



Title of Program: Diagnostic Test Accuracy Reviews in Neonatal Medicine

Speakers/Moderators: Roger F. Soll, Gautham Suresh, Mohan Pammi

Planning Committee: Jeffery D. Horbar, Madge E. Buus-Frank, Roger F. Soll

Date: October 22, 2018

Learning Objectives:

The goal of this session is for participants to be able to: identify the underlying principles of diagnostic accuracy in reviews in neonatal medicine; to demonstrate their understanding of diagnostic test accuracy review findings; to transfer their understanding of findings of DTA reviews into clinical decision scenarios; and to apply their learning to the specific review of Molecular assays for the diagnosis of sepsis in neonates.

DISCLOSURE:

Is there anything to disclose? *No financial interests to disclose*

COMMERCIAL SUPPORT ORGANIZATIONS (if applicable): *No Commercial Support*

In support of improving patient care, this activity has been planned and implemented by The Robert Larner College of Medicine at The University of Vermont and Cochrane Neonatal. The University of Vermont is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

The University of Vermont designates this live activity for a maximum of *1 AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This program has been reviewed and is acceptable for up to 1 Nursing Contact Hours.



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Diagnostic Test Accuracy Reviews in Neonatal Medicine

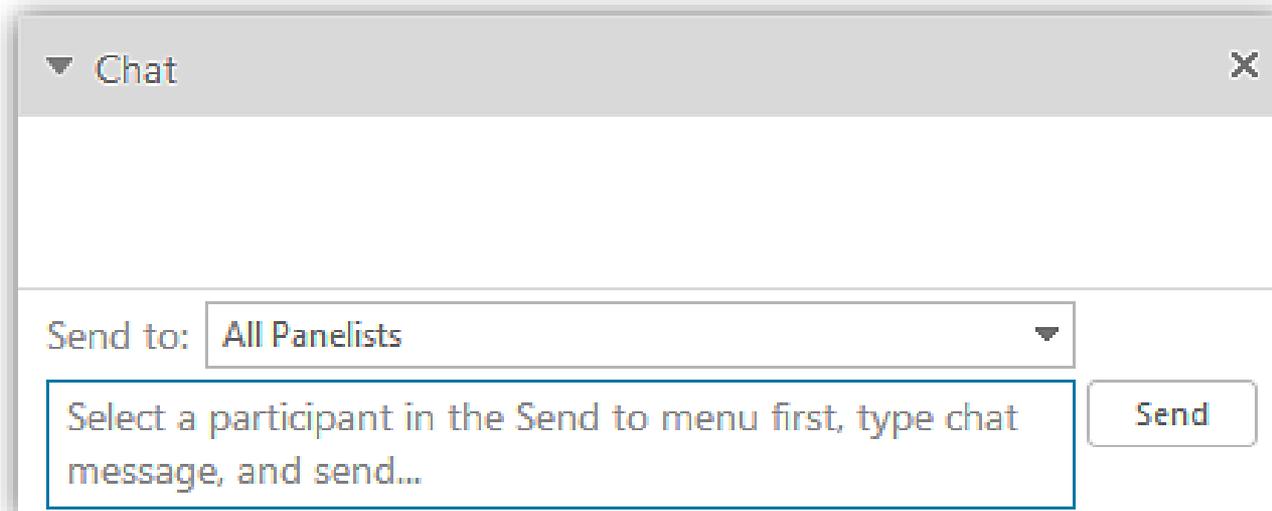


Cochrane Web Seminar October 22nd 2018

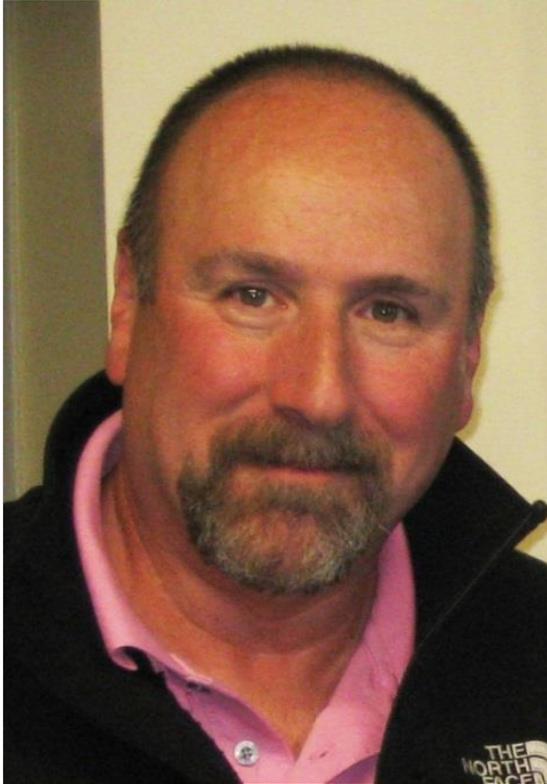
Trusted evidence. Informed decisions. **Better health.**

The Basics

- Follow the slides on your screen.
- Listen to the Audio Broadcast via your computer speakers.
- If the computer audio is not working well, click  at the bottom of the Participants panel and follow the prompts to call in on the telephone.
- Send questions and comments via Chat to “All Panelists”.



Introduction



WELCOME!

Roger F. Soll, MD
H. Wallace Professor of Neonatology
University of Vermont

Disclosure

Roger F. Soll is the Coordinating Editor of
Cochrane Neonatal and
President of Vermont Oxford Network.

Gautham Suresh and Mohan Pammi are
Editors of Cochrane Neonatal.



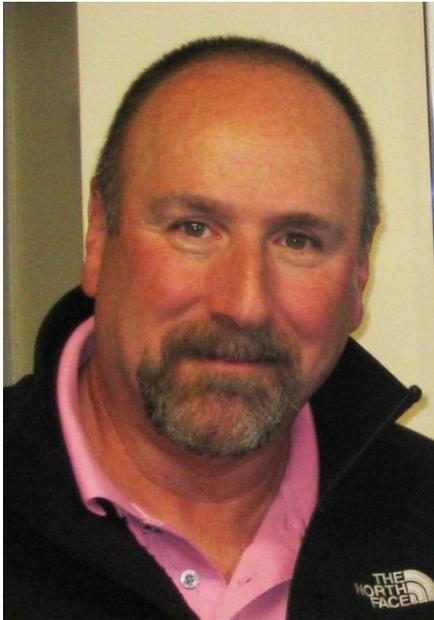
Cochrane

*Preparing, maintaining and promoting
the accessibility of systematic reviews
of the effects of health care interventions*

Cochrane Neonatal

*Prepares and disseminates
evidence-based reviews of the effects
of therapies in the field of neonatal medicine*

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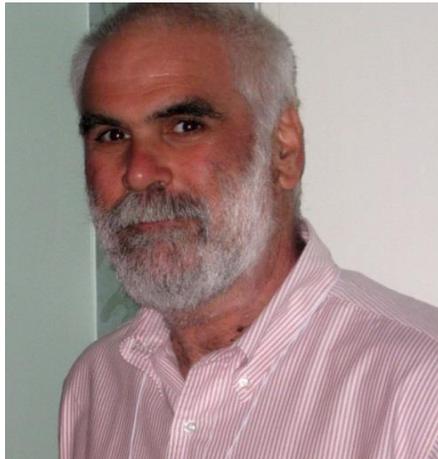


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With Thanks...

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“Overuse and waste remain significant problems in the US health care system, by one estimate accounting for ~34% of all health care spending in 2011, then assessed at ~\$2.7 trillion”.

Timmy Ho, MD, Dmitry Dukhovny, MD, MPH, John A.F. Zupancic, MD, ScD, Don A. Goldmann, MD, Jeffrey D. Horbar, MD, DeWayne M. Pursley, MD, MPH. Choosing Wisely in Newborn Medicine: Five Opportunities to Increase Value. Pediatrics 2015

Moderator/Discussant



DIAGNOSTIC TEST ACCURACY REVIEWS IN NEONATAL MEDICINE: General Concepts

Gautham Suresh, MD DM
Baylor College of Medicine

Ultimate Question

How will doing the test
change your management?



Choosing Wisely[®]

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To help physicians become better stewards of finite health care resources by developing lists of testing and treatment practices that are not evidence-based and whose necessity should be questioned and discussed



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Why Perform Diagnostic Tests?



Assign patient: disease vs. non-disease state

Classify severity of disease

Classify according to prognosis

Predict response to therapy

Predict future course of illness

- “Because that’s the way it is done”
- Psychological effects
 - Reassurance from “normal” results
 - Feeling of doing something
 - Parents feel “better doctors do more tests”
 - “It’s useful to know what’s in the neighborhood”
(for tracheal aspirates)
- Incentives
 - Profits
 - Medico-legal concerns

Bayesian Approach

Likelihood of Sepsis

100%

Treatment threshold

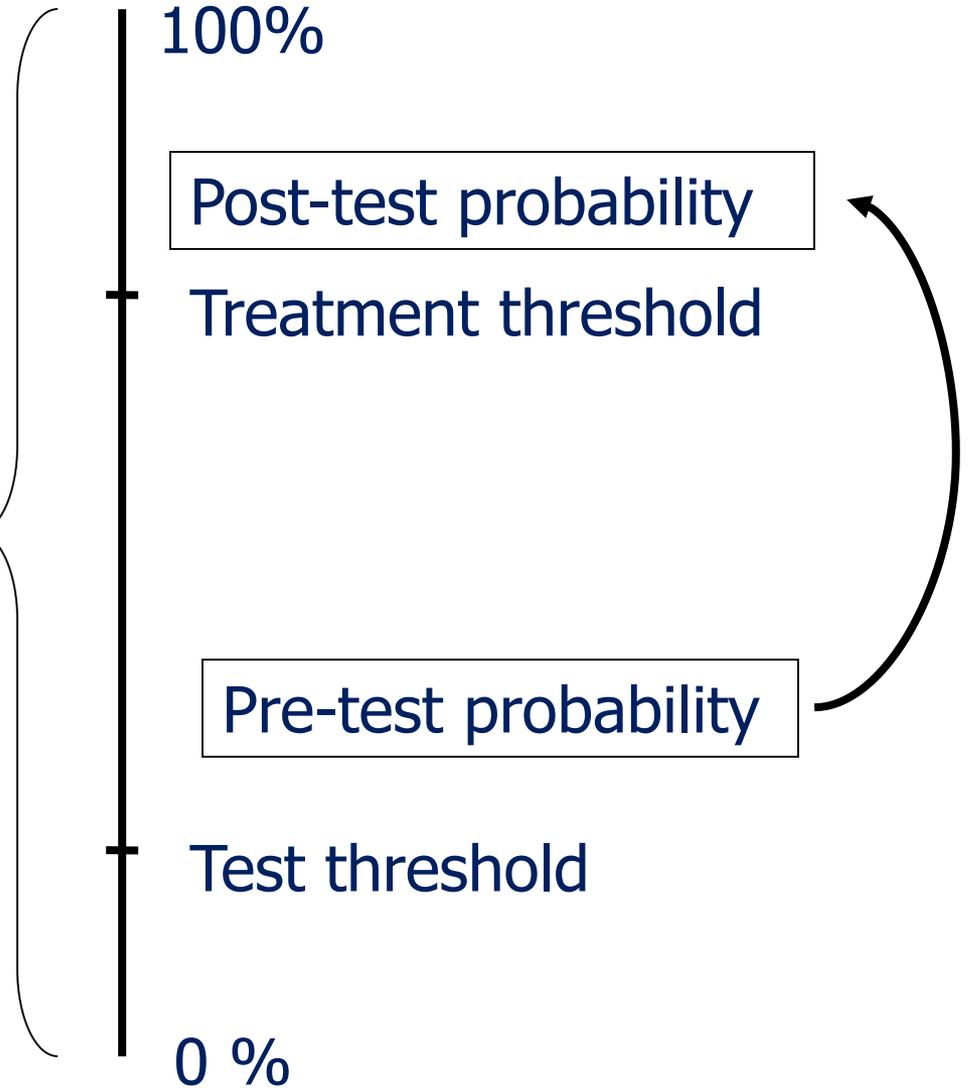
Test threshold

0 %

How useful is the CBC in moving you up or down this line?

Bayesian Approach

Likelihood of disease



A test is useful only if its result moves you across test or treatment threshold

Positive Likelihood Ratio

Probability of person **with** disease having a **positive** test

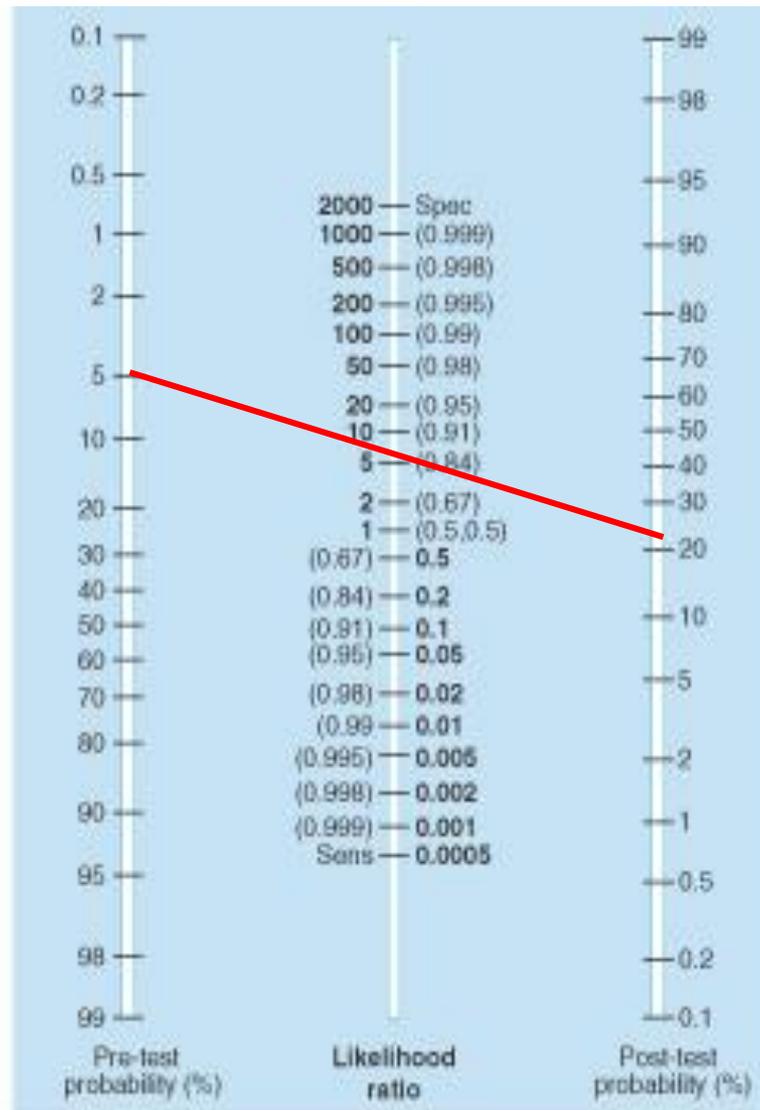
Probability of person **without** disease having a **positive** test

Negative Likelihood Ratio

Probability of person **with** disease having a **negative** test

Probability of person **without** disease having a **negative** test

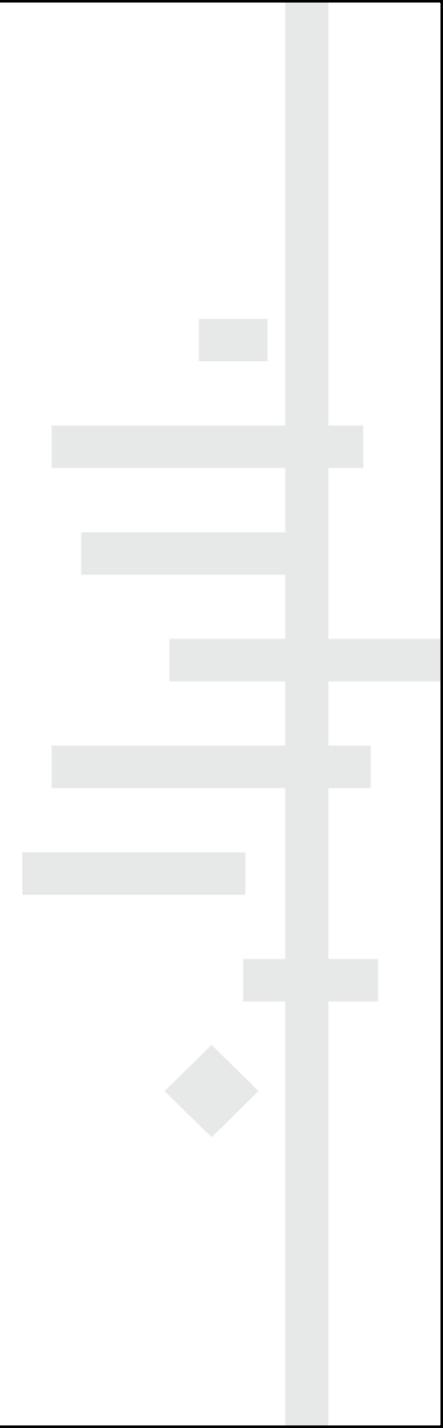
Likelihood Ratio Nomogram





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Single Studies of Diagnostic Tests



Annals of Internal Medicine

RESEARCH AND REPORTING METHODS

QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies

Penny F. Whiting, PhD; Anne W.S. Rutjes, PhD; Marie E. Westwood, PhD; Susan Mallett, PhD; Jonathan J. Deeks, PhD; Johannes B. Reitsma, MD, PhD; Mariska M.G. Leeflang, PhD; Jonathan A.C. Sterne, PhD; Patrick M.M. Bossuyt, PhD; and the QUADAS-2 Group*

Ann Intern Med. 2011;155:529-536.

Evaluating a Paper on Diagnostic Testing: Risk of Bias

1. Patient selection
2. Index test
3. Reference standard
4. Patient flow and timing

Evaluating a Paper on Diagnostic Testing Patient (Participant) Selection

1. Was a consecutive or random sample of patients enrolled?
2. Was a case–control design avoided?
3. Did the study avoid inappropriate exclusions?

Yes / No / Unclear

Evaluating a Paper on Diagnostic Testing: Index Test

Were the index test results interpreted without knowledge of the results of the reference standard?

If a threshold was used, was it prespecified?

Yes / No / Unclear

Evaluating a Paper on Diagnostic Testing: Reference Standard

Was an independent gold-standard test used?

Is the reference standard likely to correctly classify the target condition?

Were the reference standard results interpreted without knowledge of the results of the index test (blinded)?

Yes / No / Unclear

Evaluating a Paper on Diagnostic Testing: Patient Flow and Timing

Was there an appropriate interval between index tests and reference standard?

Did all patients receive a reference standard (Was it applied to all patients, irrespective of the results of the diagnostic test)?

Did all patients receive the same reference standard?

Were all patients included in the analysis?

Yes / No / Unclear

Evaluating a Paper on Diagnostic Testing: Applicability

Are there concerns that the following do not match the review question?

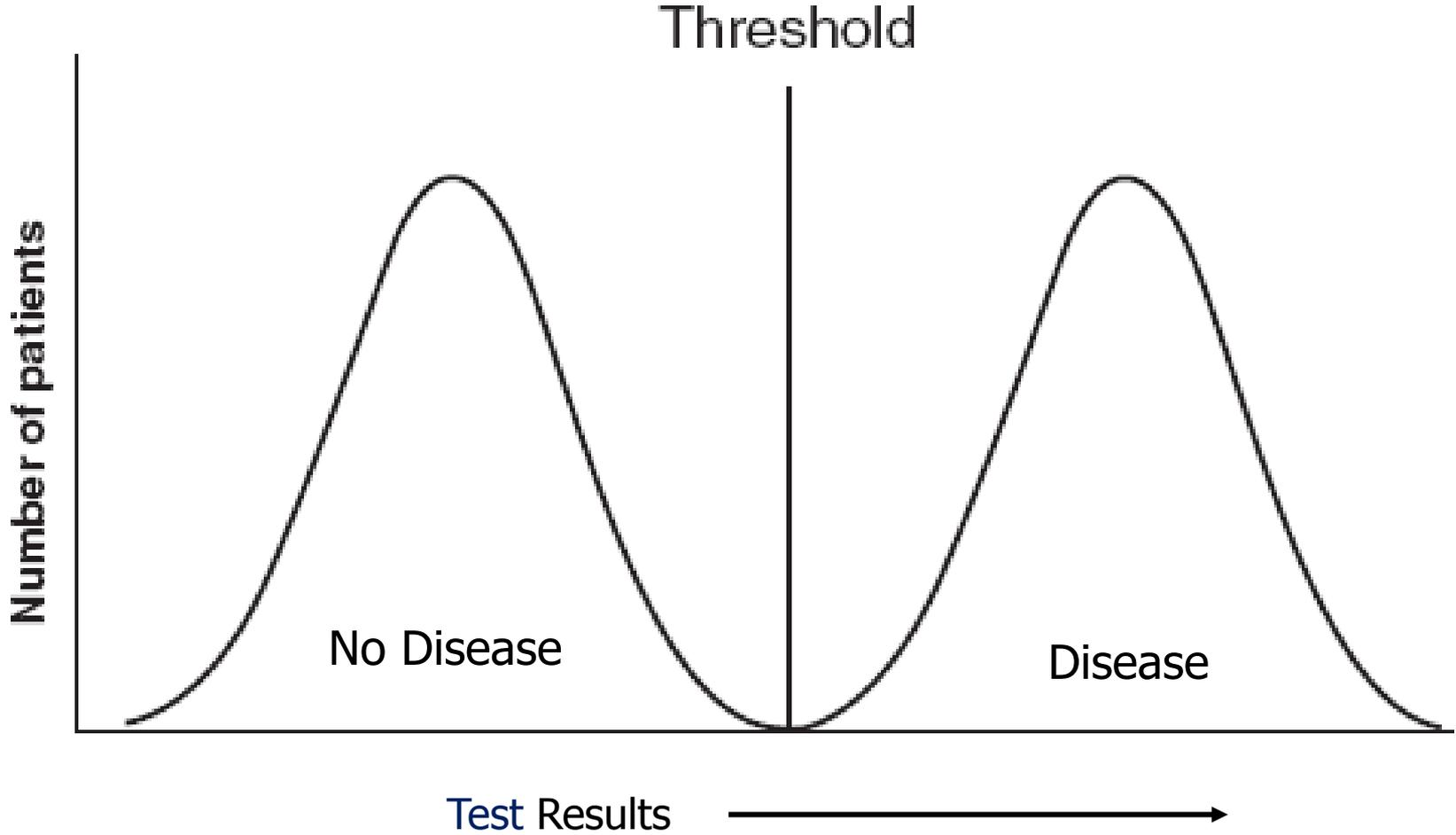
- Included patients - was the diagnostic test evaluated in an appropriate spectrum of patients (not just florid or asymptomatic patients)?
- Index test, its conduct, or interpretation
- Reference standard

High / Low / Unclear

Evaluating a Paper on Diagnostic Testing: What is an Abnormal Test?

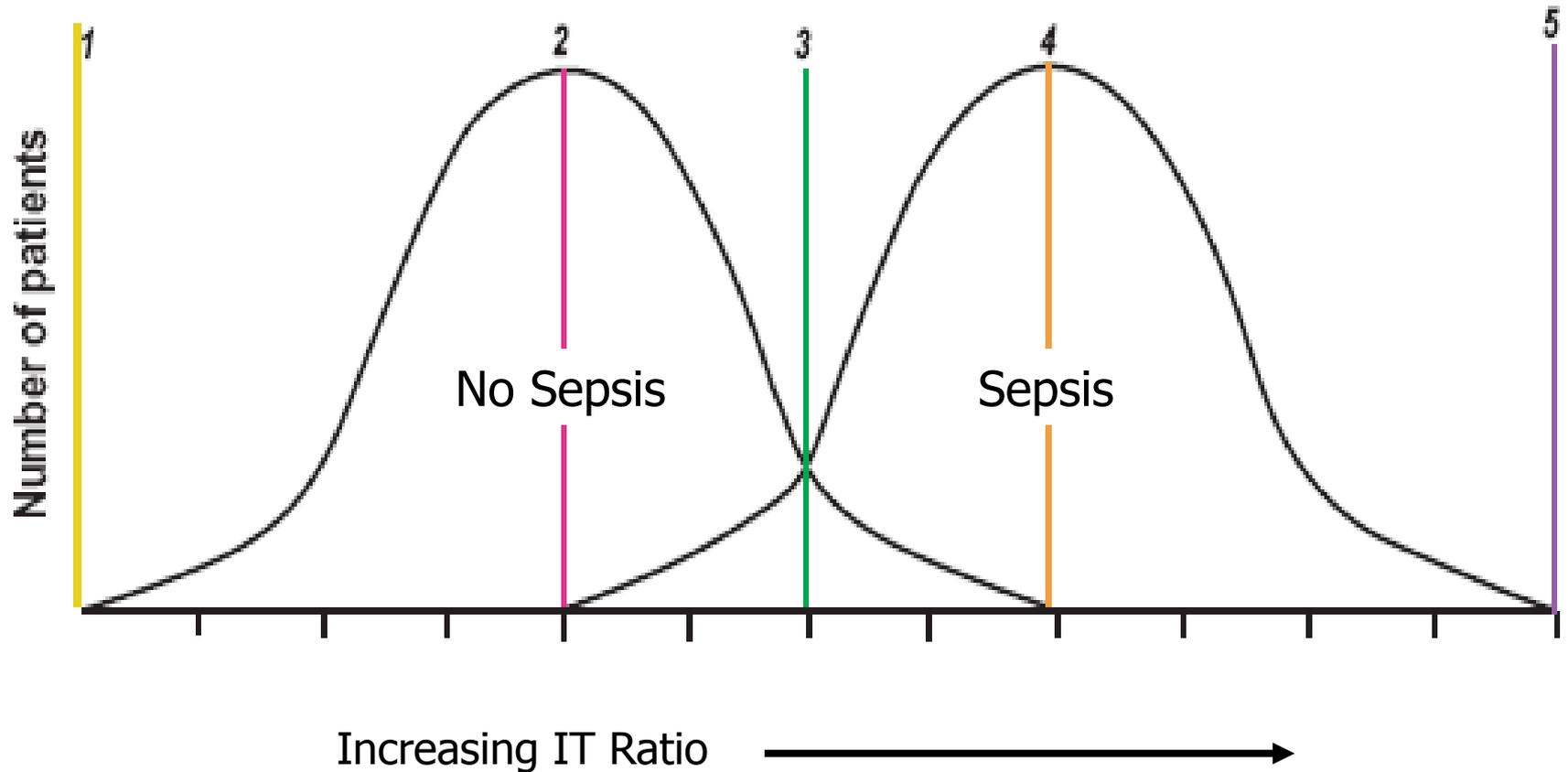
1. Outside 2 SD, or outside 10 to 90th percentile
2. Level at which risk of disease is increased
3. Range where target disease highly probable
4. Range in which Rx does > good than harm

Ideal Test (Continuous Measures)



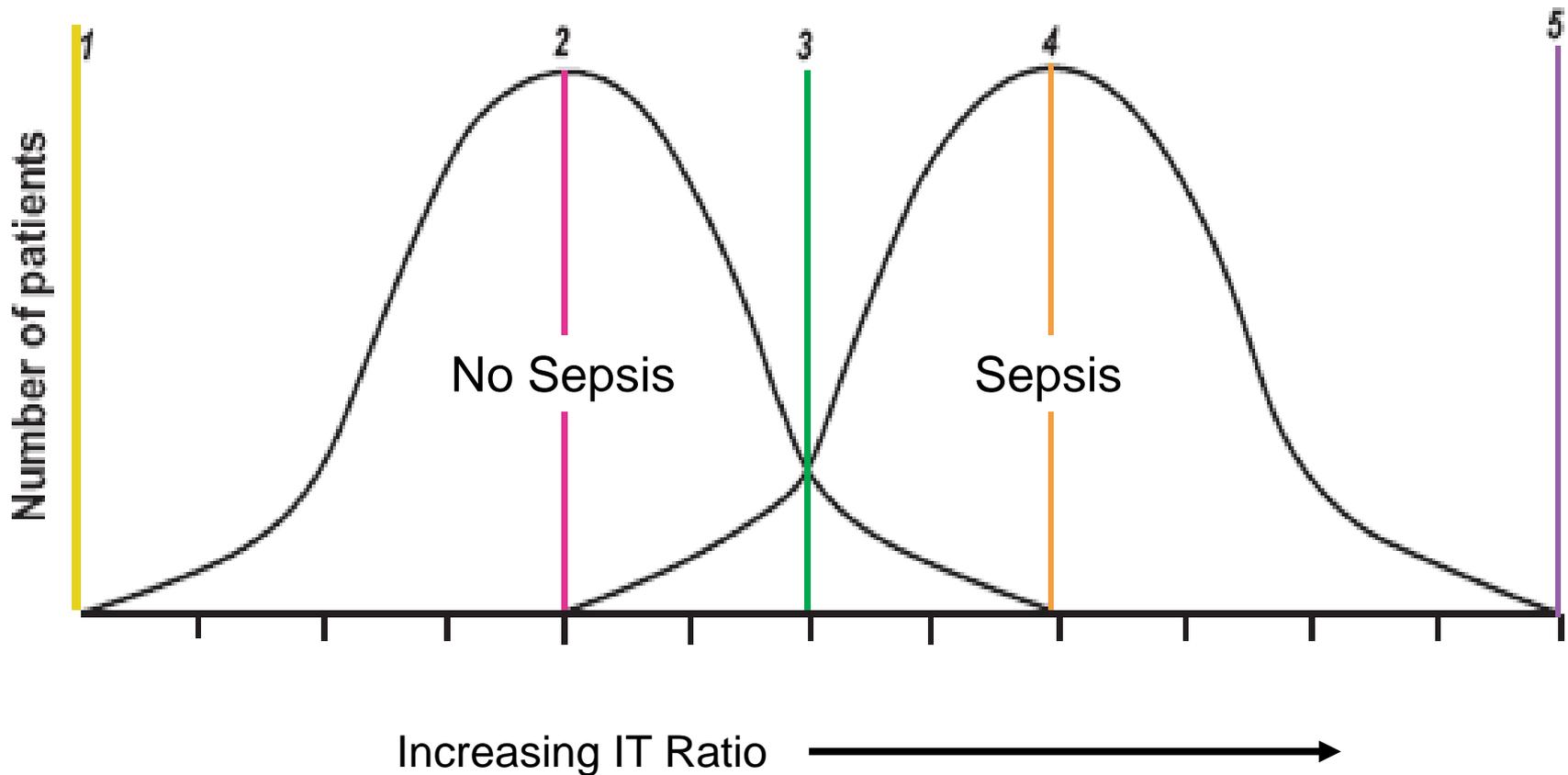
Actual Tests

Varying Thresholds



Actual Tests

Varying thresholds results in trade-offs between false positives and false negatives



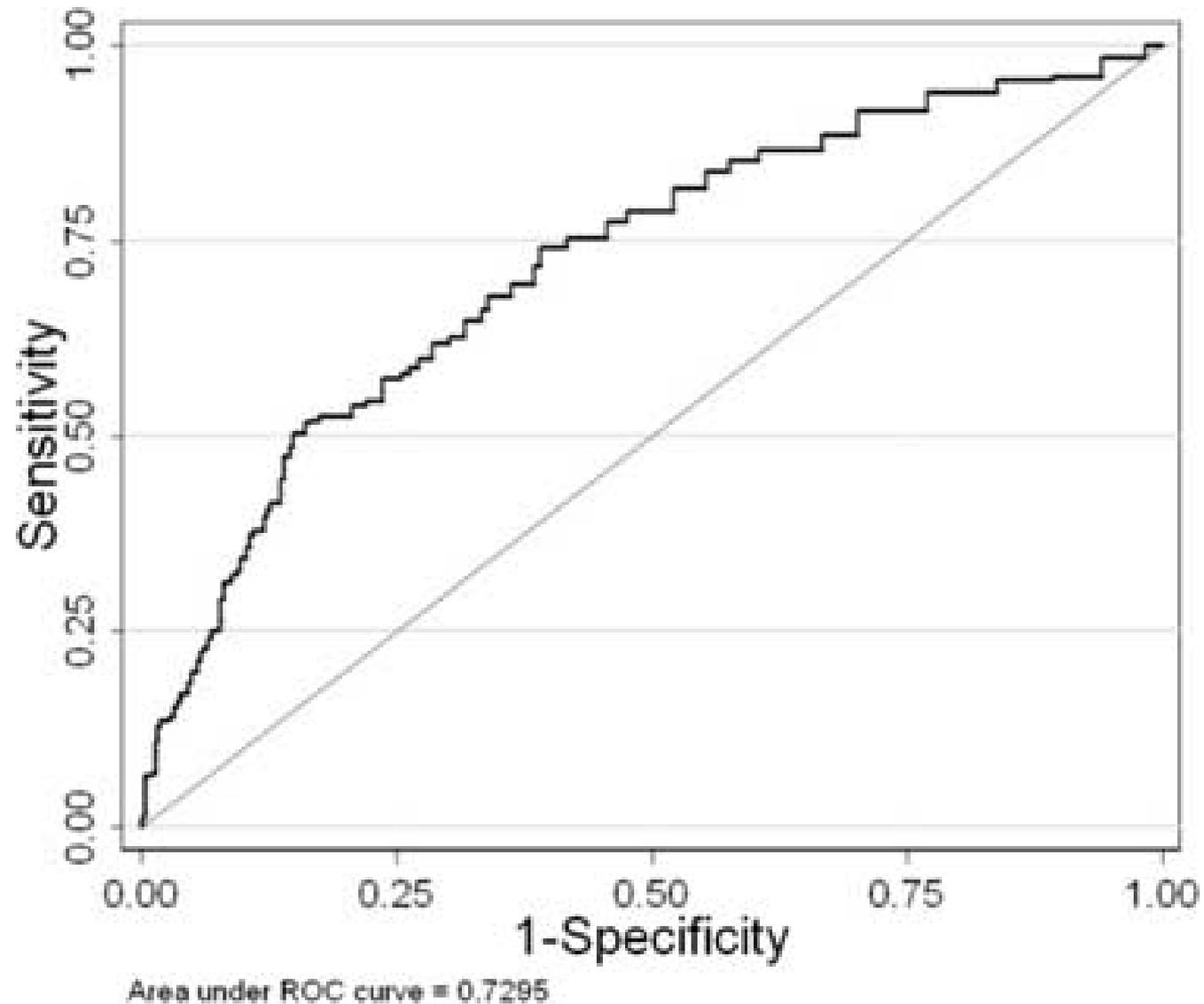
Accuracy of Test

	Disease Present	Disease Absent	
Diagnostic Test Positive	True Positive	False Positive	
Diagnostic Test Negative	False Negative	True Negative	

Accuracy of Test

	Disease Present	Disease Absent	
Diagnostic Test Positive	6 (60%) (True Positive)	300 (30%) (False Positive)	306
Diagnostic Test Negative	4 (40%) (False Negative)	700 (70%) (True Negative)	704
	10	1000	1010

Receiver Operating Characteristic Curve



Mnemonics

SENSITIVITY

PID – positive in disease

SnOut: Tests with a high sensitivity rule OUT the disease

SPECIFICITY

NIH – Negative in health

SpIn: Tests with a high specificity rule IN the disease

Systematic Reviews of Diagnostic Test Accuracy

Identify all available evidence

Evaluate the quality of published studies

Produce estimates of test performance and impact based on all available evidence

Account for variation in findings between studies

Questions/ Discussion?



Guest Discussant



Mohan Pammi, MD, PhD
Baylor College of Medicine

Neonatal Sepsis

Bacterial and fungal sepsis in neonates

- early-onset (≤ 72 hr), 1.5% to 1.9% of VLBW infants
- late-onset (> 72 hr), 10 to 20% of VLBW infants

Mortality -18 to 36%

Morbidity- PDA, BPD, ROP, increased hospital stay

Non-specific clinical signs and symptoms

Early diagnosis and treatment may improve outcomes

Diagnosis of Sepsis

Gold standard or Reference standard

Microbial cultures of blood, CSF or other sterile body fluids

Reference Standard- Cultures

Assumed to have low sensitivity

- Low degree of neonatal bacteremia or fungemia
- Small inoculation volumes in culture bottles
- Intrapartum antibiotics



Results in 24 to 72 hours

Alternative Tests for Sepsis

Sepsis diagnostic test	Sensitivity	Specificity
White cell indices		
WBC < 5000	0.2	0.96
WBC < 1000	0.3	1.0
I:T ratio greater than 0.20	0.55	0.74
Serum biomarkers		
CRP	0.6 to 0.84	0.84 to 1.0
Procalcitonin	0.91	0.65
Tumor necrosis factor α	0.6 to 0.82	0.86 to 0.93
Interleukin-6	0.58 to 0.89	0.84 to 0.96

Ideal Test to Replace Blood Cultures

Rapid results

High sensitivity

- not to miss infections

High specificity

- reliably exclude sepsis to avoid unnecessary antibiotics

Detect all organisms relevant to neonatal sepsis

Not be affected by maternal antibiotics

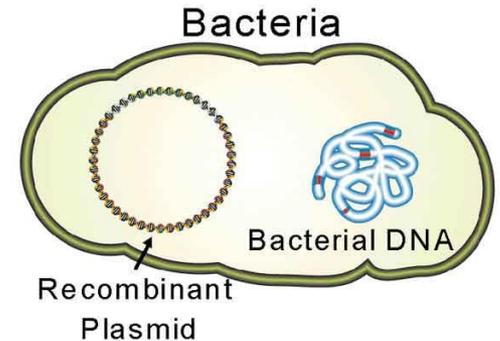
Why Molecular Assays?

Molecular assays

- Rapid results – 6 to 8 hrs
- May have higher sensitivity

Index test- Molecular assays

Any assay that involves extraction and evaluation of nucleic acid from bacteria or fungi



Amplification of microbial DNA

1. Broad-range conventional PCR assays
2. Real-time PCR
3. Post-PCR sequencing or hybridization
4. Multiplex-PCR- multiple organisms
5. Species or genus-specific assays





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Molecular Assays for the Diagnosis of Sepsis in Neonates

Mohan Pammi MD, PhD,

Angela Flores MD,

James Versalovic MD, PhD,

Mariska Leeflang PhD

Trusted evidence. Informed decisions. [Better health.](#)



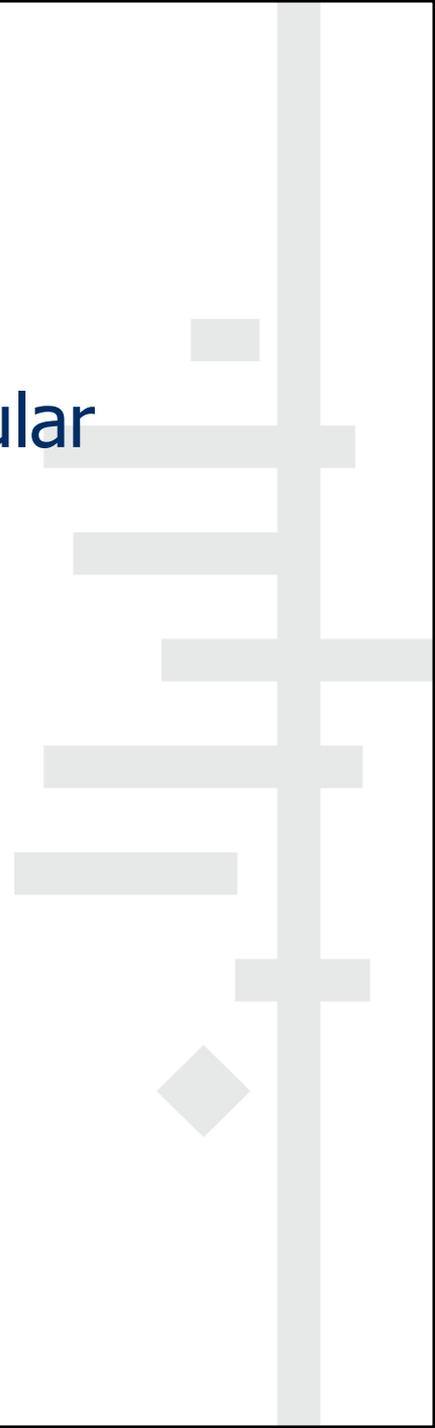


Objectives

1. Assess the diagnostic accuracy of molecular assays for the diagnosis of culture-positive bacterial and fungal sepsis in neonates

2. Explore heterogeneity

- Subgroup analysis by gestational age and type of sepsis onset
- Sensitivity analysis



Types of participants

- Neonates with clinically suspected bacterial or fungal sepsis

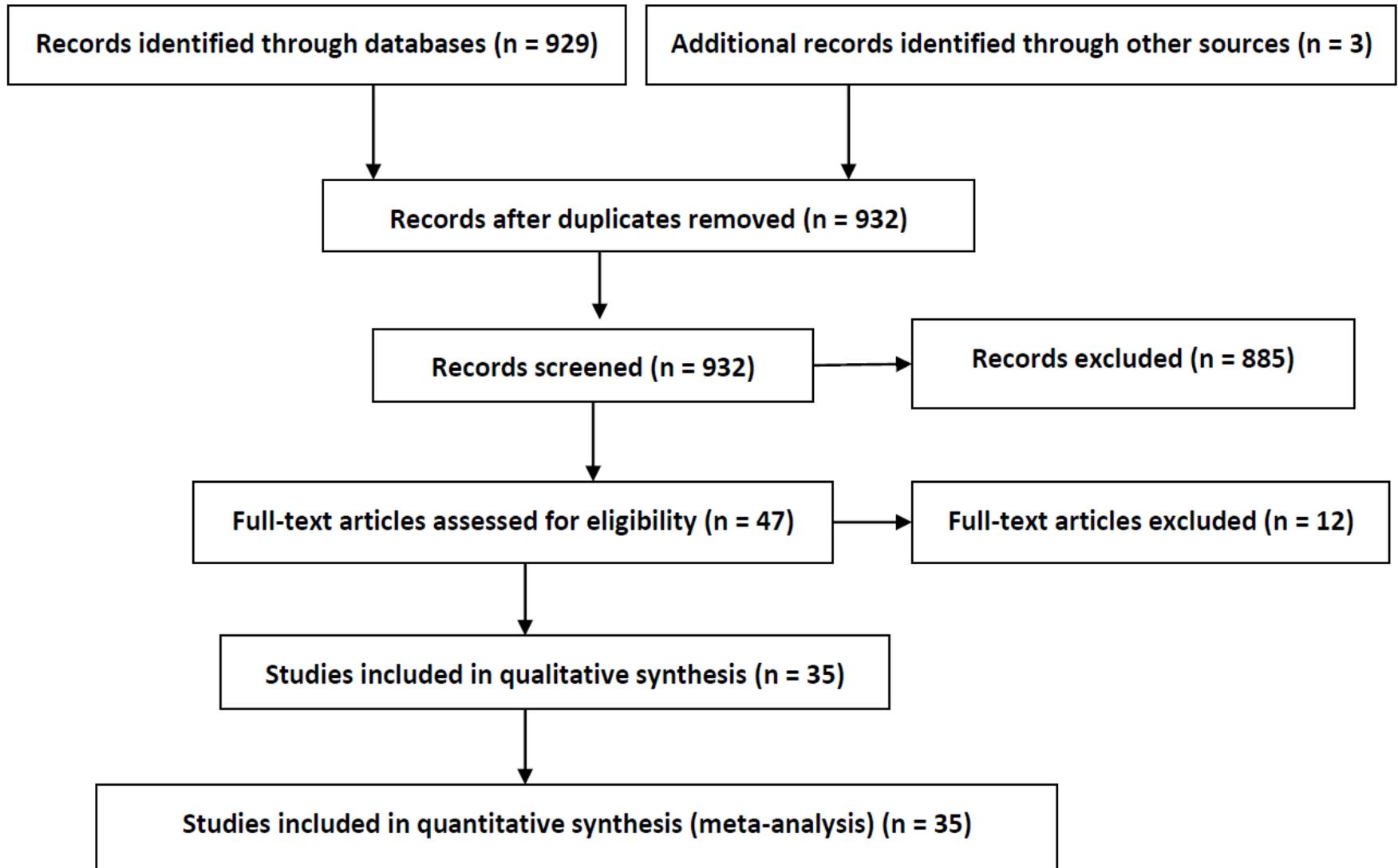
Types of studies

- Prospective or retrospective, cohort or cross-sectional

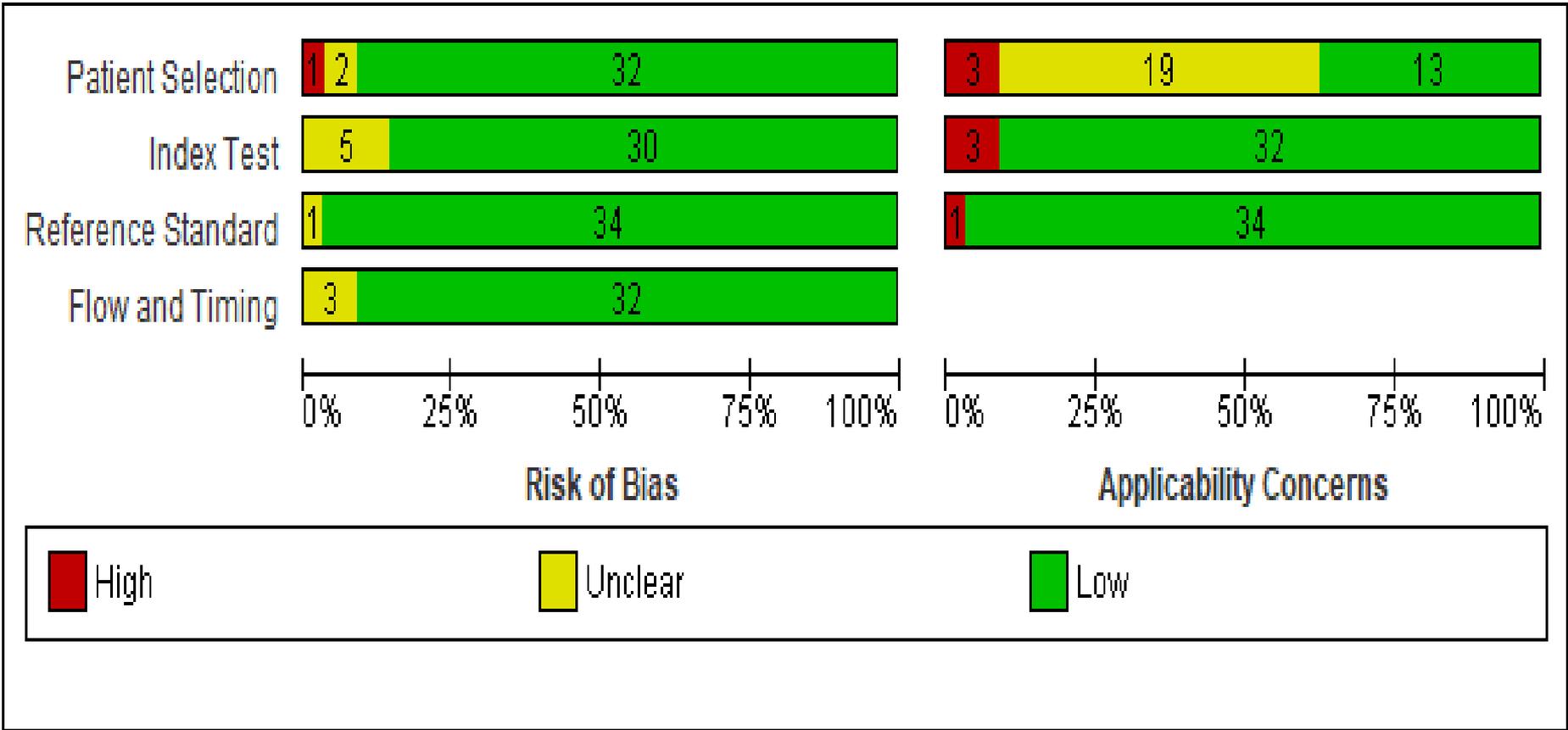
Exclusion

- Studies with only positive or negative samples, Index test, Reference standard and target condition

Search Results



Methodological Assessment using QUADAS2



RESULTS

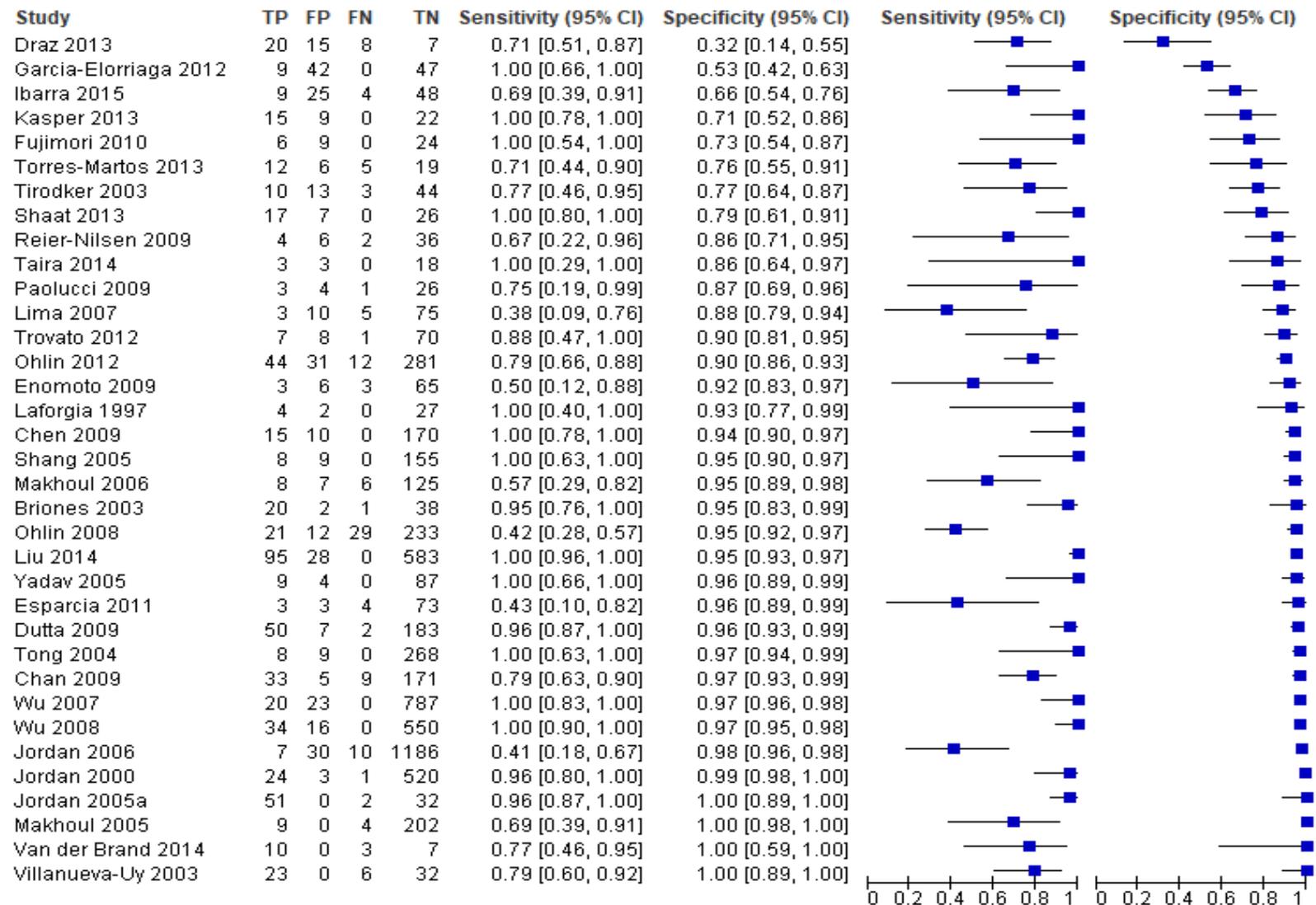
Meta-analyses

- bivariate random-effects model using statistical software STATA

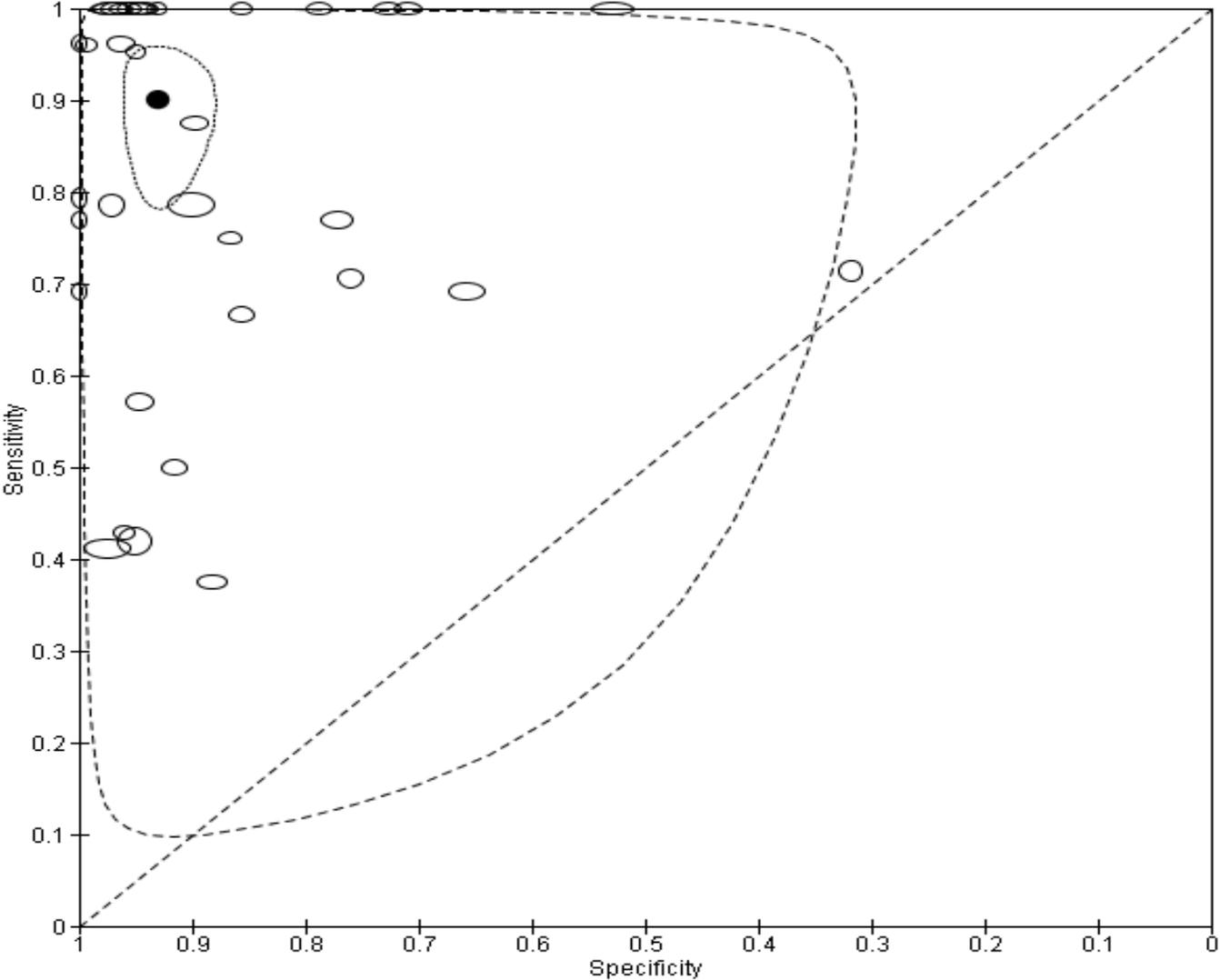
GRADE rating of evidence

- Downgraded for inconsistency and imprecision
- We did not find significant publication bias
 - Deeks' test for publication bias

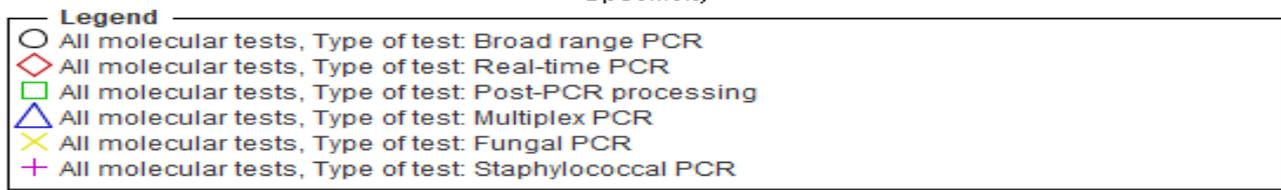
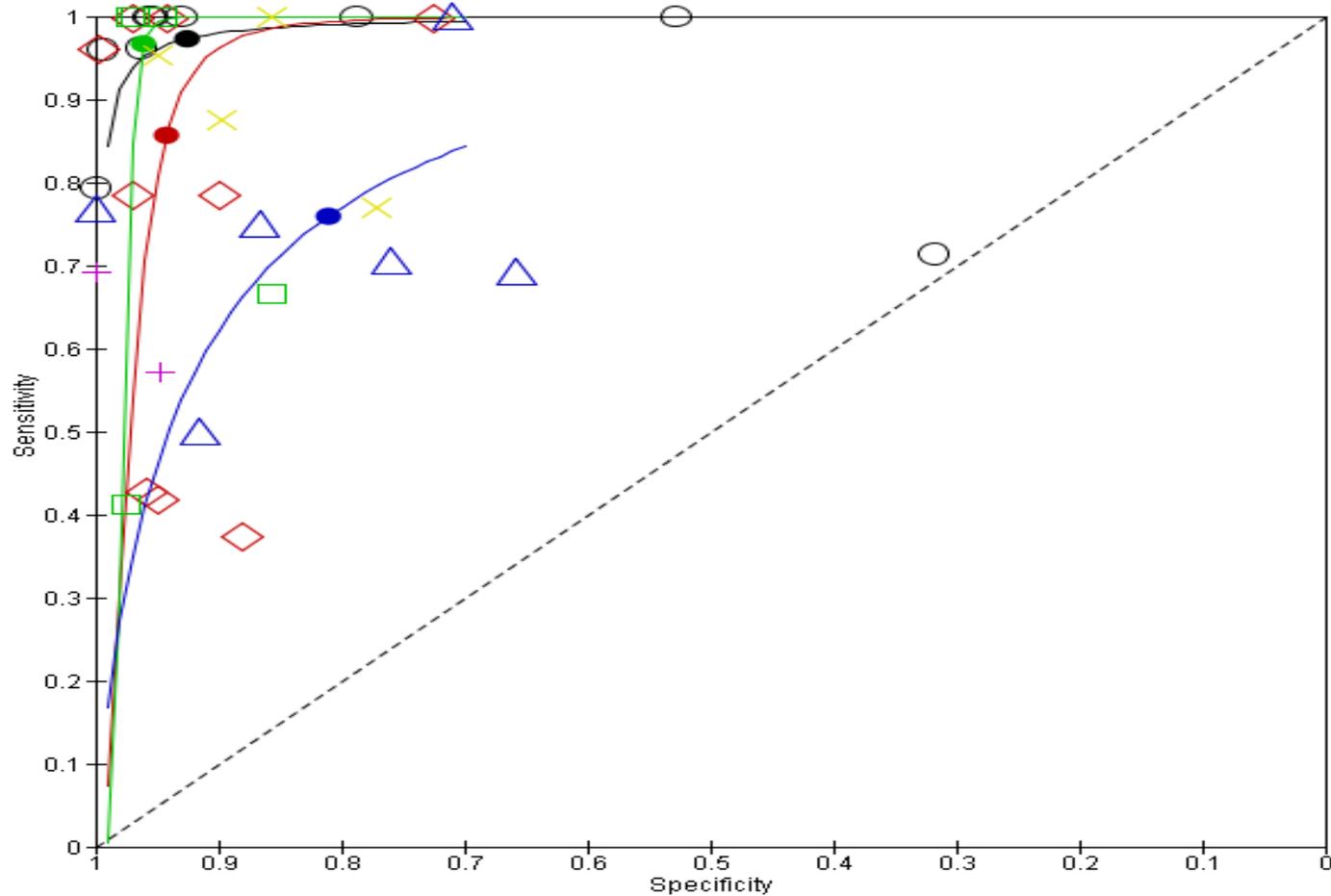
Forest Plot of Sensitivity and Specificity



Summary Receiver Operating Characteristic Space



Subgroup Analysis: Type of Molecular Test



Summary of Findings Table

	Groups	Studies (n)	Sensitivity (95% CI)	Specificity (95% CI)	Quality of evidence using GRADE
	All studies	35	0.90 (0.82 to 0.95)	0.93 (0.89 to 0.96)	Moderate
Type of test	Broad-range PCR	9	0.97 (0.86 to 1.00)	0.93 (0.77 to 0.98)	Moderate
	Real-time PCR	9	0.86 (0.59 to 0.96)	0.94 (0.90 to 0.97)	Moderate
	Post-PCR processing	5	0.97 (0.40 to 1.00)	0.96 (0.93 to 0.98)	Low
	Multiplex PCR	6	0.76 (0.60 to 0.88)	0.81 (0.70 to 0.89)	Low
	Staphylococcal PCR*	2	-	-	Low
	Fungal PCR*	4	-	-	Low
Quality	Good methodologic studies only	22	0.90 (0.78 to 0.96)	0.93 (0.88 to 0.96)	Moderate

	Groups	Studies	Sensitivity (95% CI)	Specificity (95% CI)	Quality of evidence GRADE
Type of sepsis	EOS	2	-	-	Low
	LOS	10	0.79 (0.69 to 0.86)	0.94 (0.85 to 0.98)	Low
	Mixed EOS and LOS	23	0.94 (0.84 to 0.98)	0.92 (0.87 to 0.95)	Moderate
Gestational age	Preterm	5	0.89 (0.75 to 0.96)	0.87 (0.71 to 0.94)	Low
	Mixed term and preterm	30	0.90 (0.80 to 0.96)	0.94 (0.90 to 0.96)	Moderate
Prevalence	< 15%	20	0.94 (0.80 to 0.99)	0.95 (0.92 to 0.97)	Moderate
	15% to 30%	8	0.85 (0.67 to 0.94)	0.88 (0.79 to 0.94)	Low
	> 30%	7	0.87 (0.75 to 0.93)	0.93 (0.64 to 0.99)	Low
Specimen	Blood only	32	0.92 (0.84 to 0.96)	0.93 (0.89 to 0.95)	Low
	Blood and CSF	3	-	-	Moderate

Applicability in Clinical Practice

Diagnostic tests in clinical practice

- **Replace** the reference standard
- **Triage** tests
 - Who gets the reference standard
- **'Add-on'** tests
 - In addition to the reference standard

Comparative accuracy: assessing new tests against existing diagnostic pathways, Bossuyt BMJ 2006

Applicability in Clinical Practice

1000 VLBW neonates screened for EOS (prevalence was 2%)

- Sens 0.90 and Spec 0.93
- Miss 2 cases of sepsis
- Unnecessarily treat 69 neonates without sepsis.

1000 VLBW neonates screened for LOS (prevalence 10%)

- Miss 10 culture-positive cases
- Unnecessarily treat 63 neonates without sepsis.

Currently available molecular assays may not have sufficient diagnostic accuracy to **replace** microbial cultures

Current molecular assays do not provide antimicrobial susceptibility

Applicability in Clinical Practice

Triage test - unlikely

- An unwanted delay in performing blood cultures may ensue and may postpone treatment
- False negatives on the molecular tests will compromise neonatal safety

'Add-on' tests concurrent to blood cultures

- faster turnaround time
- Results available in six to eight hours -optimize clinical therapy
- If negative, antibiotics may be discontinued if the test assay has high specificity and high negative predictive value



Conclusions

Molecular assays- potential as '**add-on**' tests as they give rapid results that may aid clinical decisions regarding treatment (moderate to low quality evidence)

Which assay to use?

Technological advances may lead to better assays

- Design studies -high methodologic quality and minimal bias

Costs of the molecular assays need to be balanced with their ability to impact clinical outcomes





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Principles of Evidence-Based Medicine

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Please contact Colleen Ovelman at colleen.ovelman@uvm.edu with questions.