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ORIGINAL ARTICLE

# The indication area of a diagnostic test. Part II—the impact of test dependence, physician's decision strategy, and patient's utility

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**Abstract**

**Objectives:** Any diagnostic test has an indication area of prior probabilities wherein the gain in diagnostic certainty outweighs its loss. Here, we investigate whether indication area and the maximum diagnostic gain are robust measures if we assume test dependence, alternative physician's heuristics, and varying patient's utilities.

**Study Design and Setting:** Three mathematical functions for the dependence of test sensitivity (Se) and specificity (Sp) on the prior disease probability were studied. In addition, three different decision heuristics for further management were explored for the case that ''no test'' would be done. Finally, the valuation of test outcomes was varied. A sensitivity analysis was performed to determine the impact of the alternative assumptions on the indication area and maximum diagnostic gain.

**Results:** By assuming test dependence, the indication area shifts to higher priors and increases the maximum diagnostic gain. Decision strategies assuming a ''threshold before treat'' can inadvertently widen the indication area and increase the maximum diagnostic gain. Varying patient utilities will usually reduce the net diagnostic gain. A sensitivity analysis revealed the robustness of the model.

**Conclusion:** The indication area and the maximum diagnostic gain are robust measures of test performance and are easier to interpret than the classical performance measures. 

*Keywords:* Prior test probability; Posterior test probability; Indication area; Physician heuristics; Patient utility; Diagnostic gain

## 1. Introduction

> ''A useful diagnostic test does several things: It provides an accurate diagnosis, supports the application of a specific efficacious treatment, and ultimately leads to a better clinical outcome for the patient.''
>
> David L. Sackett, 1991 [1]

For any test and its combination of the sensitivity (Se) and specificity (Sp), there is a range of prior disease probabilities (priors), that is, the indication area, at which the gain in diagnostic certainty is higher than the loss in certainty [2,3]. In part I, we described a mathematical model to calculate the ''indication area'' based on test Se and Sp [4]. Except for net diagnostic loss at low and high extreme priors, we also found for each test a single prior at which the net gain in diagnostic certainty is maximum, this is called the diagnostic max. The diagnostic max generally ranges between a net diagnostic gain of 0.0 for a noninformative test (Se = 50% and Sp = 50% or TP rate = FP rate) and 1.0 for a perfect test (Se = 100% and Sp = 100%). To calculate the net diagnostic gain, we used a decision tree analysis comparing ''test'' and ''no test,'' for which we made three important model assumptions.

### 1.1. Independence of Se and Sp from prior

In part I, we assumed that the intrinsic measures of test performance Se and Sp are independent of the prior. However, previous studies have shown that Se and Sp vary between populations with different priors [5–12].

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**What is new?**

**Key findings**

- A previous study introduced the indication area and diagnostic max as an easy way to interpret comprehensive measure of diagnostic test performance. Three-way sensitivity analysis of the model assumptions shows that the indication area and diagnostic max are robust measures of test performance.

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

- We tested three main assumptions of indication area and diagnostic max: the independence of test Se and Sp from disease probability, the physician's heuristics to treat without further testing, and the patient's utilities for false-positive test results.
- Sensitivity analyses showed that each assumption can greatly influence the net diagnostic gain of a test. A three-way sensitivity analysis showed that the assumptions outweigh each other. A sensitivity analysis is recommended for patients with a prior close to a threshold.

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

- The indication area and maximum diagnostic gain can be used to assess at which prior disease probabilities a diagnostic test adds more certainty compared with no testing.

### 1.2. Decision strategy

The indication area and the diagnostic max of a clinical test not only depend on the test characteristics (Se and Sp), but also on the decision if ''no test'' is done.

The higher the prior, the more likely a physician will classify a patient as diseased and will act accordingly, that is, to start treatment. Vice versa, the lower the prior, the more likely a ''wait and see'' approach will be chosen. In our model, we assumed a linear relation between the probability to act and the prior ($\psi_{prior}$ = prior). However, there are more realistic decision strategies, or physician's decision heuristics, that determine the likelihood that a physician and patient decide to ''wait and see'' or to ''act.'' We modeled these heuristics as a mathematical $\psi$-factor (from ''psychological factor''). The $\psi_{prior}$ incorporates the pressure of the patient to be treated or not, the current clinical protocol or guideline used by the physician, the inclination of the physician to treat or not (whether the physician is risk seeking or risk averse), and the level of clinical experience.

### 1.3. Utilities

A useful diagnostic test not only provides more diagnostic certainty to support the application of optimal treatment, but should ultimately lead to a better test outcome for the patient [1]. In part I, we assumed equal weights to correct diagnoses [true positive (TP) and true negative (TN)] and false diagnoses [false positive (FP) and false negative (FN)] [4]. Thereby, we neglected the differences in the utility of each possible test outcome, such as the benefits of appropriate and timely action and treatment, and the harms and costs of overdiagnoses and overtreatment (FP), and of missed diagnoses (FN). Although simplification of clinical reality is a limitation of our model, it should be noted that the same assumption applies to any simple reporting of Se, Sp, and predictive values, although hardly ever explicitly mentioned.

In the present study, we perform Se analyses to investigate the effects of (in)dependence of Se and Sp of the prior (non-)linear functions displaying the association between the decision strategy and the prior, and various utilities in terms of health benefit and harms, on the estimation of the indication area and diagnostic max.

## 2. Methods

### 2.1. Decision tree

Fig. 1 presents the decision tree for the evaluation of a diagnostic test, where the issue is to choose between ''test'' or ''no test.'' The upper branch of the tree shows the consequences if the test at hand is done, with the probability that the test is positive, and the complementary probability that the test is negative. The subsequent complementary probabilities and valued outcomes apply to TP or FP and TN or FN test results, respectively. We denoted $U_{TP}$, $U_{FP}$, $U_{TN}$, and $U_{FN}$ as corresponding utilities or patient preferences.

The lower branch of the decision tree describes the physician's decision if no test was done. The physician's assessment as to whether the patient is classified as diseased (positive) or healthy (negative) is based on the physician's judgment of the prior, which is motivated by age, gender, complaints, medical history, physical examination, and estimation of the probability to experience potential benefits and harms. This clinical judgment, which depends on the prior, is encompassed by the largely unknown heuristic function $\psi_{prior}$.

A full description of the decision tree can be found in part I of this article [1]. Data modeling and data fitting were done in GraphPad Prism 4 (GraphPad Software, La Jolla, California, USA), the analyses in Microsoft Excel 2007 (Microsoft, Redmond, Washington, USA).

### 2.2. Dependence of Se and Sp from prior

Li and Fine [11] investigated three mathematical models for the dependence of Se and Sp on the prior probability of