ICD-10 CODE REQUEST FOR GENE EXPRESSION ASSAY

MARCH 2021

Immunexpress

Sepsis Dx Challenge: Decisions Still Rely On Clinical Variables

Critical unmet need in diagnosing sepsis: No diagnostic gold standard and delayed diagnosis increases mortality and cost

Lack of a rapid, sensitive, reliable diagnostic test to provide physicians with actionable results to rule in sepsis with high confidence and expedite intervention with prompt therapeutic administration for a potential life-threatening situation

Current Diagnostic Options Have Low Specificity & Sensitivity For Sepsis:

- Multiple non-specific clinical inputs such 2 SIRS criteria, lactate levels, WBC, SOFA score
- Blood cultures to confirm infection
- Broad non-specific biomarkers such as CRP and PCT
- Downstream bacterial or viral detection panels, followed by antibiotic sensitivity testing, (AST)

Burden of sepsis inaccurate culture - increased hospital charges and Length of Stay (LoS) . False positive blood cultures led to a 46% increase in charges and a 25% increase in LoS.[1]

Current Challenges Can't Address:

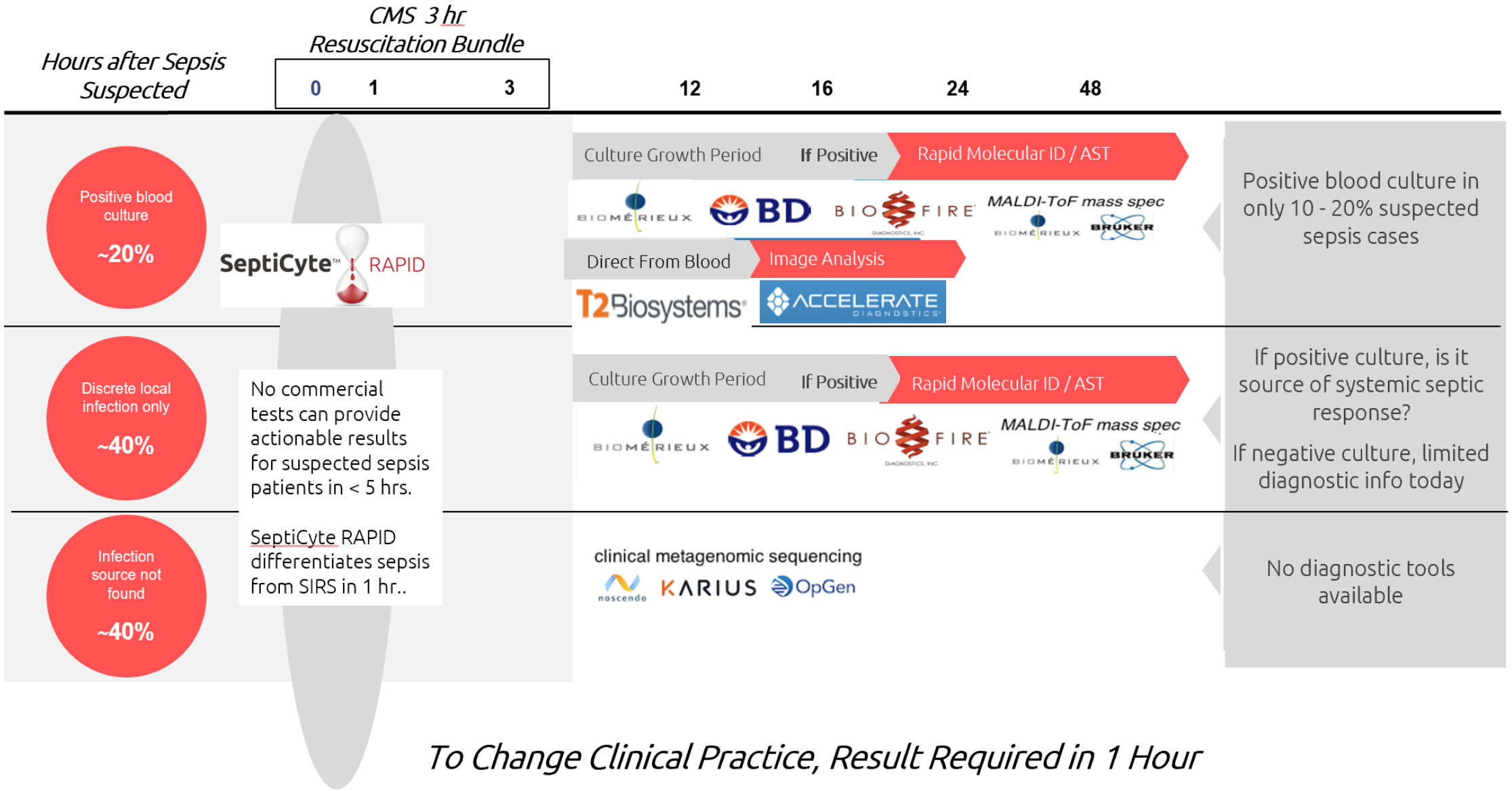
- Discriminating SIRS (non-infectious inflammatory syndrome) from sepsis – Dx uncertainty is high
- Slow turn around times (eg. confirmatory culture, 24-72 hrs)
- Cultures only provide results in 10-12% of patients (imperfect Gold Standard)
- Need to implement appropriate antibiotic Rx within 1- 3 hours
- Concerns about antibiotic stewardship

Clinical Dx of Sepsis on admission to ICU corresponds poorly with true presence of infection. 43% of patients treated for sepsis unlikely to have infection.[2]

Higher costs & mortality associated with delayed sepsis Dx. $18k/11.4% for Pts. with Dx at admission vs $51k/25.6% for Pts. not Dx at admission.[3]

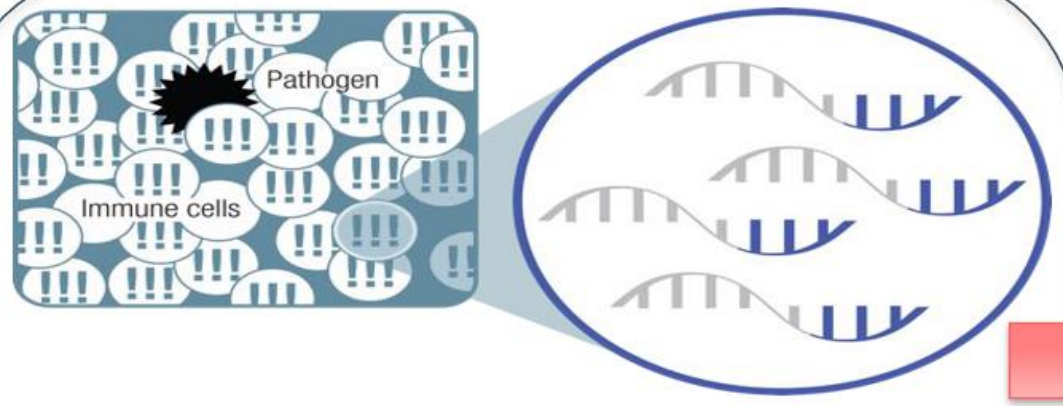
1. Gander, R. M. et al. J of Clin Micro 47, 1021–1024 (2009).
2. Klein Klouwenberg et al. Critical Care 2015 19: 319
3. Kristina E Rudd et al Lancet 2020 395: 201-211

Addressing the Sepsis Dx Workflow Challenges



To Change Clinical Practice, Result Required in 1 Hour

The Immunexpress Solution – SeptiCyte® Technology



Measures Host Response Signals

- Measures mRNA in White Blood Cells (WBCs)
- Quantifies expression in multiple WBC genes
- Specific to infection in systemic inflammation
- Independent of type of pathogen causing sepsis (Gram positive, Gram negative, viral, fungi/yeast, parasite)
- Not reliant on finding pathogen in blood sample

1 hour

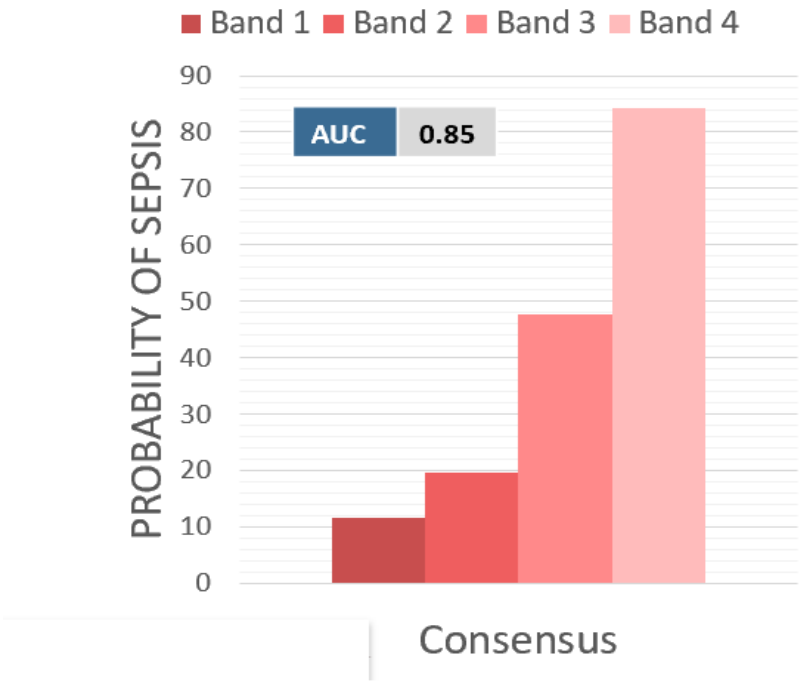
Likelihood of Sepsis: SeptiScore 0 - 15

Clinical Interpretation of Result

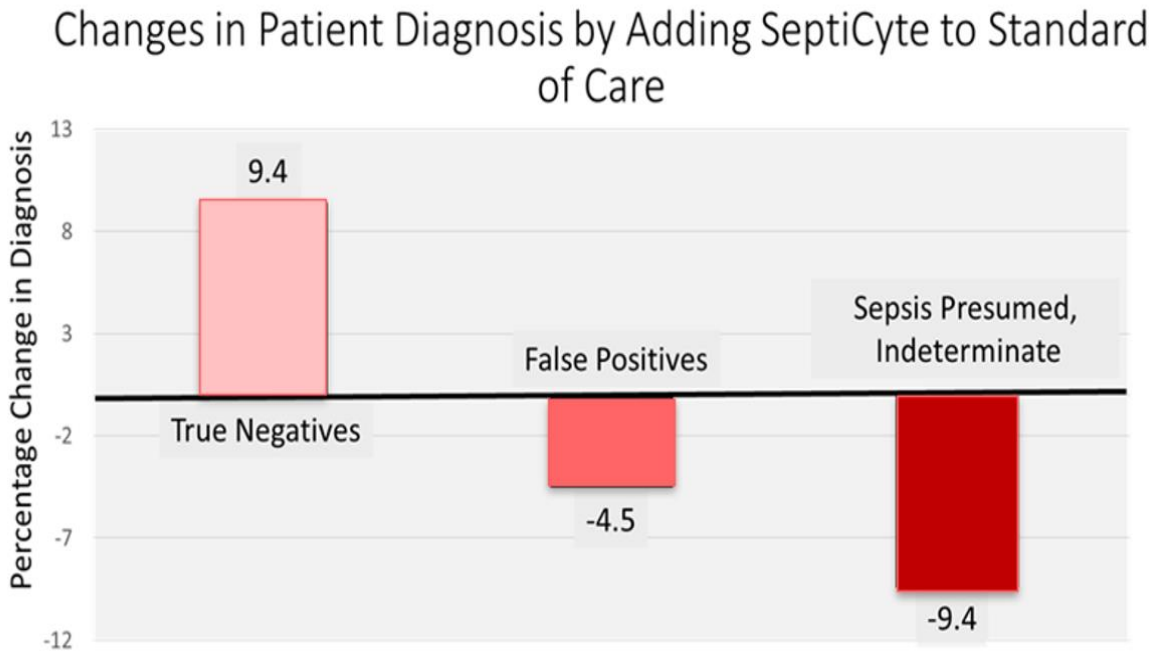
- Reports likelihood of sepsis
- Independent of severity
- Actionable information in ~100% *suspected* sepsis patients

SeptiCyte LAB FDA 510K Validation And Clinical Impact

Miller et al Am J Resp Crit Care Med 2018[1]
- 447 Adult ICU Admissions
- 8 sites
- SeptiCyte performance compared with Dx adjudication panel - 3 physicians



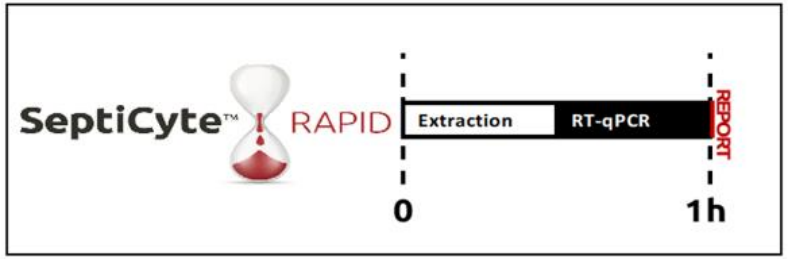
McHugh ID Week 2018[2]
- 265 Adult ICU Admissions
- SeptiCyte impact evaluated by Dx adjudication panel - 3 physicians



SeptiCyte RAPID: A Sample-To-Answer Platform For SeptiCyte LAB

Due to the workflow complexity and 6 hr TAT of SeptiCyte LAB the SeptiCyte assay was transitioned to a more rapid and simple workflow using the Idylla™ platform

RAPID



The test is performed on single-use, disposable, multi-chambered fluidic cartridge. All cartridge steps are fully automated and completely integrated

SIMPLE

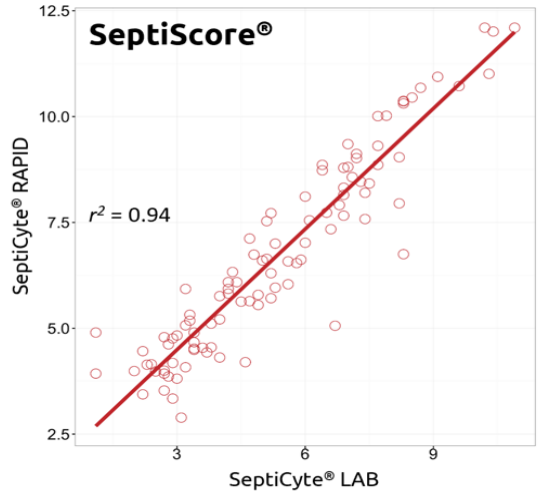
SAMPLE HANDLING	SAMPLE EXTRACTION	PCR & QUANTIFICATION
• RNA-stabilized whole blood • Minimal sample handling • Barcode traceability • No sample incubation time	• Fully integrated sample extraction • Total nucleic acid purification • On-board processing controls	• Quantitative and Precise • Dried reagents • Ambient storage (no cold chain)

SeptiCyte RAPID Intended Use And Correlation With Predicate Device

- SeptiCyte™ RAPID is a gene expression assay using reverse transcription polymerase chain reaction to measure the relative expression levels of host response genes isolated from whole blood collected in PAXgene® Blood RNA Tube.

- SeptiCyte™ RAPID is used in conjunction with clinical assessments, vital signs and laboratory findings as an aid to differentiate infection-positive (sepsis) from infection-negative systemic inflammation in patients suspected of sepsis.

- SeptiCyte™ RAPID generates a score (SeptiScore™) that falls within one of three discrete Interpretation Bands based on the increasing likelihood of infection-positive systemic inflammation. SeptiCyte™ RAPID is intended for in-vitro diagnostic use.

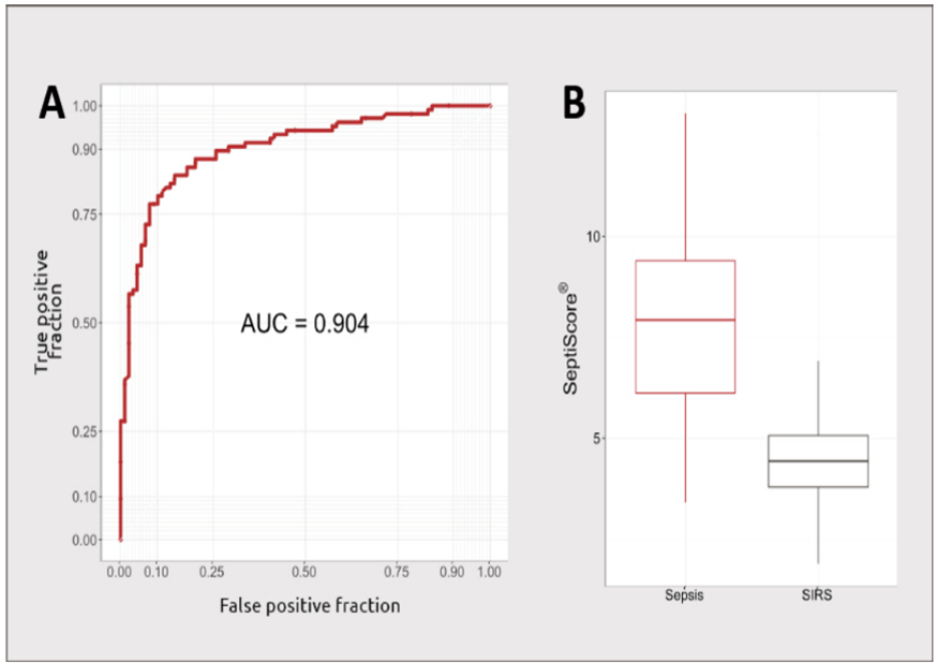


Study Method / Result Highlights

- Comparison between manual kit and Idylla cartridge
- High correlation between tests formats
- N = 100 clinical samples* tested
- Results compared to previous FDA 510k studies

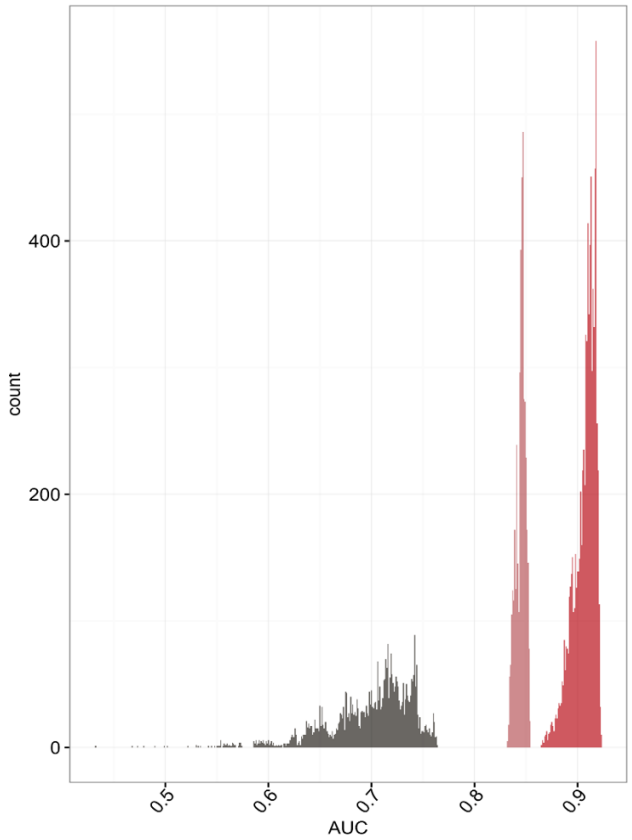
*Miller, Lopansri, Burke, et al. Validation of a Host Response Assay, SeptiCyte LAB, for Discriminating Sepsis from Systemic Inflammatory Response Syndrome in the ICU. Am J Respir Crit Care Med. 2018 Oct 1;198(7):903-9

SeptiCyte RAPID Ability To Differentiates Sepsis vs SIRS



(A) Receiver operating characteristic curve for SeptiScore®, calculated for the dataset (N = 195).

(A) SeptiCyte RAPID strongly discriminates sepsis (N = 106) from SIRS (N = 89) cases



Models with all demographics, vital signs & lab but no PCT or SeptiScore

= + PCT

= + PCT + SeptiScore

Area under the curve (AUC) distributions for logistic models of 14 variables, (demographics, vital signs & lab*, including SeptiScore & PCT).

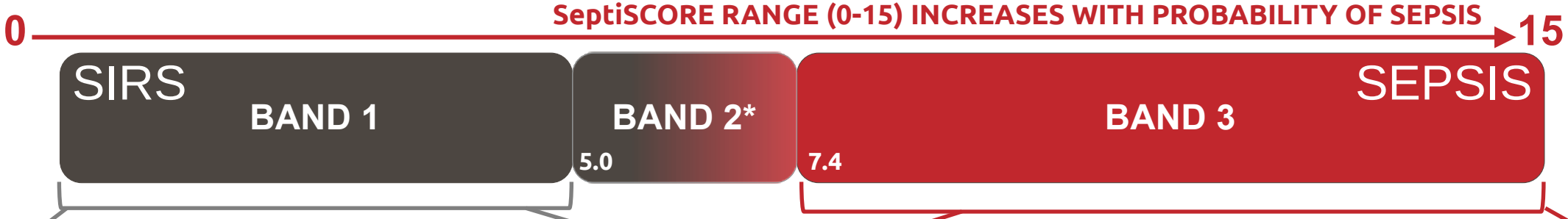
"Consensus" RPD was the comparator.

* Lactate, WBC & Glucose

R Brandon et al. Clinical performance of a rapid sepsis test on a near-patient molecular testing platform. #P481 ISICEM 2020 Brussels

Miller R, Lopansri B, McHugh L, Rapisarda A, Seldon T, Burke J. 2015. Validation of a novel host response assay to distinguish SIRS and sepsis in critically ill patients. Am. J Respir Crit Care Med . 2018 Oct 1; 198(7):903-913

SeptiCyte RAPID – Sensitivity and Specificity (N=356)



LOW RISK OF SEPSIS

BAND 1	Performance Estimate**	
	Lower (Forced)	Upper (Consensus)
Cohort size (N)	356	324
Sensitivity	0.92	0.93
Sepsis probability	13%	10%
SIRS probability	87%	90%
Likelihood Ratio	0.20	0.17

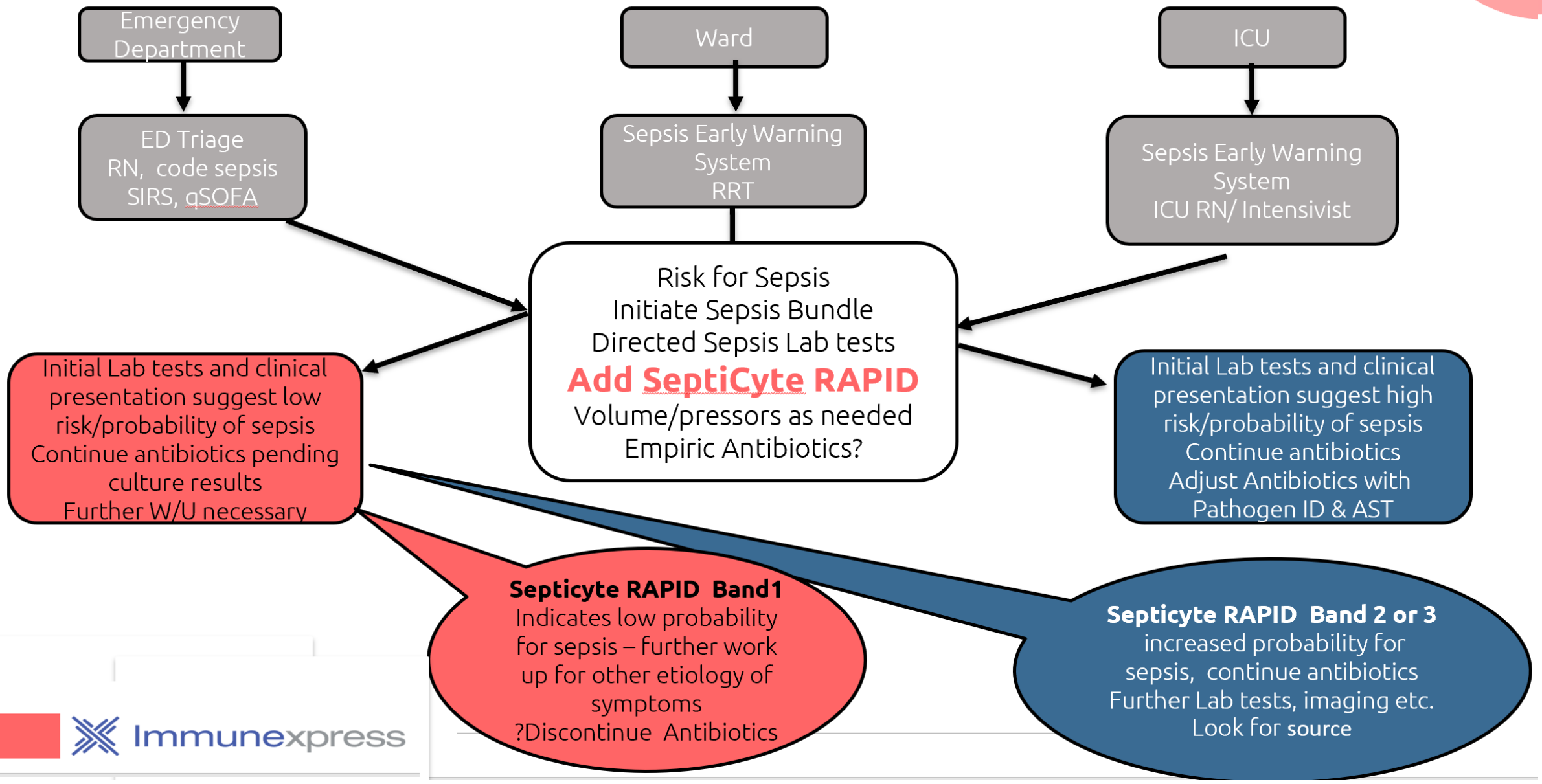
HIGH RISK OF SEPSIS

BAND 3	Performance Estimate**	
	Lower (Forced)	Upper (Consensus)
Cohort size (N)	356	324
Specificity	0.89	0.90
Sepsis probability	79%	80%
SIRS probability	21%	20%
Likelihood Ratio	5.12	5.90

* Band 2 results indicate an INTERMEDIATE RISK of sepsis. SIRS probability = 66 – 69% ; Sepsis probability = 31 – 34%

** Upper and lower performance estimates are defined as a range based on the confidence in the reference method (retrospective physician diagnosis). Lower estimates include indeterminate cases. Upper estimates only include cases with a consensus diagnosis by the physician panel.

Diagnosing Sepsis – Clinical Workflow in Sepsis Low Risk



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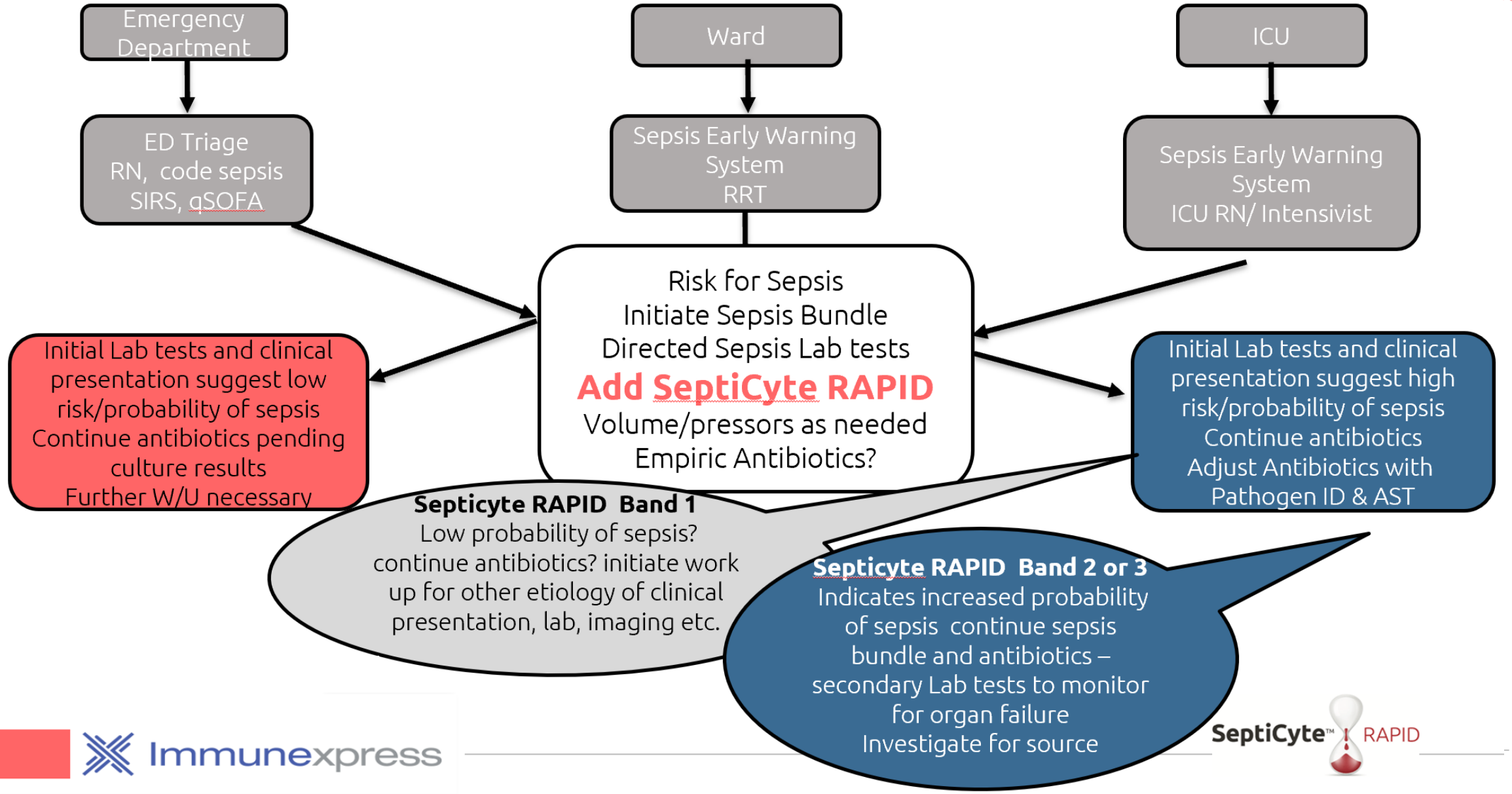
Diagnosing Sepsis – Clinical Workflow In Sepsis High Risk



Proposed SeptiCyte RAPID Clinical Utility

- Sepsis Diagnostic
  - Rapid, accurate and early in sepsis diagnostic work up
  - Facilitates early treatment
  - Decreases delayed diagnosis of SIRS/INSI*
  - Not impacted by early antibiotic administration
  - Improve compliance with sepsis bundle parameters
  - Decreased mortality with appropriate early therapy or INSI workup
- Diagnostic Stewardship
  - SeptiCyte included in directed order set
  - Decreases initial tests ordered
  - Directs appropriate early testing for alternate diagnosis
- Antibiotic Stewardship
  - Early appropriate initiation of antibiotics
  - Early cessation of antibiotics if INSI

A unique ICD–10 code for SeptiCyte RAPID would…

1)Impact ease and accuracy of sepsis coding

2)standardize sepsis research studies or assessments

Ultimately driving adoption in the sepsis clinical workflow to improve healthcare and economic outcomes.

*Infection negative systemic inflammation

SeptiCyte™ RAPID

Where Coders Can Find SeptiCyte RAPID ?

SeptiCyte RAPID could be found…

1)Ordered within the hospital Sepsis Order Set

2)Results reported in Patient Lab tests

3)Results documented or discussed by Care Provider in progress notes or discharge report.

Sepsis Order Sets – 2 models

Individual

Care Provider orders tests individually under a sepsis order set. eg:

Laboratory Tests

- ❑ CBC, diff and platelets
- ❑ Bilirubin
- ❑ Lactate
- ❑ BUN and Creatinine
- ❑ CRP
- ❑ **SeptiCyte RAPID**
- ❑ Troponin
- ❑ PCT
- ❑ IL6
- ❑ ESR
- ❑ Glucose
- ❑ d-Dimer
- ❑ INR
- ❑ Urine for UA and culture
  Blood Culture

Inclusive

Developed by multidisciplinary sepsis team. Reviewed by medical staff, nursing and pharmacy. Care Provider marks a box in the order sheet to cover initial laboratory evaluation. Care provider must enter others as needed:

- ❑ Sepsis initial evaluation laboratory tests:

Includes CBC, Diff, platelets, Lactate, urine for UA and culture, blood culture and **SeptiCyte RAPID**

Other, add as needed:

- ❑ BUN and Creatinine
- ❑ CRP
- ❑ Troponin
- ❑ PCT

SeptiCyte™ RAPID

A Unique Code For SeptiCyte RAPID Should Be Included in the ICD-10 PCS

- Immunexpress received FDA clearance for SeptiCyte® LAB, the 1st host response gene signature assay for differentiating sepsis from SIRS, in 2017
- SeptiCyte® RAPID is the 2nd generation of this predicate device and has demonstrated equivalent performance, generating strong analytical & clinical data.
- Immunexpress submitted the 510K for SeptiCyte RAPID December 23rd. Combined clinical data easily passes primary endpoint. FDA clearance is anticipated Q2 2021
- Current ICD-10 codes do not describe a host response gene signature assay for differentiating sepsis from SIRS generating results in 1 hr. All other diagnostic tests in this category are for pathogen identification or non-specific single biomarkers.
- Inclusion of a unique code will assist in diagnostic reporting purposes
- Widespread usage of SeptiCyte RAPID would address a critical unmet diagnostic challenge in sepsis workflow and enable more precise sepsis coding