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**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

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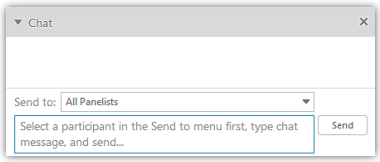
## The Basics

- Follow the slides on your screen.
- Listen to the Audio Broadcast via your computer speakers.
- If the computer audio is not working well, click 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".

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## Introduction

**WELCOME!**

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

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## 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.

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***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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## With Thanks…

Vermont Oxford NETWORK

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An initiative of the ABIM Foundation

"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

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## Moderator/Discussant

**DIAGNOSTIC TEST ACCURACY REVIEWS IN NEONATAL MEDICINE: General Concepts**

Gautham Suresh, MD DM
Baylor College of Medicine

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## Ultimate Question

How will doing the test change your management?

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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?

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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

Sackett. Clinical Epidemiology, 2nd Ed

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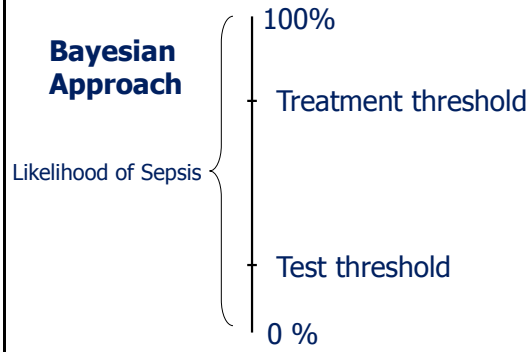
## Why Perform Diagnostic Tests?

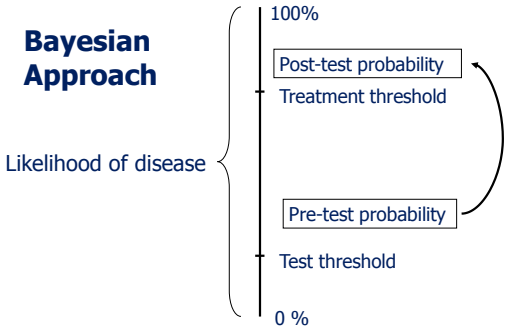
- "Because that's the way it is done"
- Psychological effects
  - Reassurance from "normal" results
  - Feeling of doing something
  - Parents feel "better doctors do more tests"
  - "It's useful to know what's in the neighborhood" (for tracheal aspirates)
- Incentives
  - Profits
  - Medico-legal concerns

**Bayesian Approach**




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

## Bayesian Approach




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

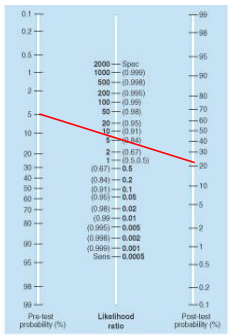
## Negative Likelihood Ratio

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.

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## Evaluating a Paper on Diagnostic Testing: Risk of Bias

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

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## 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

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## 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

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## 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

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## 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

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## 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

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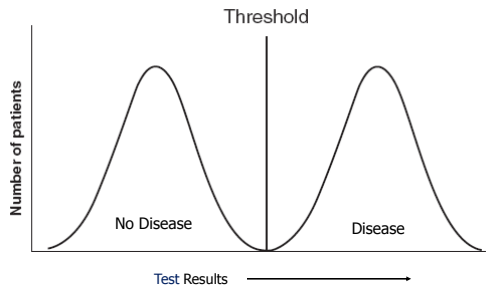
## Evaluating a Paper on Diagnostic Testing: What is an Abnormal Test?

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

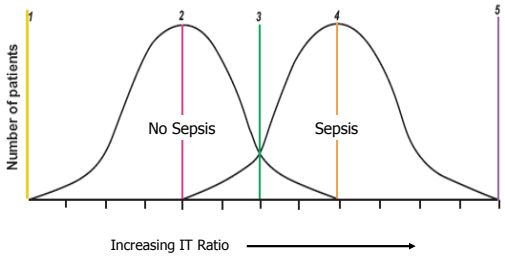
Modified from Sackett: Evidence Based Medicine

## Ideal Test (Continuous Measures)



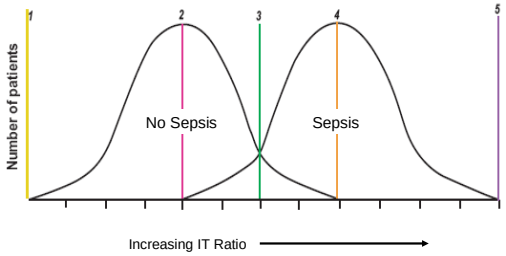

## Actual Tests

Varying Thresholds




## Actual Tests

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



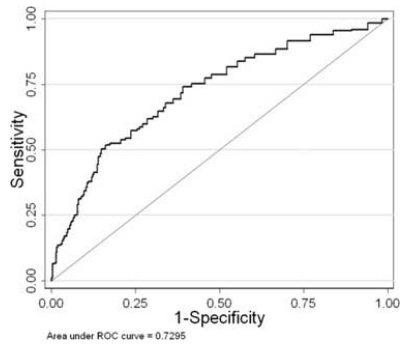

## Accuracy of Test

| | 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



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## 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 |

**Hildegaard 2015. Stewart 2018**

## 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

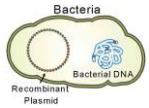
## Why Molecular Assays?

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**

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## 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

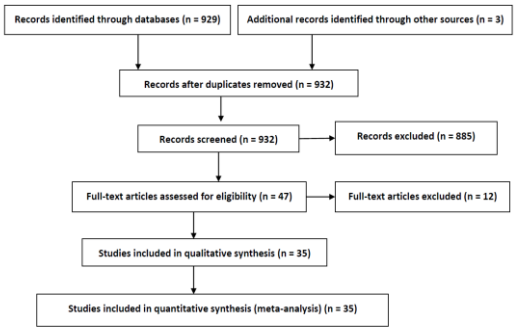
## Inclusion Criteria

**Types of participants**
- Neonates with clinically suspected bacterial or fungal sepsis

**Types of studies**
- Prospective or retrospective, cohort or cross-sectional

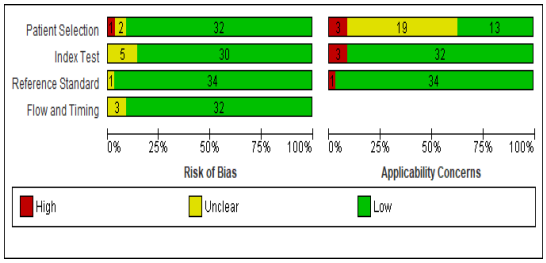
**Exclusion**
- Studies with only positive or negative samples, Index test, Reference standard and target condition

## Search Results




Nha Huynh, Librarian at Texas Medical Cente

## Methodological Assessment using QUADAS2



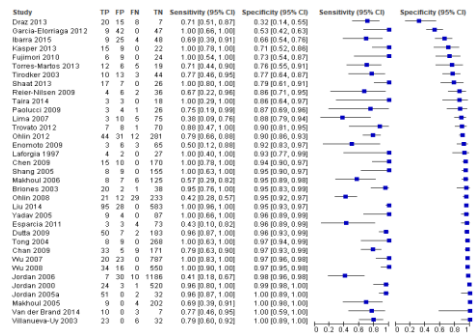

## RESULTS

Meta-analyses
- bivariate random-effects model using statistical software STATA

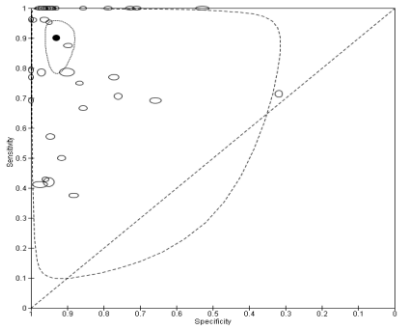
GRADE rating of evidence
- Downgraded for inconsistency and imprecision
- We did not find significant publication bias
  - Deeks' test for publication bias

**GRADE rating for diagnostic tests. Gopalakrishna 2015**

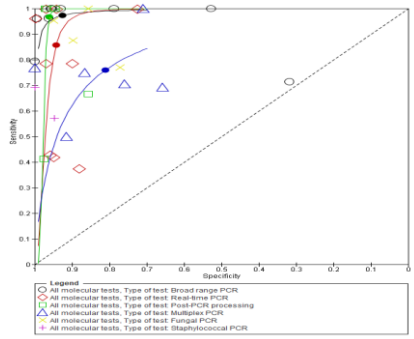
## Forest Plot of Sensitivity and Specificity



## 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

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## 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.