



HARMONY
Novel tools for test evaluation and
disease prevalence estimation



ΤΜΗΜΑ ΔΗΜΟΣΙΑΣ
ΚΑΙ ΕΝΙΑΙΑΣ ΥΓΕΙΑΣ
DEPARTMENT OF PUBLIC
AND ONE HEALTH
ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ UNIVERSITY OF THESSALY

Diagnostic test evaluation with Bayesian latent class models: An overview

Polychronis Kostoulas

Sensitivity & Specificity

Sensitivity is the ability of the test to correctly identify diseased individuals

Specificity is the ability of the test to correctly identify healthy individuals

	Diseased	Healthy	
Test (+)	80	5	85
Test (-)	20	95	115
	100	100	200

Sensitivity & Specificity

?

	Diseased	Healthy	
Test (+)	a	b	a+b
Test (-)	c	d	c+d
	a+c	b+d	a+b+c+d

$$Se = \frac{a}{a + c} \qquad Sp = \frac{d}{b + d}$$

Population 1

		T2+	T2-
D+	T1+	$P1 * Se1 * Se2$	$P1 * Se1 * (1 - Se2)$
	T1-	$P1 * (1 - Se1) * Se2$	$P1 * (1 - Se1) * (1 - Se2)$
D-		T2+	T2-
	T1+	$(1 - P1) * (1 - Sp1) * (1 - Sp2)$	$(1 - P1) * (1 - Sp1) * Sp2$
All	T1-	$(1 - P1) * Sp1 * (1 - Sp2)$	$(1 - P1) * Sp1 * Sp2$
		T2+	T2-
	T1+	$P1 * Se1 * Se2 + (1 - P1) * (1 - Sp1) * (1 - Sp2)$	$P1 * Se1 * (1 - Se2) + (1 - P1) * (1 - Sp1) * Sp2$
	T1-	$P1 * (1 - Se1) * Se2 + (1 - P1) * Sp1 * (1 - Sp2)$	$P1 * (1 - Se1) * (1 - Se2) + (1 - P1) * Sp1 * Sp2$

Two tests, one population

Population 1

T1+T2+:

$$P1 * Se1 * Se2 + (1 - P1) * (1 - Sp1) * (1 - Sp2)$$

T1+T2-:

$$P1 * Se1 * (1 - Se2) + (1 - P1) * (1 - Sp1) * Sp2$$

T1-T2+:

$$P1 * (1 - Se1) * Se2 + (1 - P1) * Sp1 * (1 - Sp2)$$

T1-T2-:

$$P1 * (1 - Se1) * (1 - Se2) + (1 - P1) * Sp1 * Sp2$$

- 5 parameters and 3 degrees of freedom
- Non-identifiable model

Two tests, Two populations

Population 1

T1+T2+:

$$P1 * Se1 * Se2 + (1-P1) * (1-Sp1) * (1-Sp2)$$

T1+T2-:

$$P1 * Se1 * (1-Se2) + (1-P1) * (1-Sp1) * Sp2$$

T1-T2+:

$$P1 * (1-Se1) * Se2 + (1-P1) * Sp1 * (1-Sp2)$$

T1-T2-:

$$P1 * (1-Se1) * (1-Se2) + (1-P1) * Sp1 * Sp2$$

Population 2

T1+T2+:

$$P2 * Se1 * Se2 + (1-P2) * (1-Sp1) * (1-Sp2)$$

T1+T2-:

$$P2 * Se1 * (1-Se2) + (1-P2) * (1-Sp1) * Sp2$$

T1-T2+:

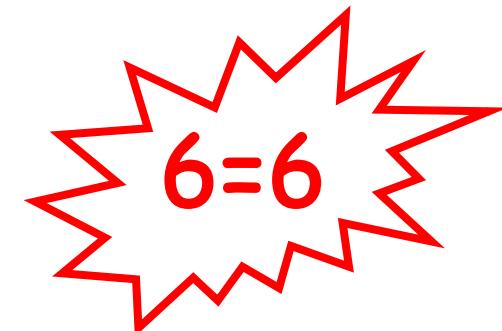
$$P2 * (1-Se1) * Se2 + (1-P2) * Sp1 * (1-Sp2)$$

T1-T2-:

$$P2 * (1-Se1) * (1-Se2) + (1-P2) * Sp1 * Sp2$$



Identifiable model!



Hui & Walter

<https://youtu.be/z6devQmW2xE>

The Hui & Walter paradigm

Estimating the error rates of diagnostic tests. Biometrics 36, 167-171., 1980

Table 1
Results of Mantoux and Tine tests for tuberculosis in two populations

Mantoux test	Population 1			Population 2		
	Tine test			Tine test		
	Positive	Negative	Total	Positive	Negative	Total
Positive	14	4	18	887	31	918
Negative	9	528	537	37	367	404
Total	23	532	555	924	398	1322

Assumptions underlying the model

- Distinct difference in the prevalence
- Constant Se and Sp
- Conditional independence

Conditional dependence

Conditional dependence

		Population 1	
		T2+	T2-
D+	T1+	$P1 * Se1 * Se2 + \gamma Se$	$P1 * Se1 * (1 - Se2) - \gamma Se$
	T1-	$P1 * (1 - Se1) * Se2 - \gamma Se$	$P1 * (1 - Se1) * (1 - Se2) + \gamma Se$
D-	T1+	$(1 - P1) * (1 - Sp1) * (1 - Sp2) + \gamma Sp$	$(1 - P1) * (1 - Sp1) * Sp2 - \gamma Sp$
	T1-	$(1 - P1) * Sp1 * (1 - Sp2) - \gamma Sp$	$(1 - P1) * Sp1 * Sp2 + \gamma Sp$

$$(Se1 - 1) * (1 - Se2) \leq \gamma Se \leq \min(Se1, Se2) - Se1 * Se2$$

$$(SpT1 - 1) * (1 - SpT2) \leq \gamma Sp \leq (SpT1, SpT2) - SpT1 * SpT2$$

Conditional dependence

Population 1

$$T1+T2+: P1*Se1*Se2 + \gamma Se + (1-P1)*(1-Sp1)*(1-Sp2) + \gamma Sp$$

$$T1+T2-: P1*Se1*(1-Se2) - \gamma Se + (1-P1)*(1-Sp1)*Sp2 - \gamma Sp$$

$$T1-T2+: P1*(1-Se1)*Se2 - \gamma Se + (1-P1)*Sp1*(1-Sp2) - \gamma Sp$$

$$T1-T2-: P1*(1-Se1)*(1-Se2) + \gamma Se (1-P1)*Sp1*Sp2 + \gamma Sp$$

Population 2

$$T1+T2+: P2*Se1*Se2 + \gamma Se + (1-P2)*(1-Sp1)*(1-Sp2) + \gamma Sp$$

$$T1+T2-: P2*Se1*(1-Se2) - \gamma Se + (1-P2)*(1-Sp1)*Sp2 - \gamma Sp$$

$$T1-T2+: P2*(1-Se1)*Se2 - \gamma Se + (1-P2)*Sp1*(1-Sp2) - \gamma Sp$$

$$T1-T2-: P2*(1-Se1)*(1-Se2) + \gamma Se (1-P2)*Sp1*Sp2 + \gamma Sp$$

- NON – Identifiable model!
- Priors required

Variations

More than two populations

More than two tests

Semi-dependent model

Narrowing parameter space for dependencies

Non-constant sensitivities and/or specificities

The STARD family

- **STARD**
 - STARD 2015
 - STARDdem
 - STRADAS-paraTB
 - STARD-BLCM
 - STARD for Abstracts



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STARD-BLCM Checklist

TITLE OR ABSTRACT

ABSTRACT

INTRODUCTION

METHODS

Study design

Participants

Test methods

Analysis

RESULTS

Participants

Test results

DISCUSSION

OTHER INFORMATION

Section & Topic	No	Item
TITLE OR ABSTRACT	1	Identification as a study of diagnostic accuracy, using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC) and Bayesian latent class models
ABSTRACT	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)
INTRODUCTION	3	Scientific and clinical background, including the intended use and clinical role of the tests under evaluation
	4	Study objectives and hypotheses, such as estimation of diagnostic accuracy of the tests for a defined purpose through BLCM

METHODS		
<i>Study design</i>	5	Whether data collection was planned before the tests were performed (prospective study) or after (retrospective study)
<i>Participants</i>	6	Eligibility criteria and description of the source population
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)
	8	Where and when potentially eligible participants were identified (setting, location and dates)
	9	Whether participants formed a consecutive, random or convenience series

<i>Test methods</i>	10	Description of the tests under evaluation, in sufficient detail to allow replication, and/or cite references
	11	Rationale for choosing the tests under evaluation in relation to their purpose
	12	Definition of and rationale for test positivity cut-offs or result categories of the tests under evaluation , distinguishing pre-specified from exploratory
	13	Whether clinical information was available to the performers or readers of the tests under evaluation
<i>Analysis</i>	14a	<u>BLCM</u> model for estimating measures of diagnostic accuracy
	14b	Definition and rationale of prior information and sensitivity analysis
	15	How indeterminate results of the tests under evaluation were handled
	16	How missing data of the tests under evaluation were handled
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory
	18	Intended sample size and how it was determined

RESULTS		
<i>Participants</i>	19	Flow of participants, using a diagram
	20	Baseline demographic and clinical characteristics of participants
	21	Not applicable: the distribution of the targeted conditions is unknown, hence the use of BLCM
	22	Time interval and any clinical interventions between the tests under evaluation
<i>Test results</i>	23	Cross tabulation of the tests' results (or for continuous tests results their distribution by infection stage)
	24	Estimates of diagnostic accuracy under alternative prior specification and their precision (such as 95% credible/probability intervals)
<i>Discussions</i>	25	Any adverse events from performing the tests under evaluation

DISCUSSION	
	26 Study limitations, including sources of potential bias, statistical uncertainty, and generalisability
	27 Implications for practice, including the intended use and clinical role of the tests under evaluation in relevant settings (clinical, research, surveillance etc.)
OTHER INFORMATION	
	28 Registration number and name of registry
	29 Where the full study protocol can be accessed
	30 Sources of funding and other support; role of funders

Considerations

Biological considerations

Methodological considerations

Convergence diagnostics

Goodness of fit tests

Prior selection – The ParaTB paradigm

Biological considerations

- Support your work from a biological perspective
 - e.g. definition of infection in latent analysis

Definition of infection

- Define which status you are estimating Se & Sp for.
- Different test combinations give different Se's and Sp's
- You are based on the cross-classified test results
 - e.g. ELISA and FC culture for paratuberculosis
 - see (Nilesen et al., 2002; Kostoulas et al., 2006a; 2006b)



No Gold Standard

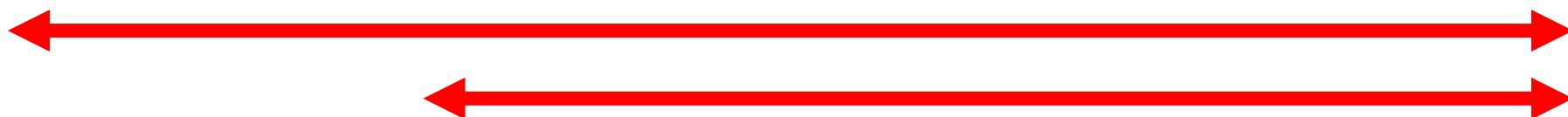
Definition of the targeted infection status gets complicated but... "better"

Target Variable
Bias



Detectable immune response (ELISA)

Detectable isolation of the pathogen (Culture)





Statistically sound modeling &
description

The interested reader must be able to reproduce your methods (and results) with the information you provide

Explicit description of the BLCM model

Model Assumptions

Biologically justify model building

Conditional dependencies

Identifiability

Conditional dependencies

Identifiability



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Thank you!