Diagnostic ability assessment of quantitative medical tests

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Introduction

- Accurate diagnosis of a health condition is of utmost importance.
- Appropriate treatment depends on knowing the condition affecting the patient.
- Research studies examine the ability of diagnostic tests to discriminate between individuals with or without the condition of interest.

Introduction

- A diagnostic test is a measurement taken from an individual with the aim of diagnosing a disease or condition.
- Binary and continuous diagnostic tests.

Binary tests

- Some diagnostic tests are binary (dichotomous).
  - Antigen test for COVID-19 ($+$ versus $-$)
- Binary tests are sometimes the result of dichotomizing a continuous test by means of a threshold.
  - Cholesterol levels in blood ($\geq$ 200mg/dL, which indicates cardiovascular risk, versus $<$ 200mg/dL)

Binary tests: Notation

- Disease status (true condition, gold standard):
  - $D \rightarrow$ Diseased (condition present)
  - $\bar{D} \rightarrow$ Non-diseased (condition absent, healthy)
- Diagnostic test result:
  - $Y \rightarrow$ Positive, $+$ (test results indicate the condition is present)
  - $\bar{Y} \rightarrow$ Negative, $-$ (test results indicate the condition is absent)

Decision matrix

	True condition		
Test	D	$\bar{D}$	Total
Y	TP	FP	TP + FP
$\bar{Y}$	FN	TN	FN + TN
Total	TP + FN	FP + TN	n

Table 1: 2×2 general decision matrix of a binary test

TP: true positives, TN: true negatives,
FP: false positives, FN: false negatives.

[Pepe, 2003, Zhou et al., 2011, Nakas et al., 2023]

Sensitivity and specificity

- **Sensitivity:** the probability of detecting the condition when it is present:

$$\text{Sens} = \text{P}\left(Y|D\right) = \frac{\text{TP}}{\text{TP} + \text{FN}}.$$

- **Specificity:** the probability of excluding the condition when it is absent:

$$\text{Spec} = \text{P}\left(\bar{Y}|\bar{D}\right) = \frac{\text{TN}}{\text{FP} + \text{TN}}.$$

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Continuous tests

- In many situations, the diagnostic test is continuous rather than binary.
- Example: Prostate-Specific Antigen (PSA) (ng/mL) is used to distinguish between individuals with or without prostate cancer.

Continuous tests

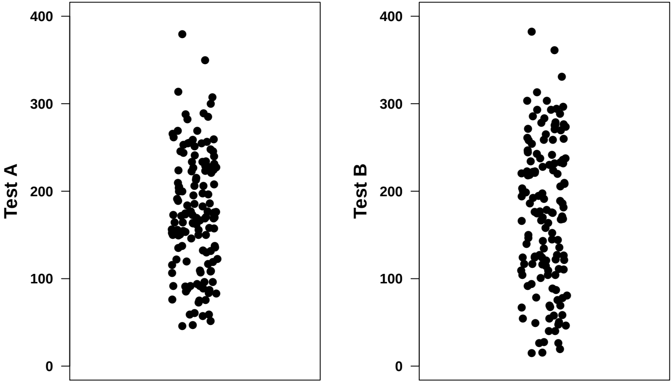

Figure 1: Two examples: quantitative diagnostic test

Continuous tests

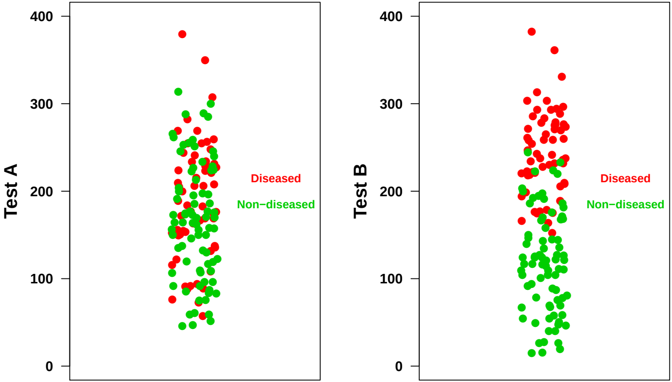

Figure 1: Two examples: quantitative diagnostic test

Continuous tests: Notation

- Disease status (true condition, gold standard):
  - $D \rightarrow$ Diseased (condition present)
  - $\bar{D} \rightarrow$ Non-diseased (condition absent, healthy)
- Continuous diagnostic test: X.
- We assume that higher values of X are indicative of disease (if not, change the labels!).

Decision matrix

- Threshold for X: c.
- We consider: $X \geq c \rightarrow$ positive, $X < c \rightarrow$ negative.

Test	**True condition** D	$\bar{D}$	Total
$X \geq c$	$\mathrm{TP}(c)$	$\mathrm{FP}(c)$	$\mathrm{TP}(c) + \mathrm{FP}(c)$
$X < c$	$\mathrm{FN}(c)$	$\mathrm{TN}(c)$	$\mathrm{FN}(c) + \mathrm{TN}(c)$
Total	$\mathrm{TP}(c) + \mathrm{FN}(c)$	$\mathrm{FP}(c) + \mathrm{TN}(c)$	n

Table 2: 2×2 general decision matrix of a continuous test

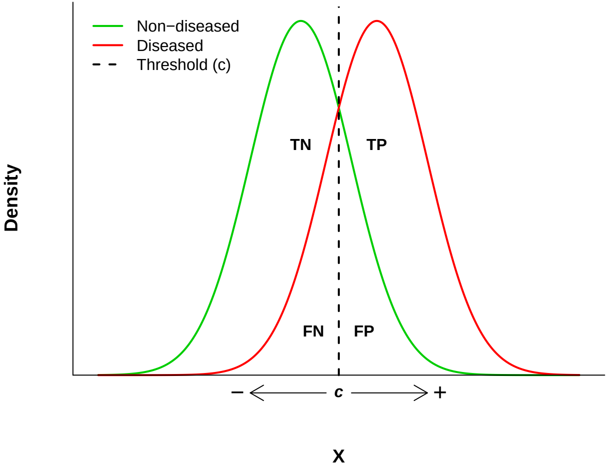

Figure 2: Example of a continuous diagnostic test

Sensitivity and specificity

Then, the sensitivity and specificity of X depend on c:

$$\text{Sens}\,(c) = \text{P}\,(X \geq c \mid D)\,,$$

$$\text{Spec}\,(c) = \text{P}\left(X < c \mid \bar{D}\right).$$

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ROC curves

- The ROC[1] curve is defined as the whole set of possible sensitivities and specificities we can obtain from the dichotomization of X with different thresholds [Pepe, 2003], that is,

$$\{(1 - \text{Spec}\,(c)\,, \text{Sens}\,(c))\,,\ c \in (-\infty, \infty)\}$$

- Plot: x-axis $\rightarrow$ $1 - \text{Spec}$; y-axis $\rightarrow$ Sens.
- The ROC curve is a monotone increasing function.
- It summarizes the ability of the test to discriminate among the two true states.

[1] Receiver Operating Characteristic

ROC curves

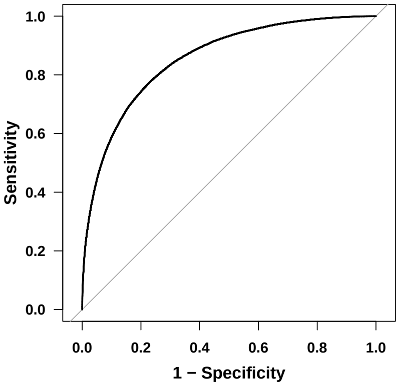


Figure 3: Example of an ROC curve

Area under the ROC curve (AUC)

- It is often useful to summarize the ROC curve by a single number [Pepe, 2003, Zhou et al., 2011].
- Area under the ROC curve $\rightarrow$ AUC.
- $0.5 < \text{AUC} \leq 1$.

AUC

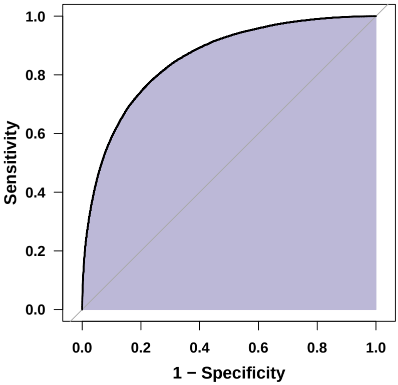
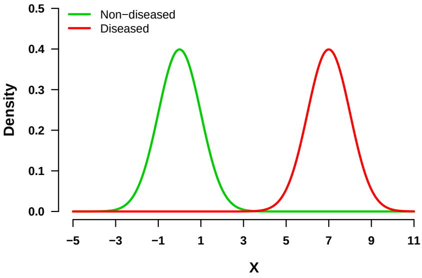


Figure 4: Example of an ROC curve with AUC in grey

$$AUC = 1$$



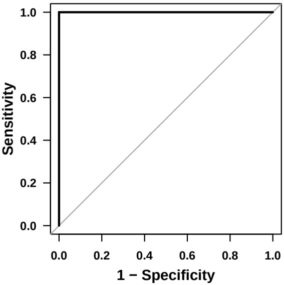


Figure 5: Perfect test

$$\text{AUC} = 0.5 \rightarrow \text{Chance line}$$

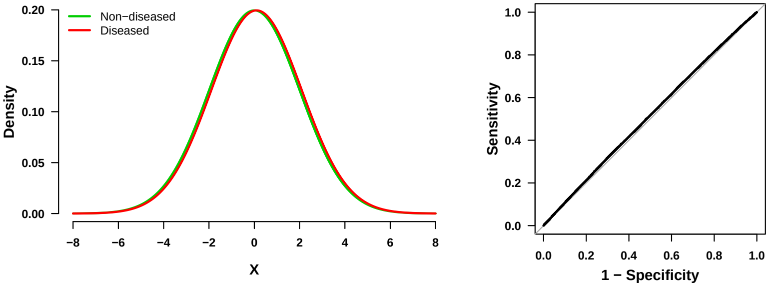


Figure 5: Uninformative test

In practice, diagnostic tests have ROC curves in between these two situations.

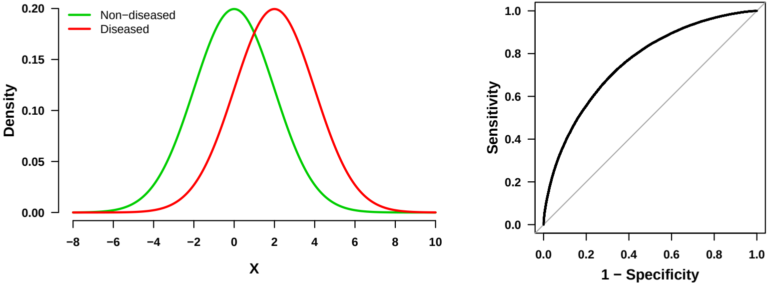


Figure 5: Common situation in real-world problems

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Optimum threshold estimation

- Categorisation of continuous variables is sometimes disfavoured → loss of information [Cohen, 1983].
- However, it simplifies the classification of patients according to their state.
- Mean, median, quartiles, etc., are frequently used as thresholds, but they are arbitrary and highly sample-dependent.

Optimum threshold estimation

- Categorisation of continuous variables is sometimes disfavoured $\rightarrow$ loss of information [Cohen, 1983].
- However, it simplifies the classification of patients according to their state.
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Statistically viable strategies are needed for threshold estimation.

Optimum threshold estimation

- Aim: find a threshold that is optimal in some sense.
- The choice of a threshold depends on the trade-off that is considered to be acceptable between the two types of error (FP/FN).
- Plenty of methods have been proposed in the literature.

Youden index method

- Youden index maximisation [Youden, 1950]: c such that

$$J(c) = \text{Sens}\,(c) + \text{Spec}\,(c) - 1$$

  is maximum.
- Threshold that leads to the point of the ROC curve farthest from the chance diagonal.

Youden index method

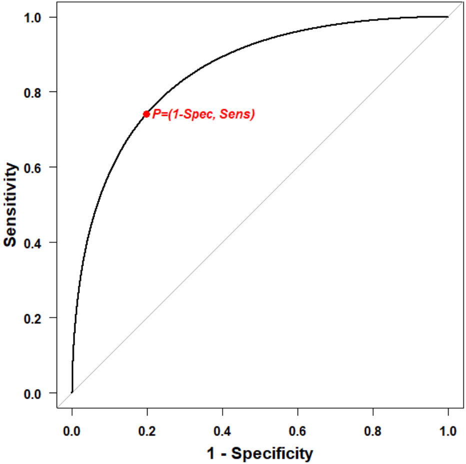

Figure 6: Illustration of Youden index maximisation

Youden index method

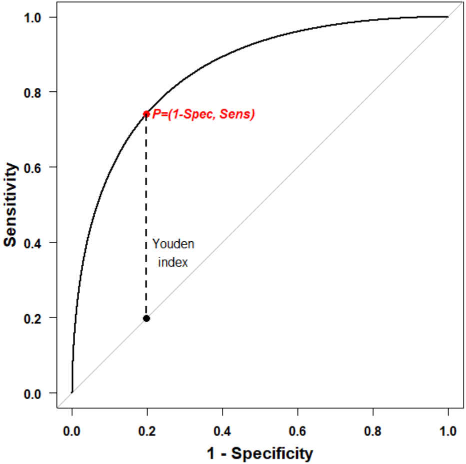

Figure 6: Illustration of Youden index maximisation

Distance to the ideal marker

- Threshold that leads to the point of the ROC curve closest to $(0, 1)$.
- c such that

$$\sqrt{(1 - \text{Spec}\,(c))^2 + (1 - \text{Sens}\,(c))^2}$$

is minimum.

Distance to the ideal marker

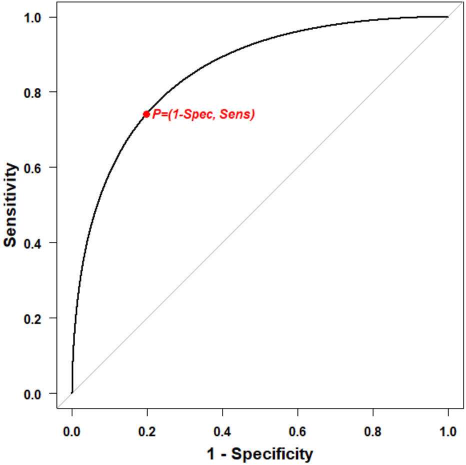

Figure 7: Illustration of minimisation of the distance to the ideal marker

Distance to the ideal marker

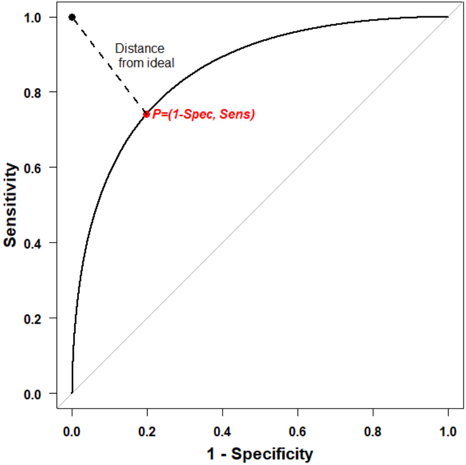

Figure 7: Illustration of minimisation of the distance to the ideal marker

Cost function approach

- A more general approach is to consider a cost function [Jund et al., 2005, Skaltsa et al., 2010].
- It accounts for all possible classifications: TP, TN, FP, FN.
- Cost function:

$$C(c) = \mathrm{TP}\,(c) \cdot C_{\mathrm{TP}} + \mathrm{FN}\,(c) \cdot C_{\mathrm{FN}} + \mathrm{FP}\,(c) \cdot C_{\mathrm{FP}} + \mathrm{TN}\,(c) \cdot C_{\mathrm{TN}},$$

where

C_{TP}: cost of a true positive,
C_{TN}: cost of a true negative,
C_{FP}: cost of a false positive,
C_{FN}: cost of a false negative.

Cost function based optimum threshold

The cost function $C(c)$ can be rewritten as:

$$C(c) = D\left(\mathrm{Sens}\left(c\right) + R \cdot \mathrm{Spec}\left(c\right) + G\right),$$

where

$$D = n\rho\left(C_{\mathrm{TP}} - C_{\mathrm{FN}}\right), \quad R = \frac{(1-\rho)\left(C_{\mathrm{TN}} - C_{\mathrm{FP}}\right)}{\rho\left(C_{\mathrm{TP}} - C_{\mathrm{FN}}\right)},$$

$$G = \frac{\rho\, C_{\mathrm{FN}} + (1-\rho)\, C_{\mathrm{FP}}}{\rho\left(C_{\mathrm{TP}} - C_{\mathrm{FN}}\right)},$$

$\rho =$ disease prevalence, $n =$ sample size.

Cost function based optimum threshold

It can be shown that the cost minimising threshold c is the one such that

$$\frac{f_D(c)}{f_{\bar{D}}(c)} = R,$$

where $f_D(c)$ and $f_{\bar{D}}(c)$ are the density functions for the diseased and the non-diseased subpopulations, and

$$R = \left(\frac{1-\rho}{\rho}\right) \cdot \left(\frac{C_{\mathrm{TN}} - C_{\mathrm{FP}}}{C_{\mathrm{TP}} - C_{\mathrm{FN}}}\right).$$

Cost function based optimum threshold

- This approach requires specification of costs for all classification results.
- C_{FP}, C_{FN} are allowed to be different $\rightarrow$ Flexibility and adaptation to the problem.
- $R = 1 \rightarrow$ Youden index maximisation.

Cost function based optimum threshold

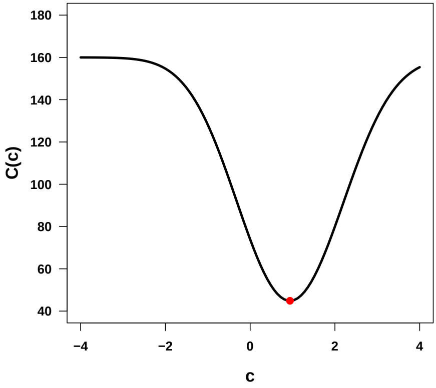

Figure 8: Example of cost function

Cost function based optimum threshold

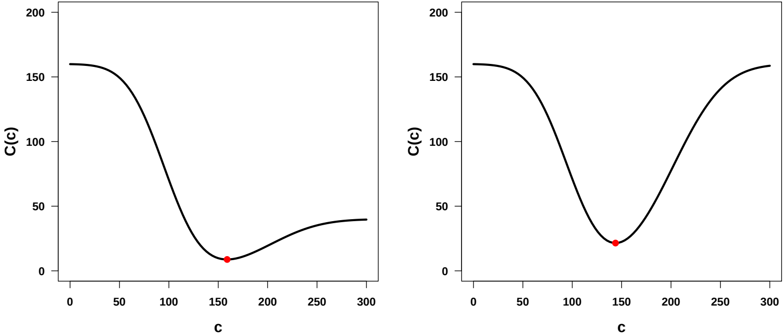

Figure 9: Left: $C_{\mathrm{TP}} = C_{\mathrm{TN}} = 0, C_{\mathrm{FP}} = C_{\mathrm{FN}} = 1$; right: $C_{\mathrm{TP}} = C_{\mathrm{TN}} = 0$, $C_{\mathrm{FP}} = 1, C_{\mathrm{FN}} = 4$

Estimation methods

- Parametric methods: binormality assumption.
- Non-parametric methods: empirical, smoothing.
- Confidence intervals: delta method, bootstrap.

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Example: Prostate cancer data

- A study was conducted to evaluate the clinical usefulness of the level of acid phosphatase in blood serum (APBS) to predict nodal involvement.
- Data from $n = 53$ men diagnosed with prostate cancer [López-Ratón et al., 2017].
- Status: Nodal involvement present versus absent.
- Diagnostic test: APBS, in U/L·100.
- Nodal involvement present in 20 cases (37.7%).

Example: Prostate cancer data

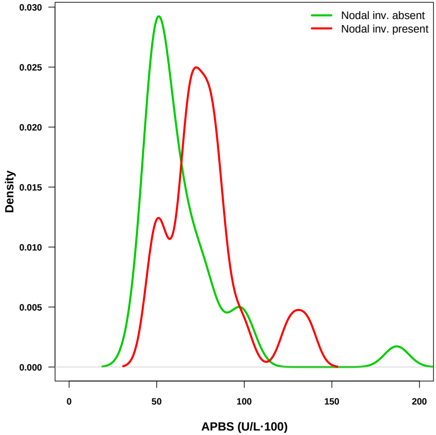

Figure 10: Prostate cancer data: density plot by status

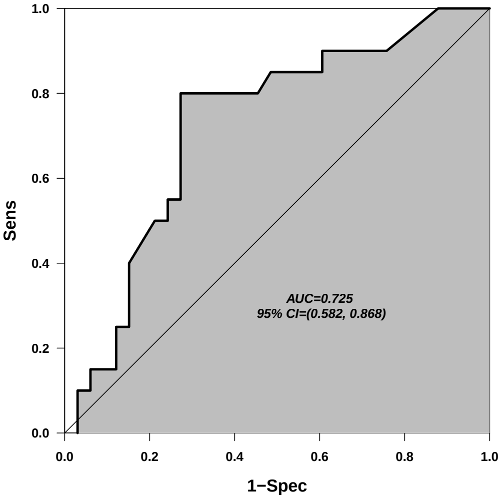

Figure 11: Prostate cancer data: ROC curve and AUC

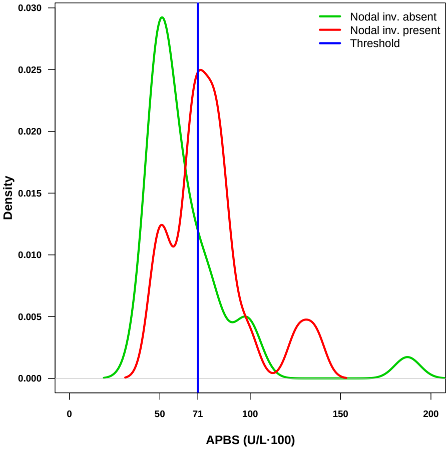

Figure 12: Prostate cancer data: densities and optimal threshold using the cost function approach (Youden index, $C_{TP} = C_{TN} = 0$, $C_{FP} = 1$, $C_{FN} = 1.65$)

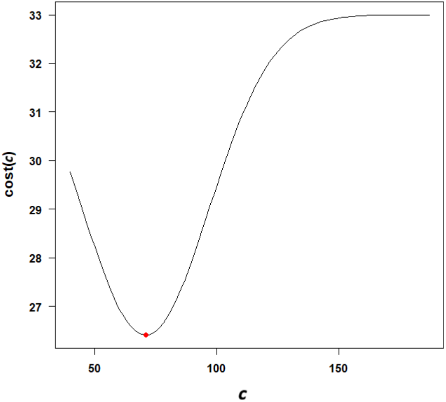

Figure 13: Prostate cancer data: Cost function assuming binormality (Youden index)

Software

R packages:

- `ThresholdROC` [Perez-Jaume et al., 2017]
- `GsymPoint` [López-Ratón et al., 2017]
- `cutpointr` [Thiele and Hirschfeld, 2021]

Contents

Conclusions

- Continuous medical tests are often used in diagnostic studies.
- ROC curves are a useful tool to evaluate their diagnostic ability.
- Youden index method is the most widely used for threshold estimation $\rightarrow$ Disadvantage: FP and FN are assumed to be equally undesirable.
- Multiple methods for optimum threshold estimation $\rightarrow$ Choice based on what "optimum" means in your problem.
- Related topics: k-state ($k > 2$) and survival problem.

Thank you for your attention!

References I

Cohen, J. (1983).
The cost of dichotomization.
Applied Psychological Measurement, 7(3):249–253.

Jund, J., Rabilloud, M., Wallon, M., and Ecochard, R. (2005).
Methods to estimate the optimal threshold for normally or log-normally distributed biological tests.
Medical Decision Making, 25(4):406–415.
PMID: 16061892.

López-Ratón, M., Molanes-López, E. M., Letón, E., and Cadarso-Suárez, C. (2017).
GsymPoint: An R package to estimate the generalized symmetry point, an optimal cut-off point for binary classification in continuous diagnostic tests.
The R Journal, 9:262–283.
https://doi.org/10.32614/RJ-2017-015.

Nakas, C. T., Bantis, L., and Gatsonis, C. (2023).
ROC Analysis for Classification and Prediction in Practice.
Chapman & Hall/CRC.

References II

Pepe, M. S. (2003).
The statistical Evaluation of Medical Tests for Classification and Prediction.
Oxford Univesity Press, Oxford.

Perez-Jaume, S., Skaltsa, K., Pallarès, N., and Carrasco, J. L. (2017).
ThresholdROC: Optimum threshold estimation tools for continuous diagnostic tests in R.
Journal of Statistical Software, 82(4):1–21.

Skaltsa, K., Jover, L., and Carrasco, J. L. (2010).
Estimation of the diagnostic threshold accounting for decision costs and sampling uncertainty.
Biometrical Journal, 52(5):676–697.

Thiele, C. and Hirschfeld, G. (2021).
cutpointr: Improved estimation and validation of optimal cutpoints in R.
Journal of Statistical Software, 98(11):1–27.

Youden, W. J. (1950).
Index for rating diagnostic tests.
Cancer, 3(1):32–35.

References III

Zhou, X. H., Obuchowski, N. A., and McClish, D. K. (2011).
Statistical Methods in Diagnostic Medicine.
John Wiley & Sons, Hoboken, New Jersey.