Introduction to diagnostic test accuracy network meta-analysis

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Outline

1. Introduce Diagnostic Test Accuracy (DTA) Studies
2. Discuss about process of conducting a systematic review with DTA meta-analysis
3. Present how to build the network geometry of DTA studies
4. Extend DTA meta-analysis methods to DTA network meta-analysis methods (DTA-NMA)
5. Identify potential implications in DTA-NMA

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Poll Question 1

Which of the following best describes your role?

- Editor of systematic reviews
- User of systematic reviews
- Systematic reviewer
- Statistician
- Methodologist
- Other

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Poll Question 2

What is your familiarity with Meta-Analysis of Diagnostic Test Accuracy studies?

- I know about it and have used it.
- I am aware of it, but have not applied it before.
- I have no idea what it is.

Diagnostic Test Accuracy studies

- Diagnostic Tests are used to ascertain whether an individual has or not a disease
- Most tests are imperfect, errors will occur - not always accurate
- ‘Reference standard’ is a test that can be used to estimate the accuracy of the imperfect tests
- Binary outcome: positive / negative test result

Statistical methods usually focus on two quantities characterizing the accuracy of a test: sensitivity and specificity

What proportion of those ***with*** the disease does the test detect? (sensitivity, SENS)

What proportion of those ***without*** the disease does the test get right? (specificity, SPEC)

Test \ Disease	⊕	⊖
⊕	TP	FP
⊖	FN	TN
	Sensitivity = TP/(TP + FN)	Specificity = TN/(TN + FP)

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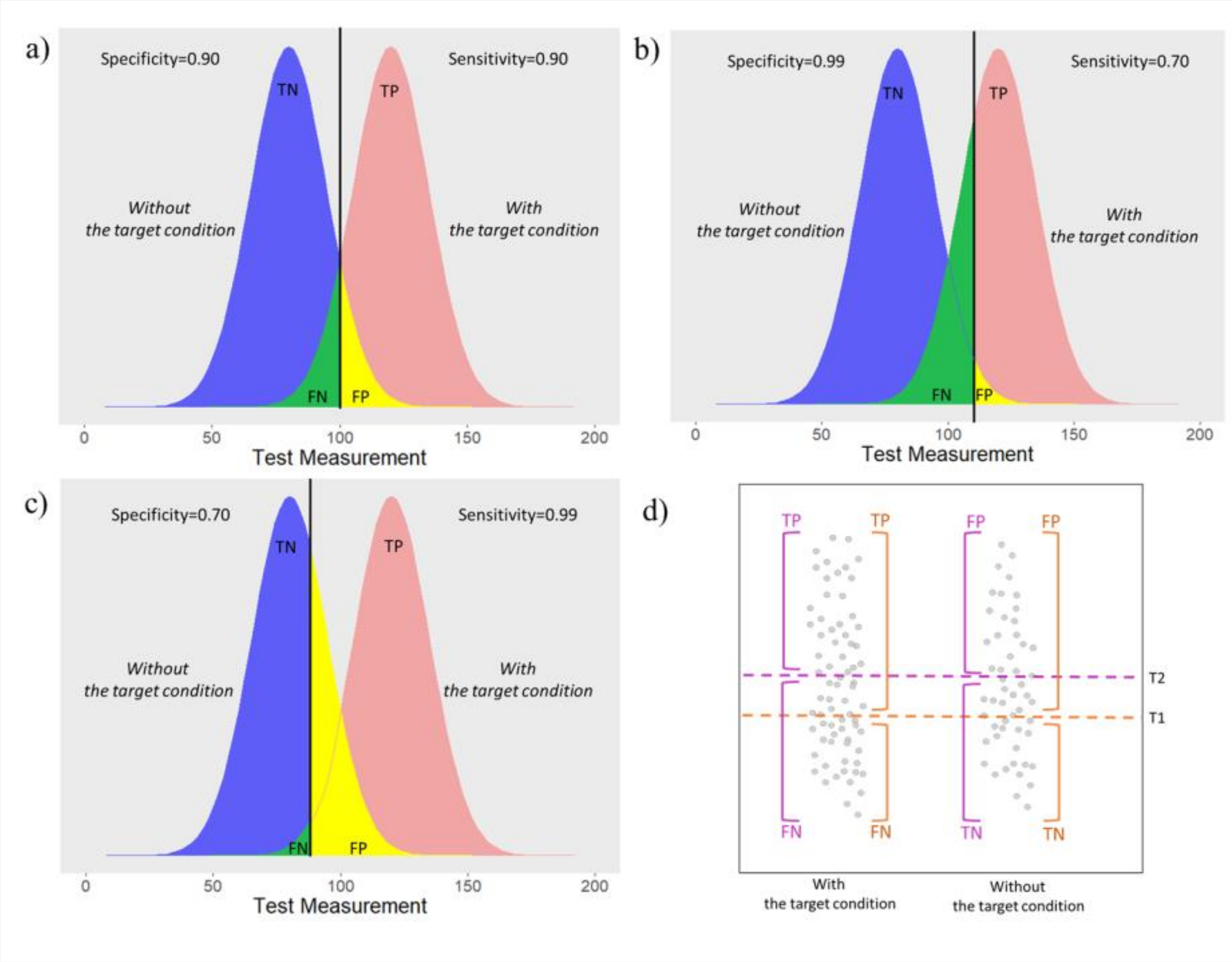
Thresholds

- Binary markers (X-rays)
- Continuous markers (blood tests)
  - Require setting cut-off values (thresholds)
  - Trade-off between sensitivity and specificity

There is a **trade-off** between sensitivity and specificity as the threshold is set in **different points**!

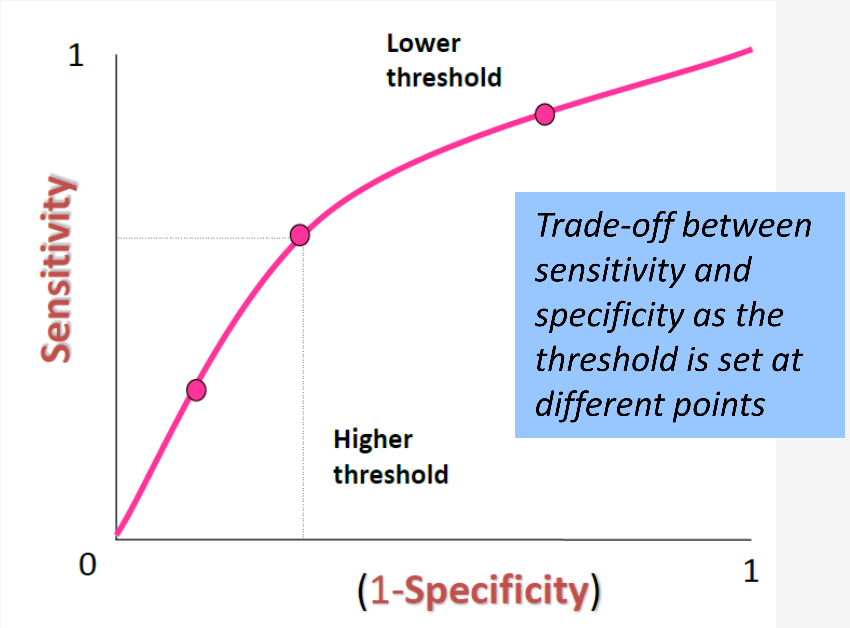


Threshold effect

- The same threshold can imply different SENS and SPEC in different groups
- A solution can be to perform Meta-Analysis at each threshold separately or a subset of thresholds

BUT…

- Restricting to a common threshold reduces data
- The common threshold may not be the threshold a reader wants to know about



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Example: The anatomy of a DTA research question

Rapid Antigen Test A for diagnosis of **COVID-19** in asymptomatic adults

Index test

Target Condition

Population

Reference Standard

PCR

Example: 2x2 table

Index test: Rapid Antigen test A for COVID-19
Reference Standard: RT-PCR

		Reference standard Result		Total
		Positive (D+)	Negative (D-)	
Index Test Result	Positive (T+)	TP= 27	FP= 2	Positive Test Results = 29
	Negative (T-)	FN= 3	TN= 98	Negative Test Results = 101
	Total	Diseased= 30	Non-Diseased= 100	Sample size = 130

- Sensitivity, Specificity (90%, 98%)
- Test identified 90% of COVID-19 diseased and 98% of non-diseased individuals

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Kim D et al. Viruses. 2021

Steps of a Systematic Review of DTA studies

1. Define the question
2. Define objectives and eligibility criteria
3. Develop protocol
4. Search for studies
5. Study selection and Data collection
6. Assess bias and applicability
7. Analyze and present results
8. Interpret results and draw conclusions

Review Question

What is the diagnostic accuracy of rapid antigen and rapid molecular tests for the diagnosis of the SARS-CoV-2 infection in adults and children according to the reference standard PCR test?

Population	Index Test(s)	Target Condition
Adults and/ or children screened/ suspected for COVID-19	COVID-19 rapid lateral flow antigen tests and rapid molecular tests (with result in ≤1h) Ref Std: PCR test	SARS-CoV-2 infection **Reference standard:** PCR

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Veroniki et al. BMC Med 2023; PROSPERO: CRD42021289712

Intervention vs DTA reviews

Intervention Reviews

Components of Intervention review research question (PICO)

- **P** opulation
- **I** nterventions
- **C** omparators
- **O** utcomes
- **S** tudy design

Diagnostic Test Accuracy (DTA) Reviews

Components of Intervention review research question (PIT)

- **P** opulation
- **I** ndex Test(s)
- **T** arget Condition
  - Reference Standard
- **S** tudy design

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Steps of a Systematic Review of DTA studies

1. Define the question
2. **Define objectives and eligibility criteria**
3. Develop protocol
4. Search for studies
5. Study selection and Data collection
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7. Analyze and present results
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Objectives of the review

Primary objective

To assess the diagnostic accuracy of rapid antigen and rapid molecular tests for the diagnosis of the SARS-CoV-2 infection in adults and children

Secondary objectives

To assess the accuracy of clinical assessment in SARS-CoV-2 infection :

- according to sample type (e.g., saliva, nasal swab)
- In symptomatic and asymptomatic participants

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Veroniki et al. BMC Med 2023; PROSPERO: CRD42021289712

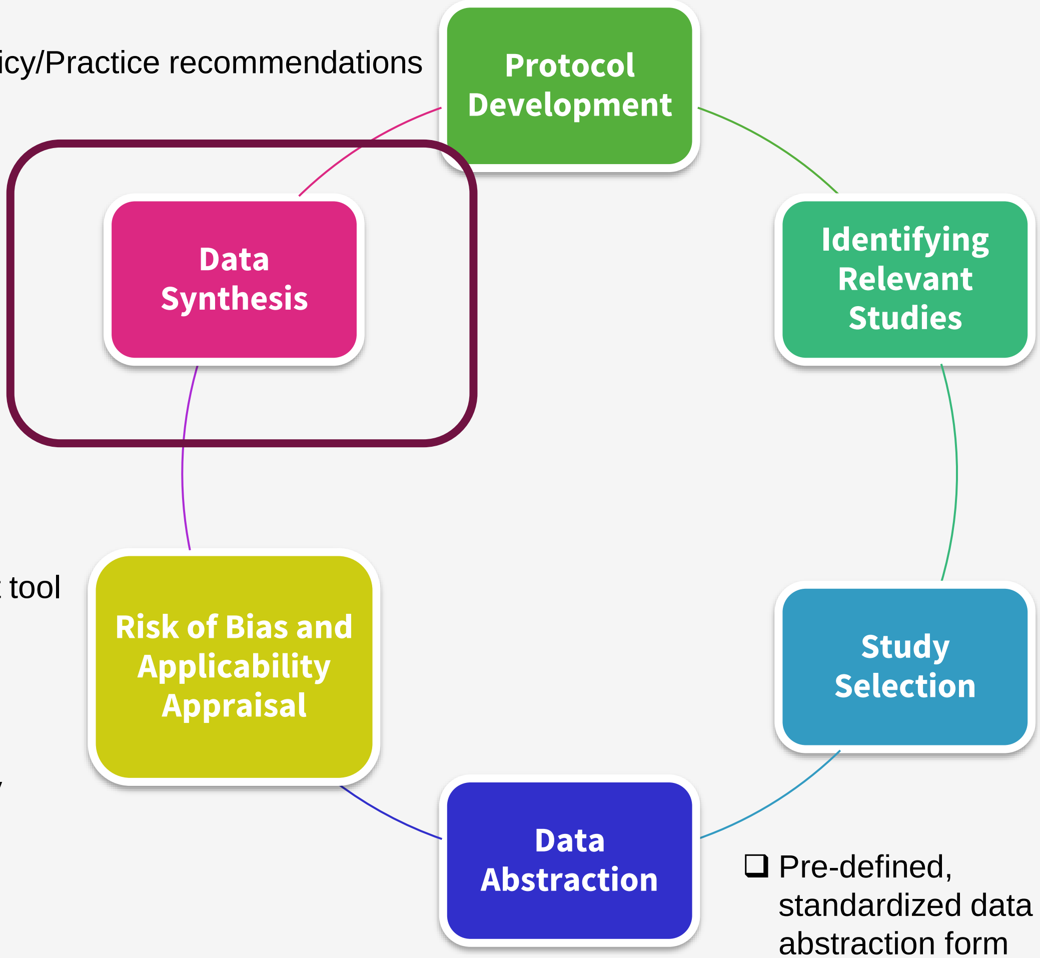
Steps of a Systematic Review of DTA studies

https://training.cochrane.org/handbook

- ❑ PICOS(T) framework, developed using PRISMA-P
- ❑ Register with PROSPERO (and publish in open access journal)

❑ Policy/Practice recommendations

❑ Meta-analysis or qualitative evidence synthesis
❑ Synthesis based on totality of evidence



- ❑ Comprehensive search (≧2 databases),
- ❑ PRESS (Peer Review of Electronic Search Strategies)
- ❑ Grey literature search and reference scanning

❑ Title and abstract screening followed by full-text screening using pre-defined eligibility criteria

3rd party

❑ Pre-defined, standardized data abstraction form

3rd party

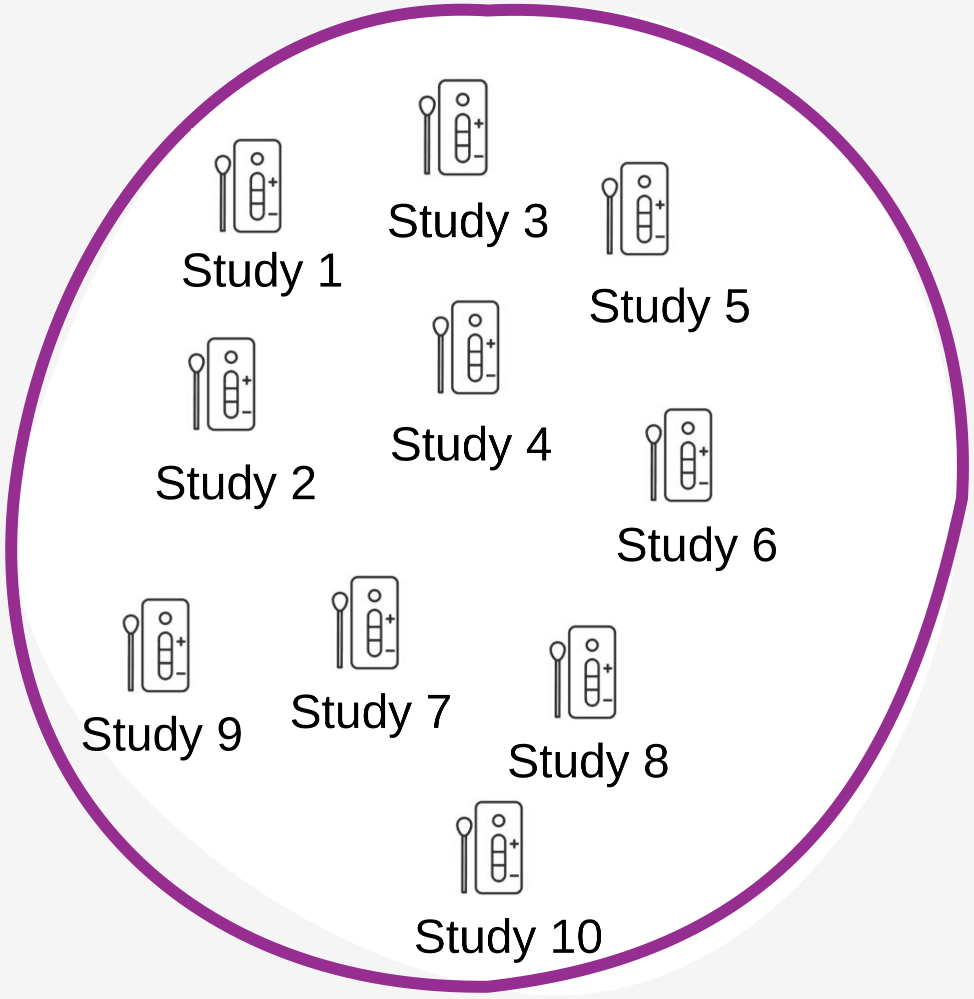
❑ Validated, study design-specific assessment tool

3rd party

- *Deeks JJ et al. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. Version 2.0. Cochrane. 2023*
- *McInnes MDF et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA. 2018*
- *Whiting PF et al. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. Ann Intern, 2011*
- *Yang B et al. QUADAS-C: A Tool for Assessing Risk of Bias in Comparative Diagnostic Accuracy Studies. Ann Intern Med. 2021*

Meta-analysis

10 studies exploring accuracy of Test A for Covid-19



- ✓ Summarize information
- ✓ Synthesis of information from individual studies, addressing the same research question
- ✓ Statistically combine study-results to obtain summary estimates

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The generic meta-analysis process

1. Calculation of an overall summary (average) of high precision, coherent with all observed data
2. Typically a "weighted average" is used where more informative (larger) studies have more say
3. Assess the degree to which the study results deviate from the overall summary
4. Investigate possible explanations for the deviations

What is **SO critical** that we have to consider in meta-analyses?

Test threshold!!!

- Accuracy varies with index test threshold
- Can we average over test thresholds?
- How would we interpret the result?
- *Thresholds can be important for both index and reference tests*

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The generic meta-analysis process

Challenges for DTA reviews

- There are **two summary statistics** for each study: SENS and SPEC
- Threshold effects induce correlations between SENS and SPEC
  - Often thresholds vary between studies
- Heterogeneity is the norm - substantial variation in sensitivity and specificity
  - Different groups can have different sensitivities and specificities at the **same threshold**

Pooling sensitivity and specificity *separately*?

- Ignores threshold as source of heterogeneity
- Is biased towards studies with high sensitivity or specificity
  - Pooled estimates of sensitivity and specificity may be biased towards 1 or 0, depending on study results

Multiple studies – Single index test

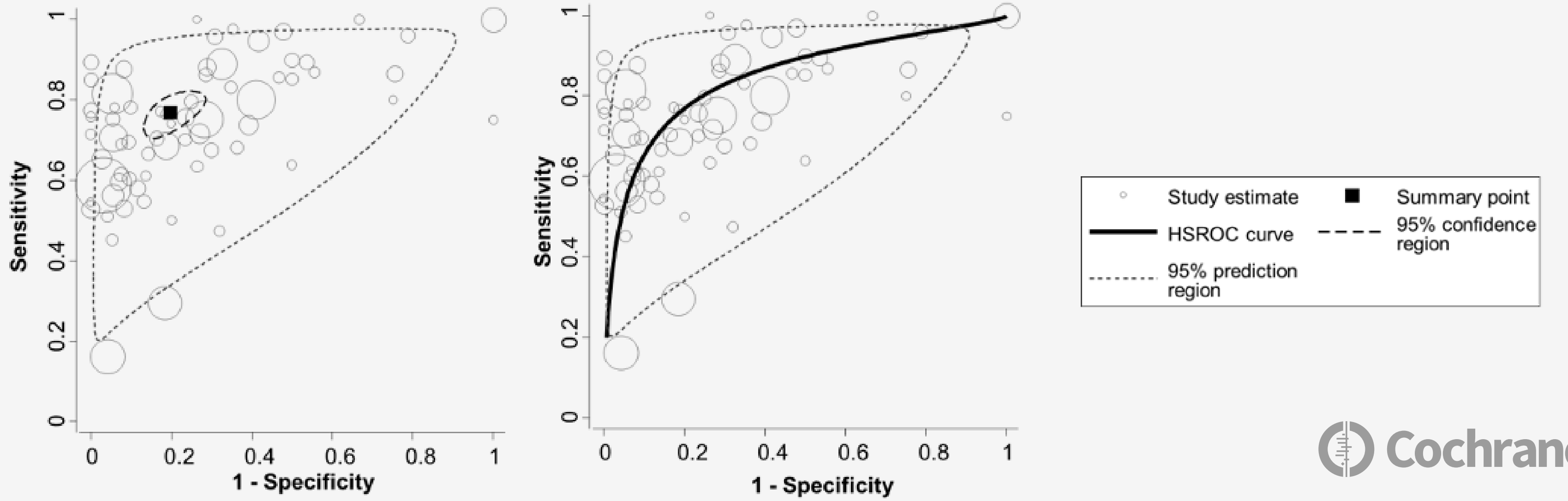
- Systematic review evaluating a single index test:
    - Aims to evaluate a diagnostic test vs. a reference standard
- How does test accuracy vary with clinical & methodological characteristics?
- The outcome is to model the test results (binary outcome: positive / negative test result) – assess the diagnostic accuracy of a single test

Bivariate model

- Single threshold
- Summary point

HSROC model

- Multiple thresholds
- Summary curve



Reitsma J et al. Journal of Clinical Epidemiology. 2005; Rutter C, Gatsonis C. Stat Med. 2001

Multiple Diagnostic Tests vs. Multiple Interventions

- Diagnostic tests are usually compared in the same subjects within a study
    - Correlated observations – the NMA methods should account for this correlation structure
    - Should estimate sensitivity & specificity: bivariate model

- Interventions are compared between independent groups (different groups of patients)
    - Use effect measures (OR, RR, RD) to compare effectiveness among treatments

		Interventions	Diagnostic tests
	Aim	Compare two treatments	Discriminate two groups
Pairwise meta-analysis	Groups	2 interventions	With/without target condition
	Outcome	Event yes/no	Test positive/negative
	Proportions	r_1, r_0	Sens, $1-$ Spec
	Effect measures	$\text{RD} = r_1 - r_0$	$J = \text{Sens} + \text{Spec} - 1$
		$\text{OR} = \frac{r_1(1-r_0)}{r_0(1-r_1)}$	$\text{DOR} = \frac{\text{Sens} * \text{Spec}}{(1-\text{Sens})(1-\text{Spec})}$
	Modeling	Univariate model, contrast-based	Bivariate model, arm-based
Multivariate pairwise meta-analysis	Groups	2 interventions	With/without target condition
	Outcome	$K \geq 2$ outcomes	$K \geq 2$ tests
	Measures	Pairs of proportions	Pairs of accuracy measures
		$(r_{1k}, r_{0k}),\ k = 1, \ldots, K$	$(\text{Sens}_k, 1 - \text{Spec}_k), k = 1, \ldots, K$
	Effect measures	$\text{RD}_k,\ k = 1, \ldots, K$	$J_k,\ k = 1, \ldots, K$
		$\text{OR}_k,\ k = 1, \ldots, K$	$\text{DOR}_k,\ k = 1, \ldots, K$
	Modeling	Multi(K)variate model	Multi($2K$)variate model

RD = risk difference; OR = odds ratio; DOR = diagnostic odds ratio; J = Youden index.

Rücker G. Springer, Cham. 2018

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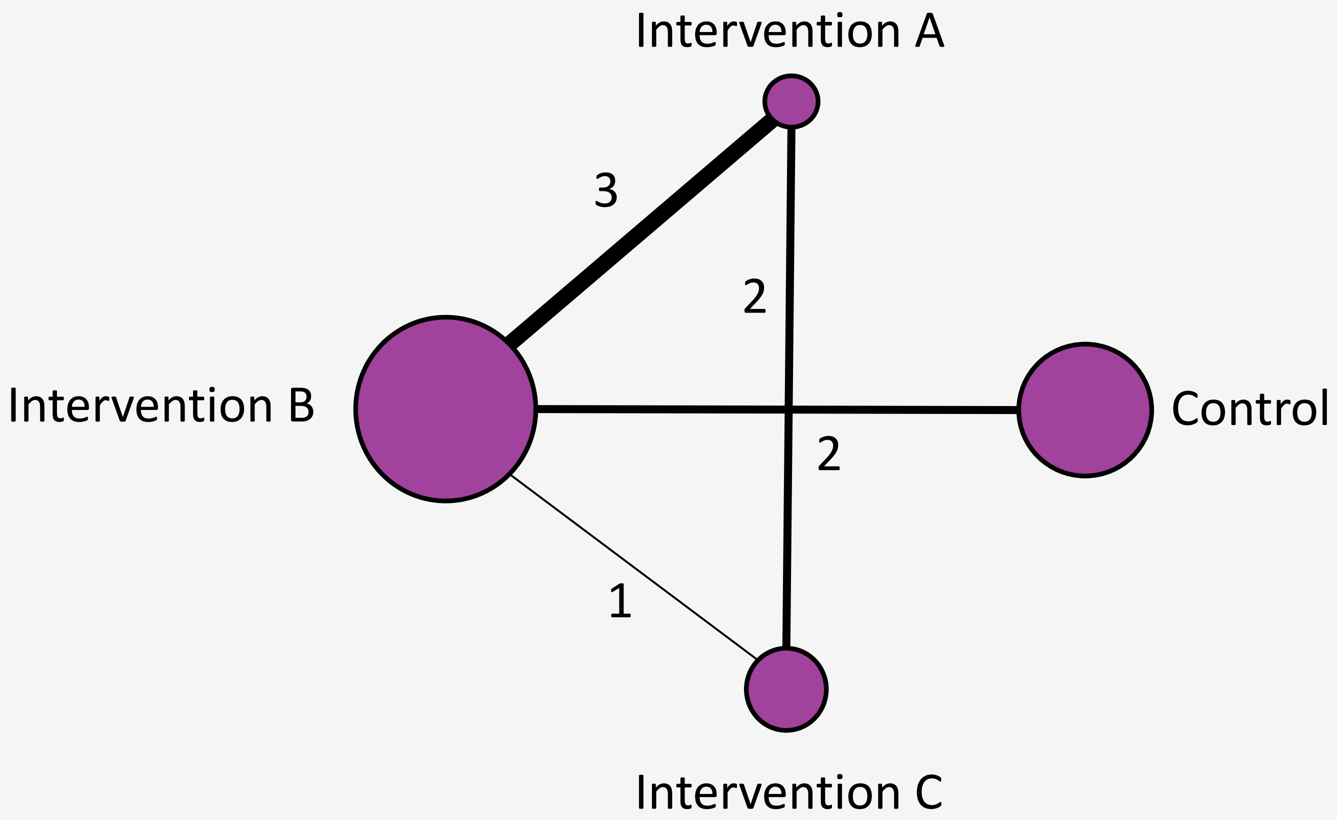
Veroniki AA, Tsokani S et al. J Clin Epidemiol. 2022; Veroniki AA et al. Meta-Research. Eds. Springer. 2021

Network of interventions

All interventions and the control group are depicted in the network plot

Studies compare at least 2 interventions (2-arm, 3-arm, etc.)



Study ID	Type of study	Intervention comparisons
1	2-arm	B vs C
2	3-arm	A vs B vs C
3	2-arm	A vs C
4	2-arm	B vs Control
5	2-arm	A vs B
6	2-arm	A vs B
7	2-arm	B vs Control

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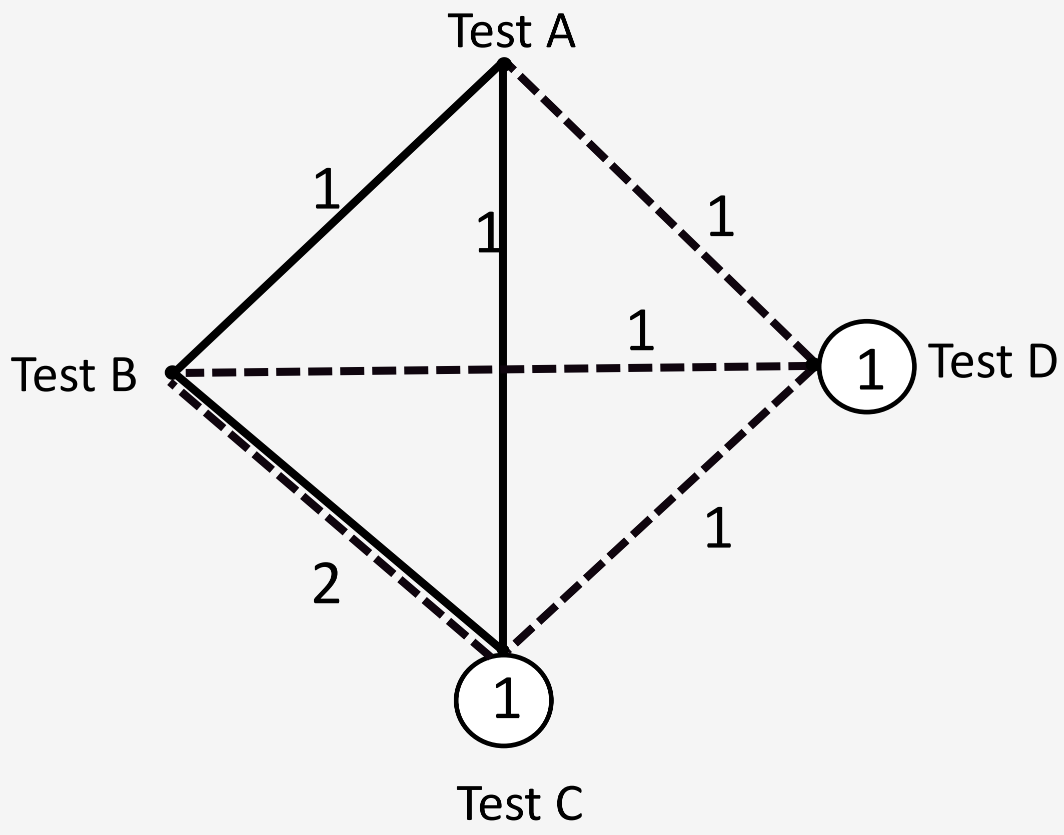
Network of diagnostic tests

Reference standard (RS) is not considered in the network but as a bridge for comparing index tests.

Index test vs RS: single-test study



Study ID	Type of study	Data	Test comparisons	Edges/Circles in the network
1	Single-test	Test D vs RS	Test D vs. RS	Circle for test D
2	Paired-test	Test B vs RS Test C vs RS	Test B vs. Test C	Dashed line connecting tests B and C
3	Triple-test	Test A vs RS Test B vs RS Test C vs RS	Test A vs. Test B Test A vs. Test C Test B vs. Test C	Closed triangle with solid line connecting tests A, B, and C
4	Paired-test	Test B vs RS Test D vs RS	Test B vs. Test D	Dashed line connecting tests B and D
5	Single-test	Test C vs RS	Test C vs. Reference	Circle for test C
6	Paired-test	Test A vs RS Test D vs RS	Test A vs. Test D	Dashed line connecting tests A and D
7	Paired-test	Test C vs RS Test D vs RS	Test C vs. Test D	Dashed line connecting tests C and D

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Scoping Review of DTA-NMA methods

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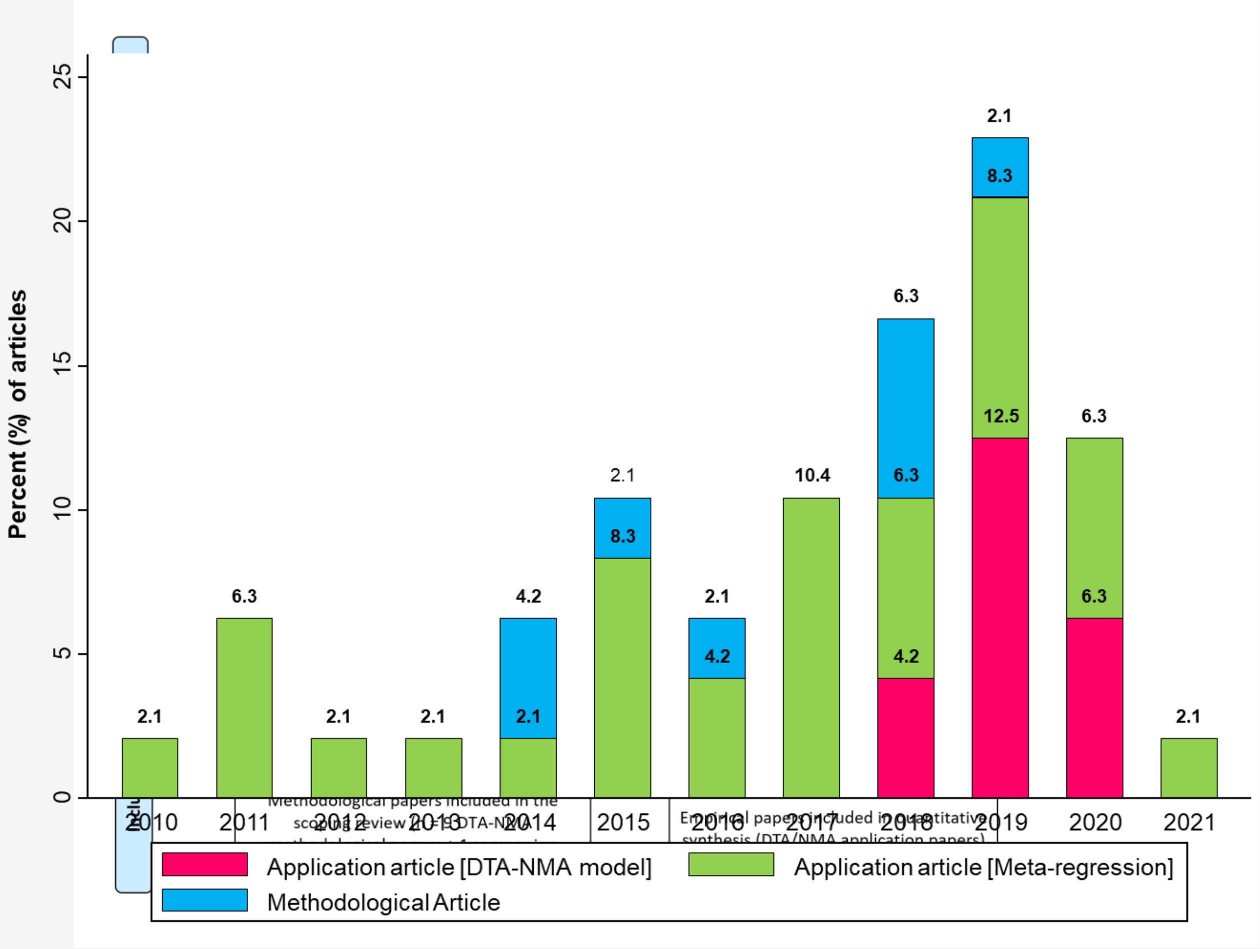
Scoping Review

- Search of PubMed, Web of Science, Scopus databases up until the 3rd March 2021
- Methodological and application papers comparing the accuracy of at least three index tests using:
  - hierarchical meta-regression models
  - models developed specifically for DTA-NMA



DTA-NMA in the literature

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Table 1. Properties of 13 diagnostic test accuracy (DTA) comparative meta-analysis methods

	Format of data tables required[a]	Arm-based model	Can model imperfect reference standards	Can model multiple thresholds	Type of studies that can be modelled	Bayesian setting	Accounts for correlation between tests	Models more than two index tests	Software
Bivariate meta-regression [21]	2 × 2	Yes	No	No	Any	No	No	Yes	R *(CopulaDTA* [24], *lme4* [25], *mada* [26], *meta4diag* [27], *Metatron* [28], *Mvmeta* [29]), Stata *(meqrlogit* [30])
HSROC meta-regression [22]	2 × 2	Yes	No	Yes[d]	Any	No	No	Yes	OpenBUGS/ WinBUGS [31] R(*NMADiagT* [32])
Trikalinos 2014 [5]	Joint classification	Yes	No	No	Single- / Paired-test	Yes	Yes	No[b]	R (*rjags* [33])
Menten-Lesaffre 2015 [4]	2 × 2	No	Yes[c]	No	Paired- / Multiple-test	Yes	No	Yes	OpenBUGS/ WinBUGS [31]
Dimou 2016 [3]	Joint classification	Yes	No	No	Single- / Paired-test	No	Yes	No[b]	Stata (*mvmeta* [34])
Cheng 2016 [Model A] [8]	Joint classification	Yes	No	No	Any	Yes	No	Yes	R (R2*jags* [35])
Cheng 2016 [Model B] [8]	Joint classification	Yes	No	Yes[d]	Any	Yes	No	Yes	R (R2*jags* [35])
Cheng 2016 [Model C] [8]	Joint classification	Yes	No	No	Any	Yes	Yes	Yes	R (R2*jags* [35])
Nyaga (ANOVA) 2018 [2]	2 × 2	Yes	No	No	Any	Yes	Yes	Yes	Stan (*rstan* [36],[37] in R)
Nyaga (beta-binomial) 2018 [38]	2 × 2	Yes	No	No	Any	Yes	Yes	Yes	Stan (*rstan* [36],[37] in R)
Ma 2018 [9][e]	Joint classification	Yes	Yes	No	Any	Yes	Yes	Yes	OpenBUGS/ WinBUGS [31], R (NMADiagT [45])
Owen 2018 [39]	2 × 2	Yes	No	Yes	Any	Yes	Yes	Yes	OpenBUGS/ WinBUGS [31]
Lian 2019 [40]	Joint classification	Yes	Yes	Yes[d]	Any	Yes	Yes	Yes	Stan (*rstan* [36],[37] in R), R (NMADiagT [45])

Abbreviations: DOR, diagnostic odds ratio; SE, standard error; DTA, diagnostic test accuracy; NMA, network meta-analysis; HSROC, hierarchical summary receiver operating characteristic.
[a] 2 × 2 data includes the number of true positives, true negatives, false positives and false negatives.

Most Popular

- Properties of DTA-NMA models differ and may influence interpretation and decision-making

DTA-NMAs:

- 'Borrow strength' across studies by simultaneously analysing multiple DTA studies
- Account for between-study correlations between sensitivity and specificity induced through threshold effects

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Joint classification tables

Index test: Rapid Antigen test A, Rapid Antigen test B for COVID-19

Reference Standard: RT-PCR

		Reference standard Result		Total
		Positive (D+)	Negative (D-)	
Index Test A Result	Positive (T+)	TP= 27	FP= 2	Positive Test Results = 29
	Negative (T-)	FN= 3	TN= 98	Negative Test Results = 101
	Total	Diseased= 30	Non-Diseased= 100	Sample size = 130

		Reference standard Result		Total
		Positive (D+)	Negative (D-)	
Index Test B Result	Positive (T+)	TP= 17	FP= 9	Positive Test Results = 26
	Negative (T-)	FN= 13	TN= 91	Negative Test Results = 104
	Total	Diseased= 30	Non-Diseased= 100	Sample size = 130

		Index Test A Result		Total
		Positive (D+)	Negative (D-)	
Index Test B Result	Positive (T+)	TP= 20	FP= 10	Positive Test Results = 30
	Negative (T-)	FN= 10	TN= 90	Negative Test Results = 100
	Total	Diseased= 30	Non-Diseased= 100	Sample size = 130

Individual Participant Data required

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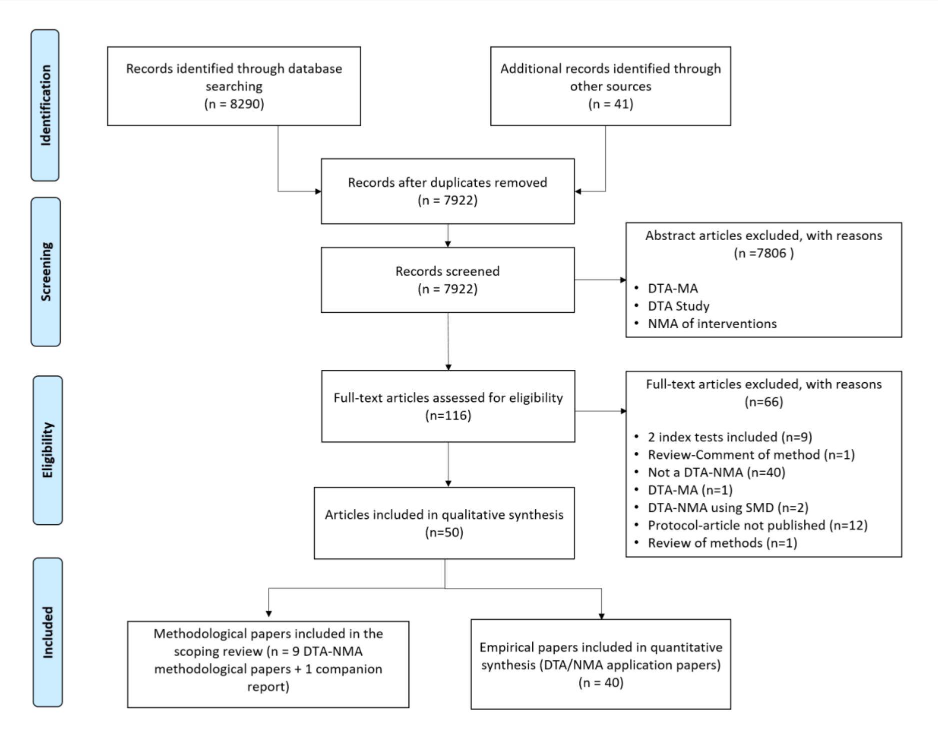
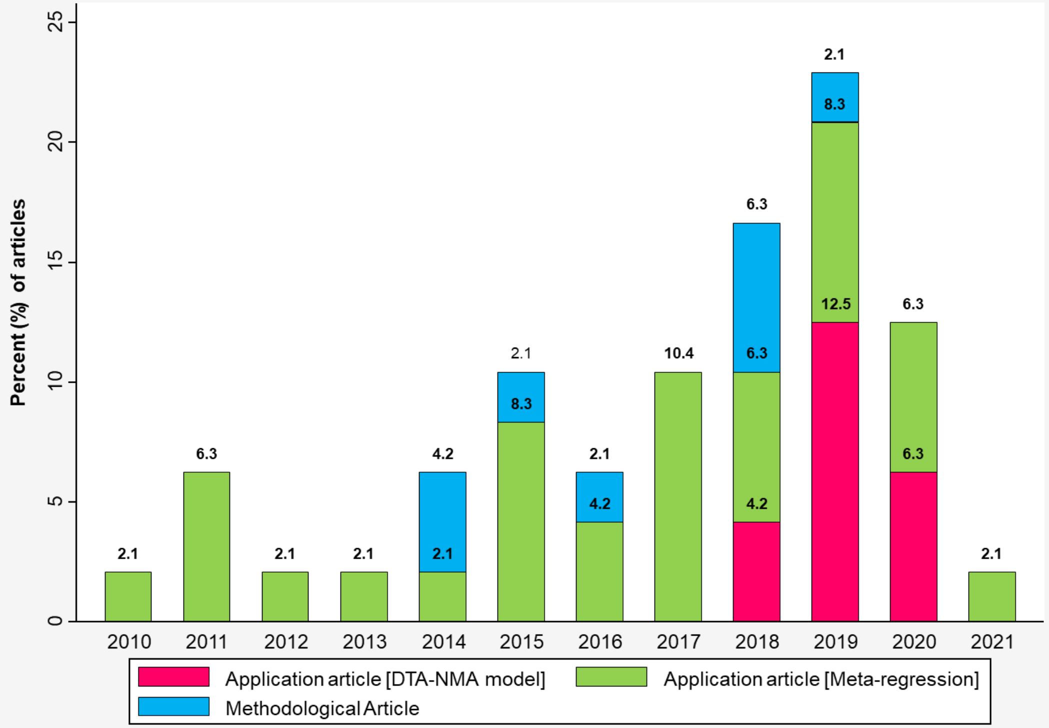
Application Papers





- Majority employed bivariate/HSROC meta-regression models
- 2x2 tables were available for 32 networks
    - 8 of these reported data at multiple thresholds per study

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DTA-NMA in the literature

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DTA-NMA in the literature

Bivariate meta-regression model

Reitsma et al. (2005)

- A covariate for test type is used to explore sensitivity and specificity between tests
- Assumes that participants undergoing different tests are independent subgroups within each study
- Does not account for the within-study correlation between tests within study

ANOVA model

Nyaga et al. (2018)

- A two-stage hierarchical model based on a two-way ANOVA model
- Allow for correlations between tests within study

Beta-binomial model

Nyaga et al. (2018)

- Sensitivity & specificity are directly modelled using a beta-binomial defined in [0,1]
- Allow for correlations between tests within study

Hierarchical Latent Class model

Menten and Lesaffre (2015)

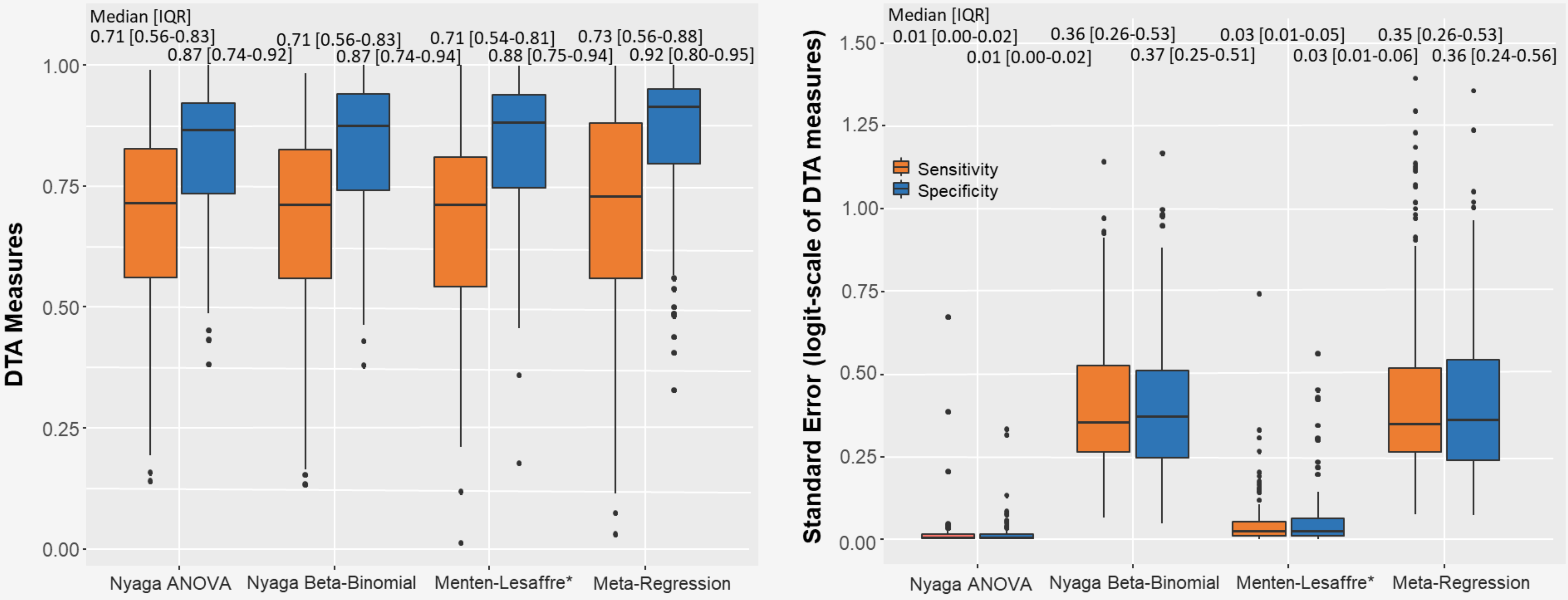
- Based on differences (contrasts) between the different tests in the network
- Allows for imperfect reference standards
- Correlations between tests from the same study are ignored

Variance component model

Owen et al. (2018)

- Allows for considering multiple thresholds
- Incorporates constraints on threshold effects

Empirical assessment of the DTA-NMA methods



- Nyaga beta-binomial model estimated lower between study heterogeneity for both sensitivity and specificity
- Owen *et al.* model showed that different test thresholds included, may cause differences in results

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In summary…

- Bivariate/HSROC meta-regression model:
  - It has been widely used over the years
  - Conservative approach and accessible to many review authors
  - **But**, it ignores the within-study correlation between tests - assumes observations are independent

- More advanced methods and models have been developed
  - Most account for correlations between tests within a study

- NMA methodology of intervention studies is not applicable to DTA studies
  - Correlated observations – tests are given to the same participants
  - Two effect sizes should be modelled (sensitivity & specificity) – pairs of accuracy measures should be modelled in multivariate models (2K-variate, with K tests).
  - Network geometry differs – single-test studies are presented (reference standard is not a node in the network)

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In summary…

- Software and Model Complexity
  - most of the detected models use Bayesian setting
  - programming challenges - code availability problems (including convergence issues)
  - time-consuming models (e.g., dataset with antigen COVID-19 tests required >48 hours to run the Nyaga ANOVA model)

- Datasets
  - within the same study different number of participants may receive the index tests of interest (i.e., missing participant data problem)
  - correlations between tests are frequently not available in the original DTA studies (i.e. the joint classification table is rarely provided in publications)

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In summary…

- There is not a single valid method for DTA-NMA analysis
  - multiple factors influence the choice of model (data availability, test thresholds, study designs, software familiarity)
  - meta-regression models ignore the within-study correlation between tests
  - selection between the methods may impact on the NMA results, especially for specificity

- Some models require joint classification tables
  - individual participant data would make this information available
  - rarely reported in DTA studies
  - difficulties in their availability-data sharing

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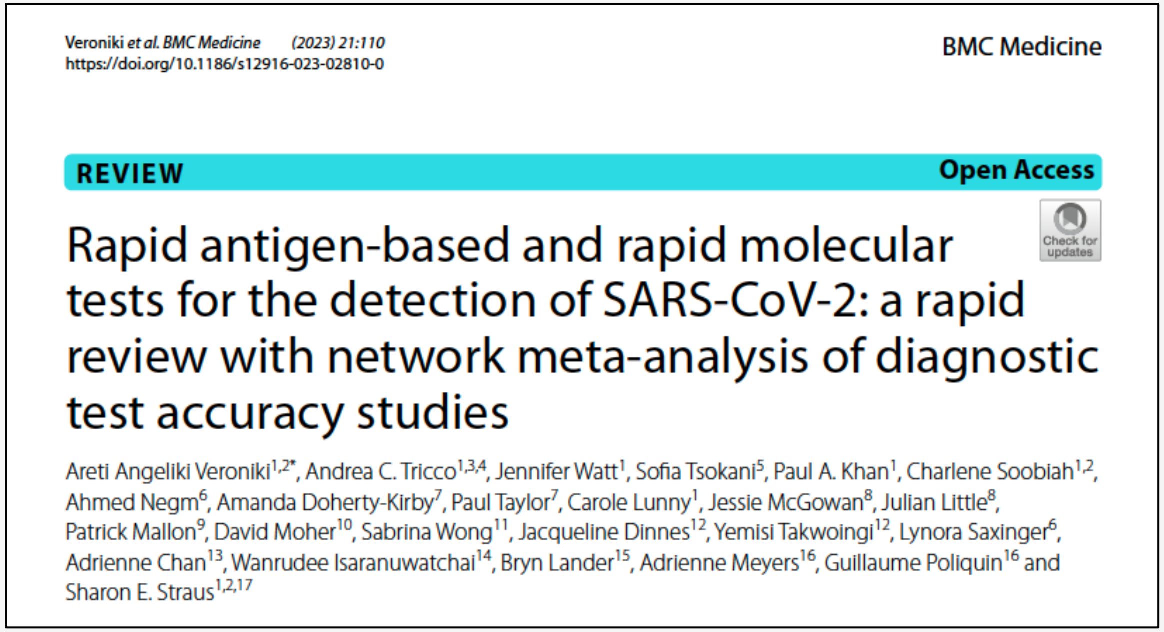
DTA-NMA Example

More than a year ago Health Canada and the Public Health Agency of Canada commissioned the team to ***conduct a review to determine the most sensitive and/or specific rapid test for the diagnosis of COVID-19***

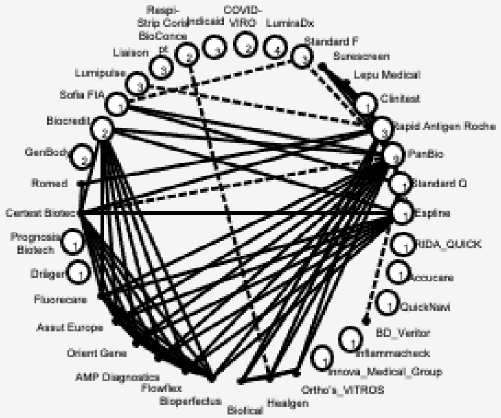

Veroniki *et al. BMC Medicine* (2023) 21:110
https://doi.org/10.1186/s12916-023-02810-0
BMC Medicine

REVIEW **Open Access**

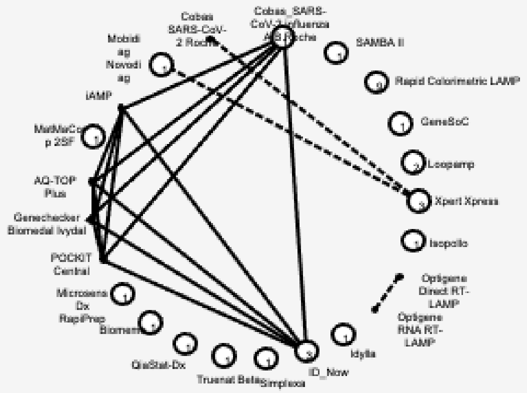
Rapid antigen-based and rapid molecular tests for the detection of SARS-CoV-2: a rapid review with network meta-analysis of diagnostic test accuracy studies

Areti Angeliki Veroniki[1,2*], Andrea C. Tricco[1,3,4], Jennifer Watt[1], Sofia Tsokani[5], Paul A. Khan[1], Charlene Soobiah[1,2], Ahmed Negm[6], Amanda Doherty-Kirby[7], Paul Taylor[7], Carole Lunny[1], Jessie McGowan[8], Julian Little[8], Patrick Mallon[9], David Moher[10], Sabrina Wong[11], Jacqueline Dinnes[12], Yemisi Takwoingi[12], Lynora Saxinger[6], Adrienne Chan[13], Wanrudee Isaranuwatchai[14], Bryn Lander[15], Adrienne Meyers[16], Guillaume Poliquin[16] and Sharon E. Straus[1,2,17]

Network plot for rapid antigen tests
68 studies, 104,961participants, 36 tests



Network plot for rapid molecular tests
27 studies, 10,449 participants, 23 tests



We set up our team considering to include the policy-makers who requested the evidence, at least one clinician/content expert, two patient partners, content experts, research methodologists, and statisticians.

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Research Question

Research question and eligibility criteria

- ***Population***: Adults and/or children screened/suspected for COVID-19
- ***Index tests***: We included studies evaluating one or more commercially available COVID-19 **rapid lateral flow antigen test** or **rapid molecular test** (providing a result in ≤1 hour) used for screening of asymptomatic individuals or the diagnosis of COVID-19 infection in symptomatic individuals
- ***Target condition***: COVID-19 infection
  - ***Reference Standard***: polymerase chain reaction (PCR) test
- ***Study design***: We included RCTs and observational studies, providing the 2x2 table data
- ***Outcome***: Sensitivity and specificity of rapid antigen and molecular tests suitable for screening and diagnosing COVID-19

Registered protocol with PROSPERO: CRD42021289712

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Data analysis

- Limited to basic descriptive summary of studies
    - Country of conduct and type of rapid test
- Kept the analysis high-level:
    - Random-effects DTA meta-analysis (bivariate model)
    - Random-effects DTA-NMA (Nyaga ANOVA model)
- Estimated sensitivity and specificity for each test along with their 95% credible intervals
- Investigated potential sources of heterogeneity that may influence diagnostic accuracy using:
    - **Subgroup analysis**: symptom status (asymptomatic vs symptomatic), sample type (e.g., saliva, nasal swab), participant type (e.g., general public, healthcare worker), and rapid molecular test category (i.e., rRT-PCR, PT-Isothermal, RT-Lamp)
    - **Meta-regression**: age
- Assessed transitivity based on the distribution of the above potential effect modifiers across test comparisons

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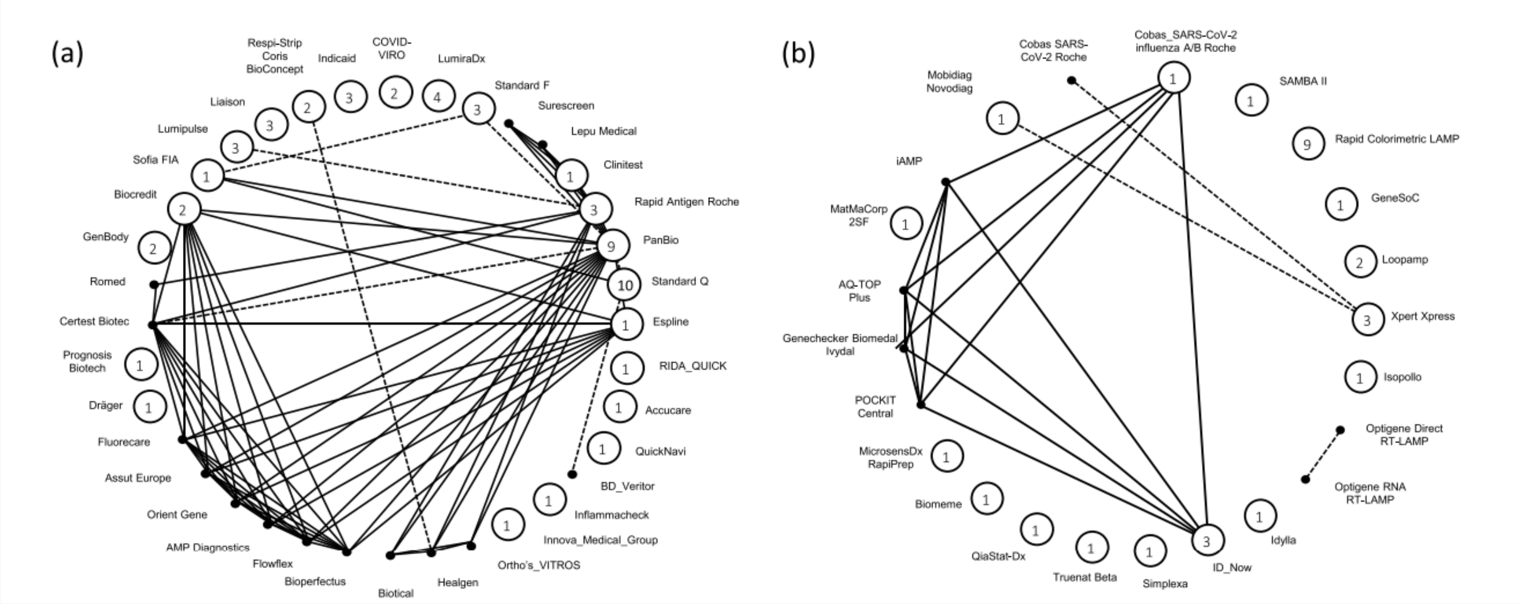
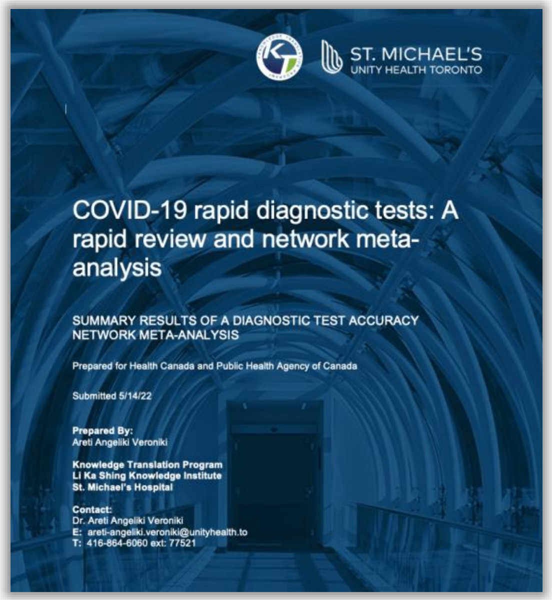
Report Findings

- Used reporting guidelines to ensure transparent and complete reporting of our research approach and findings
(e.g., PRISMA-DTA and PRISMA-NMA Checklist)

Network plot for rapid antigen tests
68 studies, 104,961participants, 36 tests

Network plot for rapid molecular tests
27 studies, 10,449 participants, 23 tests





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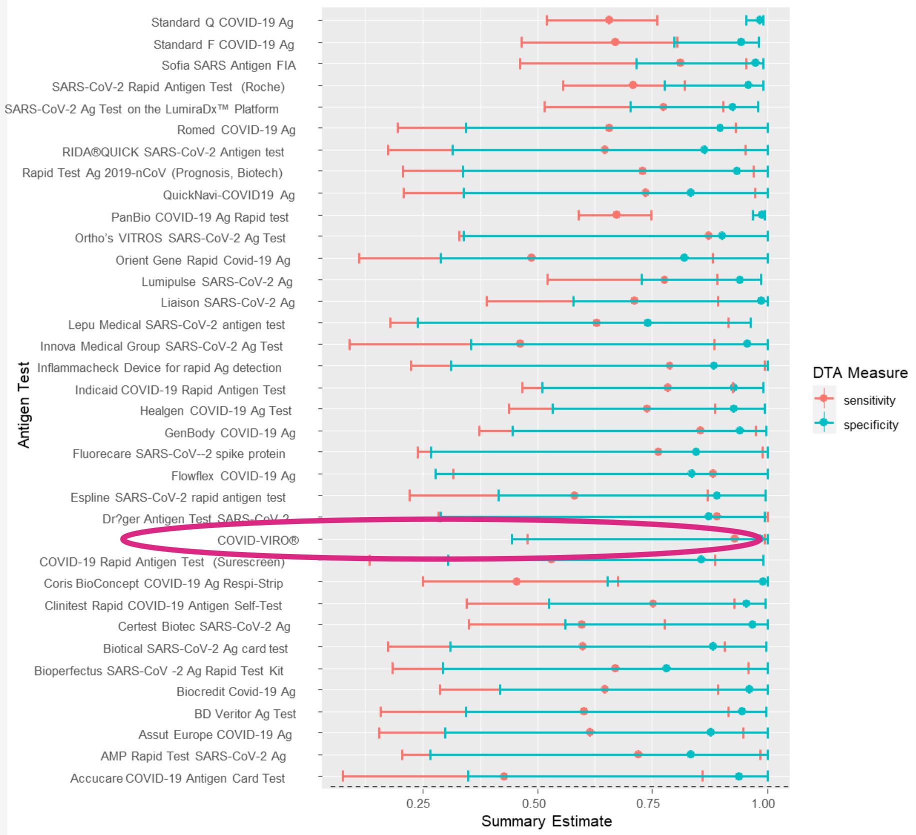
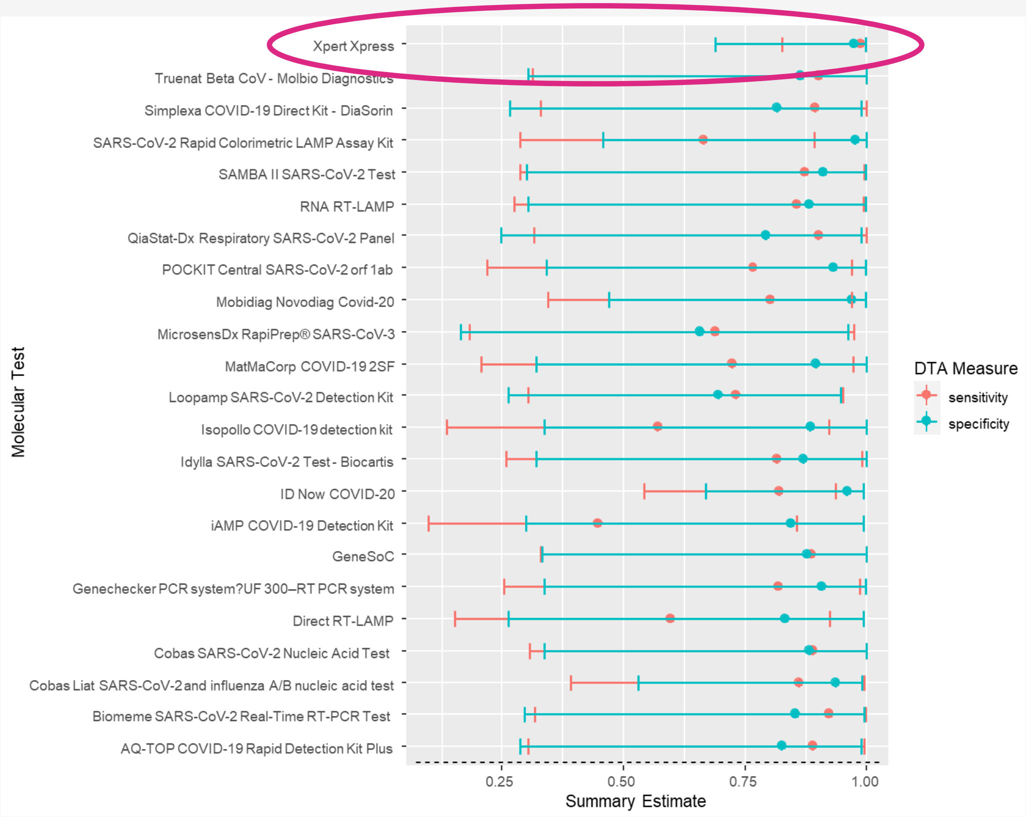
Summarized results

DTA-NMA results

Rapid antigen tests



Rapid molecular tests



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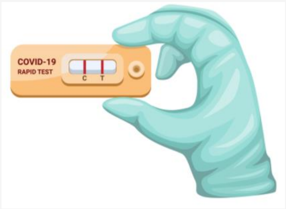
Report Findings



- Used reporting guidelines to ensure transparent and complete reporting of our research approach and findings
  (e.g., PRISMA-DTA and PRISMA-NMA Checklist)

Summarized results from the bivariate DTA meta-analysis model

			Summary estimates		Heterogeneity standard deviation	
Type	**Test**	**# Studies (# patients)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Sensitivity**	**Specificity**
Rapid molecular test	Xpert Xpress	5 (763)	0.98 (0.94, 1.00)	0.98 (0.94, 0.99)	0.79	0.53
Rapid antigen test	Standard Q COVID-19 Ag	13 (8740)	0.72 (0.53, 0.86)	0.99 (0.98, 1.00)	1.49	1.82
	PanBio COVID-19 Ag Rapid test (Abbott)	16 (32,151)	0.72 (0.61, 0.81)	0.99 (0.99, 1.00)	0.98	1.72
	SARS-CoV-2 Rapid Antigen Test (Roche)	7 (6065)	0.77 (0.55, 0.90)	0.99 (0.96, 1.00)	1.33	1.52
	Standard F COVID-19 Ag	5 (6428)	0.65 (0.50, 0.78)	0.98 (0.97, 0.99)	0.67	0.41

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There is still a lot to explore!

- Explore which factors impact on the performance of the DTA-NMA methods
- Extend the ranking metrics for multiple outcomes to DTA-NMA methods
- **DTA-NMA assumptions**: Appropriate methods are needed to explore the consistency assumption in DTA-NMA accounting for both sensitivity and specificity
- New methods are necessary to deal with and account for different study designs in a DTA-NMA

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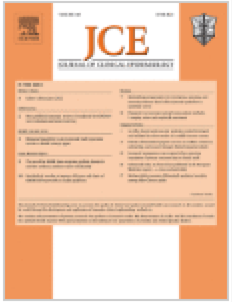
Diagnostic test accuracy network meta-analysis methods: A scoping review and empirical assessment



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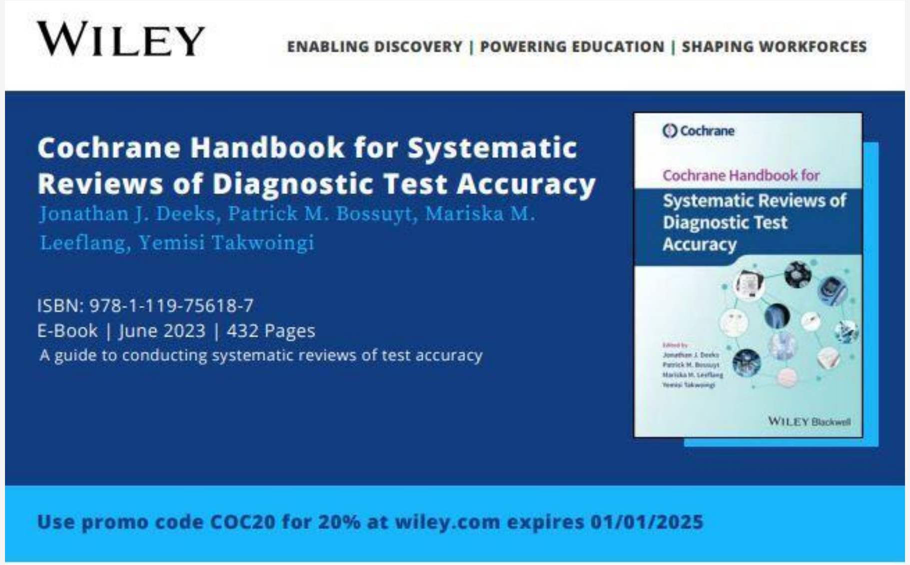
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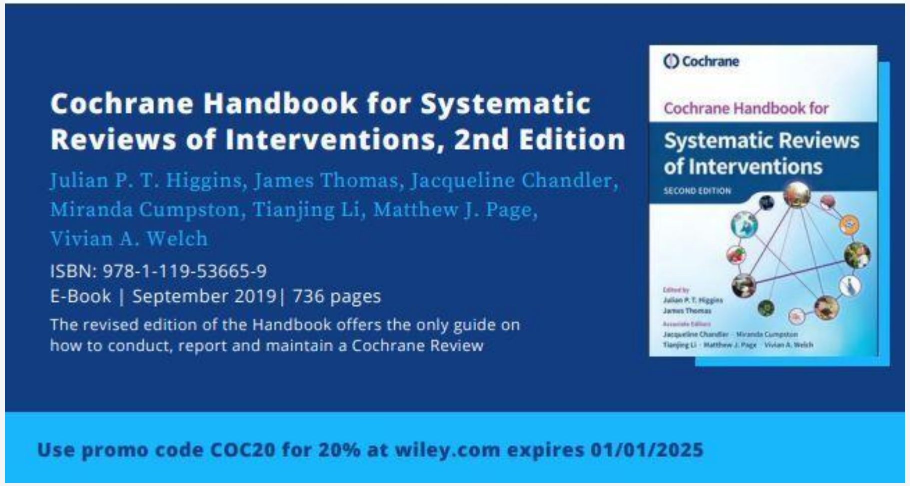
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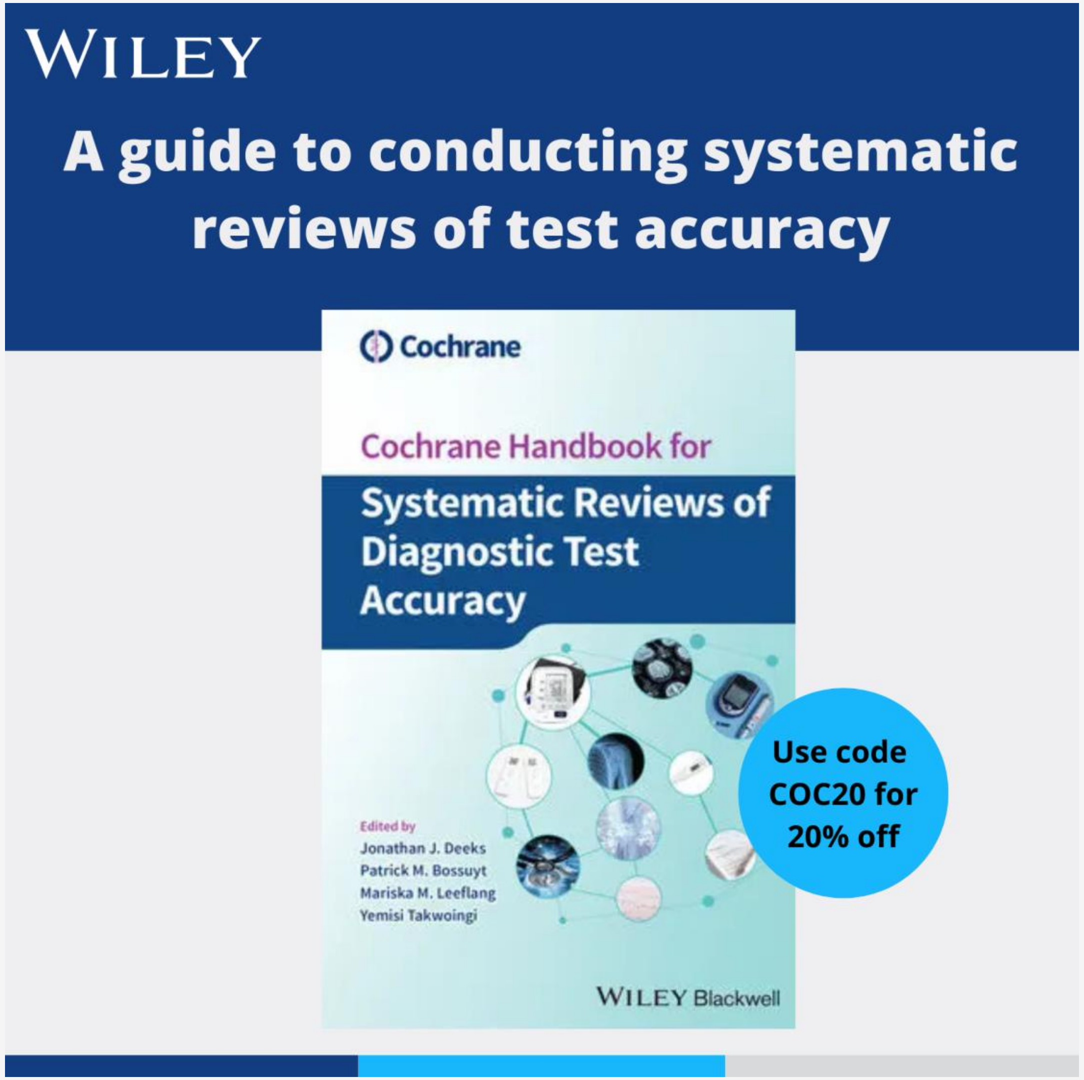
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