum of 84% for HPV or VIA we can reduce 6 premature deliveries with every 1% increase in the specificity. This trend is maintained regardless of the specificity value of the test and with sensitivity values equal to or greater than 50%.

**Major infections**

In our model, we assumed that major and minor infections are complications of treatment which means that major and minor infections can happen in any patients who receives treatment whether they have CIN or not, i.e. TP and FP.

Based on systematic reviews of treatment, we established that 0.000135 of the population treated with cryotherapy will have major infection (1).

In this example, the specificity of the test is a major determinant of the effect on major bleeding. This happens because:

- The example assesses a relatively rare disease CIN2/3 with a low prevalence of 2% which means that only 2% of the patients will be TP and FN and 98% of the patients will be TN or FP
- Major infection is a complication of treatment in patients identified as having CIN 2/3 (Test positive)
- All patients identified as having the condition will be treated and suffer from complications whether they are correctly or incorrectly identified (TP or FP)

The FP group is the main drive for the patients with major bleeding because due to the low prevalence, 98% of the patients will be TN or FP

- A higher value of specificity, will minimize the number of the patients with false positive test. On the other hand, a lower value of specificity, will increase the number of the patients with false positive test results which will impact the number of patients with major infection.

In this example, using the simple model explained above, we found that with any sensitivity value above a minimum of 50% for HPV or VIA we can reduce 13 major infections with every 10% increase in the specificity. This trend is maintained regardless of the specificity value of the test and with sensitivity values equal to or greater than 50%.

## Methods – how the fully contextualized ranges were set in the example

**Table 1. Using estimated downstream health outcomes**

With the exemplified values, with an increase of 1% sensitivity we can accept a decrease with 4.5% in specificity ( $74.5/16.6 = 4.5$ )

Increase with 1% sens	Unit value	Total value per outcome	Increase with 1% spec	Unit value	Total value per outcome
2.5 Deaths	20	50	6 Premature deliveries	2	12
3.5 Cervical cancers	7	24.5	1.3 Major infections	1	1.3
			3.3 Major bleeds	1	3.3
<b>Total value</b>		<b>74.5</b>			<b>16.6</b>

**Table 2. Using plausible shift in downstream health outcomes (increased risk of premature delivery in treated women 0.4% instead of the estimated 0.06%.)**

With the exemplified values, with an increase of 1% sensitivity we can accept a decrease with 0.8% in specificity ( $74.5/83 = 0.9$ )

Increase with 1% sens	Unit value	Total value per outcome	Increase with 1% spec	Unit value	Total value per outcome
2.5 Deaths	20	50	39.2 Premature deliveries	2	78.4
3.5 Cervical cancers	7	24.5	1.3 Major infections	1	1.3
			3.3 Major bleeds	1	3.3
<b>Total value</b>		<b>74.5</b>			<b>83.0</b>

## References

1. Santesso N, Mustafa RA, Wiercioch W, Kehar R, Gandhi S, Chen Y, et al. Systematic reviews and meta-analyses of benefits and harms of cryotherapy, LEEP, and cold knife conization to treat cervical intraepithelial neoplasia. *Int J Gynaecol Obstet.* 2016;132(3):266-71.
2. Chu H, and Guo H. A unification of models for meta-analysis of diagnostic accuracy studies. *Biostatistics.* 2009;10(1):201-3.
3. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, and Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol.* 2005;58(10):982-90.
4. Santesso N, Mustafa RA, Schunemann HJ, Arbyn M, Blumenthal PD, Cain J, et al. World Health Organization Guidelines for treatment of cervical intraepithelial neoplasia 2-3 and screen-and-treat strategies to prevent cervical cancer. *Int J Gynaecol Obstet.* 2016;132(3):252-8.

**What is new?****Key findings**

- This Grading of Recommendations Assessment, Development and Evaluation (GRADE) concept paper shows that the choice of ranges is important when rating the certainty of evidence for test accuracy, since it may affect the interpretation of the result and the degree of certainty presented.
- We present possible approaches for setting ranges for sensitivity and specificity for a single test and for a comparison of test options. The approaches are illustrated using an example of a direct comparison between two test strategies.

**What this adds to what was known?**

- The GRADE Working Group has previously clarified that the concept of certainty of evidence represents our confidence that the true effect lies above or below a threshold, or in a specified range. The frequent lack of direct evidence assessing the effect of medical tests on patient important outcomes highlights the need for a clarification of how these concepts apply to certainty ratings of test accuracy.

**What is the implication and what should change now?**

- When rating the certainty of evidence for test accuracy, it is important that systematic review authors, health technology assessors and guideline developers are transparent with the ranges they are using, the rationale for choosing them as well as with the value judgments made.
- More empirical data is needed before knowing which approaches, for defining ranges of accuracy, would be most useful for different purposes, and how to best operationalize them.

**Potential conflicts of interest as reported by the authors**

All authors are members of the GRADE Working Group

<b>Author</b>	<b>Potential conflict of interest or funding</b>
Monica Hultcrantz Monica.hultcrantz@sbu.se	Dr. Hultcrantz has nothing to disclose.
Reem Mustafa ramustafa@gmail.com	Dr. Mustafa has nothing to disclose.
Mariska M.G. Leeflang m.m.leeflang@amc.uva.nl	Dr. Leeflang has nothing to disclose.
Miranda W. Langendam m.w.langendam@amc.uva.nl	Dr. Langendam has nothing to disclose.
Schunemann, Holger holger.schunemann@mcmaster.ca	Dr. Schunemann has nothing to disclose.
Valéry Lavergne valerylavergne@gmail.com	Dr. Lavergne has nothing to disclose.
Mohammed T. Ansari tosansari@gmail.com	Dr. ANSARI has nothing to disclose.
Kelly Patricia Estrada Orozco kpestradao@unal.edu.co	None
Ariel Izcovich ariel.izcovich@gmail.com	Dr. Izcovich has nothing to disclose.
Jasvinder Singh jasvinder.md@gmail.com	No funding support was obtained for this work.
LeeYee leeyee.ebm@gmail.com	Dr. Chong has nothing to disclose.
Anne Rutjes anne.rutjes@ispm.unibe.ch	Dr. Rutjes has nothing to disclose.
Karen Steingart karen.steingart@gmail.com	Dr. Steingart reports to have received financial support for the preparation of systematic reviews and educational materials, consultancy fees from FIND (for the preparation of systematic reviews), honoraria, and travel support to attend World Health Organization guideline meetings.
Airton Stein airton.stein@gmail.com	Dr. Stein has nothing to disclose.
Nigar Sekercioglu nigars2003@yahoo.com	Dr. Sekercioglu has nothing to disclose.
Ingrid A' <inarev7@yahoo.com	Dr. AREVALO-RODRIGUEZ has nothing to disclose.
Rebecca Morgan morganrl@mcmaster.ca	Dr. Morgan has nothing to disclose.
Guyatt, Gordon guyatt@mcmaster.ca	Dr. Guyatt has nothing to disclose.
Patrick Bossuyt <a href="mailto:p.m.bossuyt@amc.uva.nl">p.m.bossuyt@amc.uva.nl</a>	Dr. Bossuyt has nothing to disclose.



## CRediT Author Statement

<b>Author</b>	<b>CRediT</b>
Monica Hultcrantz	Conceptualization, Methodology, Investigation, Writing – Original Draft
Reem A Mustafa	Conceptualization, Methodology, Investigation, Writing – Original Draft
Mariska M.G. Leeflang	Conceptualization, Methodology, Formal Analysis, Investigation, Writing – Original Draft
Valéry Lavergne	Conceptualization, Methodology, Investigation, Writing – Original Draft
Kelly Estrada-Orozco	Conceptualization, Methodology, Investigation, Writing – Original Draft
Mohammed T Ansari	Conceptualization, Methodology, Writing – Original Draft
Ariel Izcovich	Conceptualization, Writing – Review & Editing
Jasvinder Singh	Conceptualization, Writing – Review & Editing
Lee Yee Chong	Conceptualization, Writing – Review & Editing
Anne Rutjes	Conceptualization, Writing – Review & Editing
Karen Steingart	Conceptualization, Writing – Review & Editing
Airton Stein	Conceptualization, Writing – Review & Editing
Nigar Sekercioglu	Conceptualization, Writing – Review & Editing
Ingrid Arévalo Rodriguez	Conceptualization, Writing – Review & Editing
Rebecca L Morgan	Conceptualization, Writing – Review & Editing
Gordon Guyatt	Conceptualization, Writing – Review & Editing
Patrick Bossuyt	Conceptualization, Writing – Review & Editing
Miranda W Langendam	Conceptualization, Methodology, Investigation, Writing – Original Draft
Holger Schünemann	Conceptualization, Methodology, Investigation, Writing – Review & Editing