Cellular Assessment via Microfluidic Deformability Cytometry

ICD-10 Coordination and Maintenance Committee Meeting

March 2024

Cytovale

Sepsis is a Medical Emergency That Needs Actionable Risk Stratification

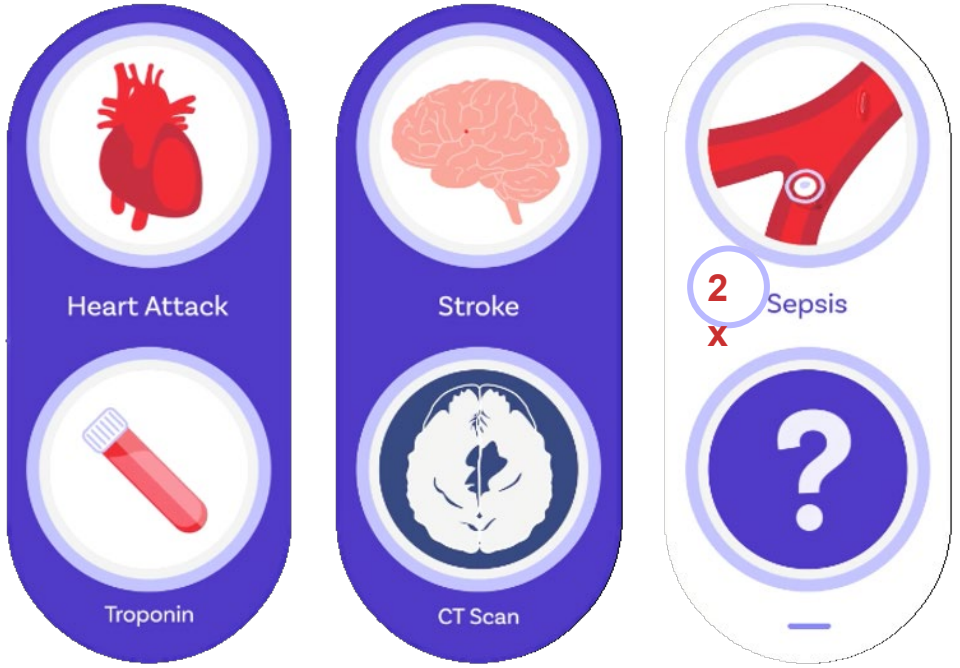
Sepsis is the leading cause of death and the costliest condition in US hospitals

$62B
Annual U.S. Healthcare Costs in Sepsis

30M+ Patients at risk
1 in 5 ED patients are at risk of sepsis

87%
Of sepsis cases present to the Emergency Dept

8%
Mortality rate increase for every hour untreated



Sepsis has **2x** cases than Stroke & Heart Attack **combined**
but no standardized, accelerated care pathway is viable

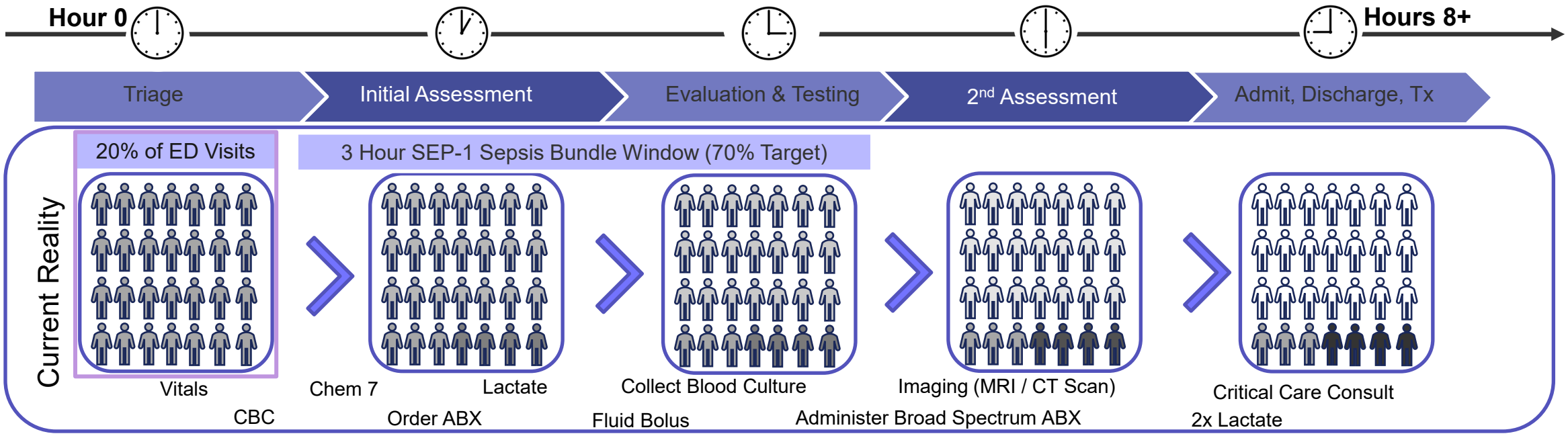
Clear unmet need for a clinically-actionable risk stratification tool

Improvement in Sepsis management is a recognized need

- CDC Launched Core Elements August 2023
- These elements were “intended to monitor and optimize hospital management and outcomes of sepsis. It complements existing sepsis guidelines”
- CDC Recommends 7 Core elements
    - Hospital Leadership Commitment
    - Accountability
    - Multi-Professional
    - Action
    - Tracking
    - Reporting
    - Education

Today's ED Sepsis Processes are Inefficient, Costly, and Ineffective

Current practices rely on subjective judgment by ever-changing staff and deliver limited results



Hospitals have difficulty quickly assessing the potentially septic population. In our recent FDA study, we observed:

Only 58 of 124 (38%) septic patients received the sepsis care bundle in 3 hours, while 59 patients without sepsis received the sepsis care bundle in 3 hours

Provider judgement often a key determinant of initiation of sepsis care…

How good are providers at recognizing sepsis?

Critical Care Providers (2016 study)[1]

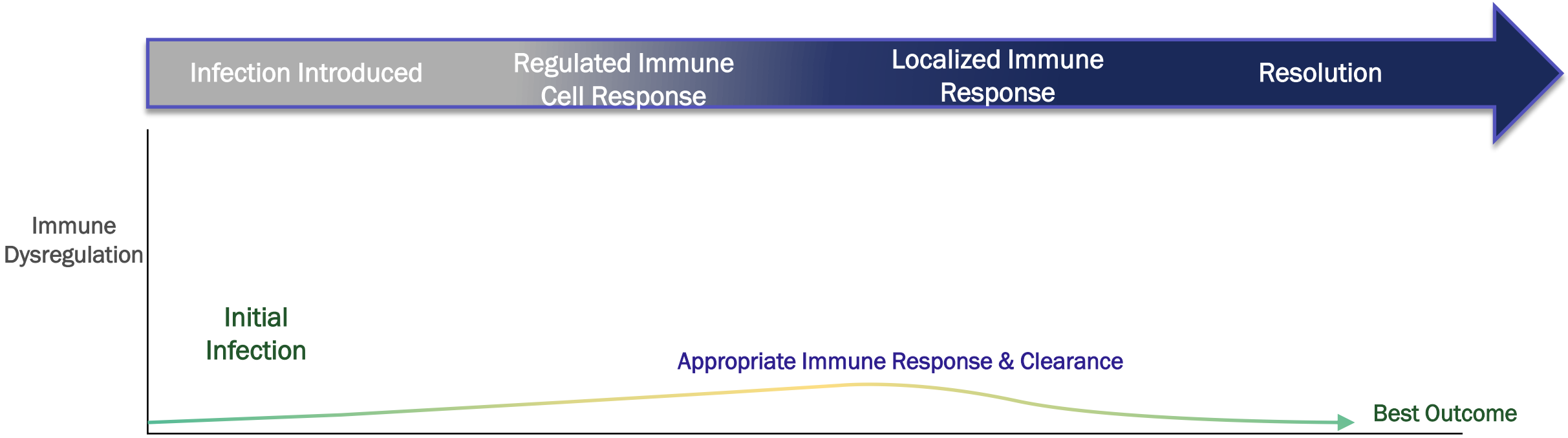
- Background/Methods
  - 94 Critical Care Providers
    - 90% academic
    - 83% felt strongly or somewhat confident in their ability to apply consensus sepsis definitions
  - Each presented 5 case vignettes (including initial presentation and subsequent hospital course)
  - 1 "control" case of septic shock with gram negative bacteremia included for baselining
  - Asked to classify as: SIRS, Sepsis, Severe Sepsis, Septic Shock or None

- Findings
  - Considering all cases, overall interrater "***agreement was poor"***
  - For 4/5 test cases (removing the control case), agreement was ***"nearly random"***

[1]*Rhee et al. Critical Care (2016) 20:89; DOI 10.1186/s13054-016-1266-9*

Sepsis is Not an Infection

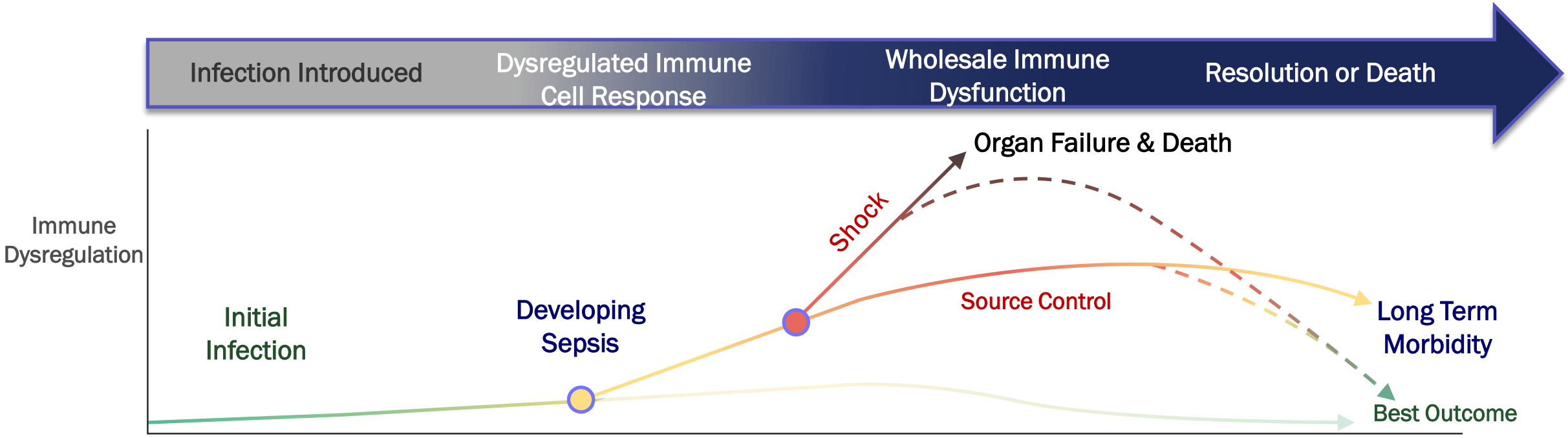
Infections are abundant and are often common, simple nuisances



[1]*Graphic adapted from Prof. Mervyn Singer, ECCMID 2022*

Sepsis is a Dysregulated Immune Response to Infection[1]

This dysregulated immune response makes sepsis a medical emergency



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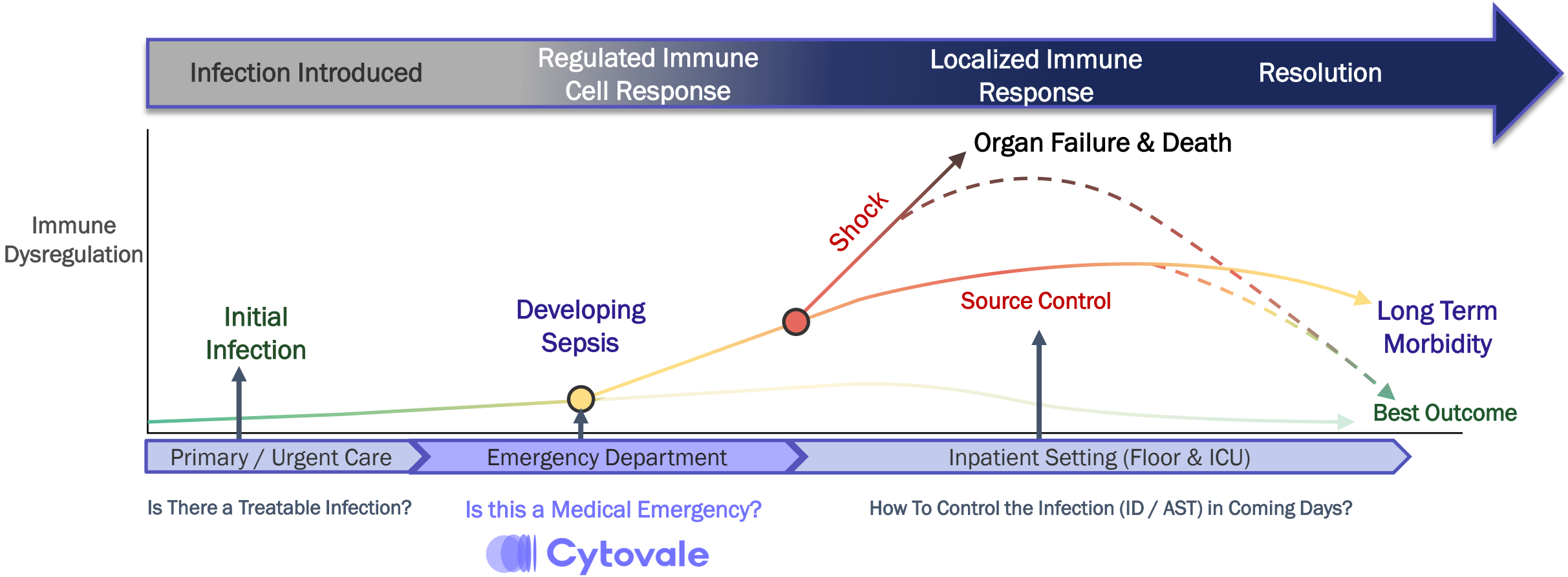

IntelliSep is focused on specifically measuring the dysregulated host response

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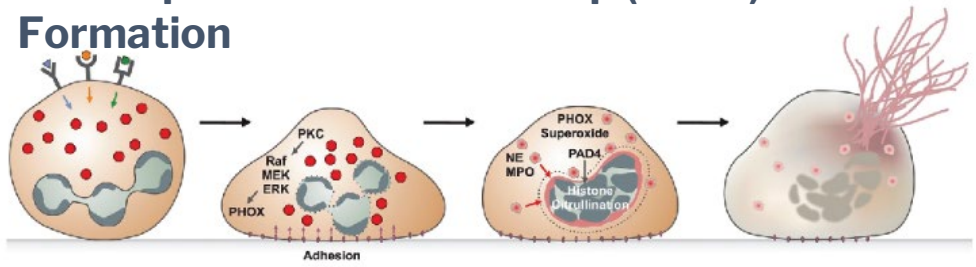
IntelliSep Quantifies Dysregulated Host Immune Response to Infection in Circulating Blood

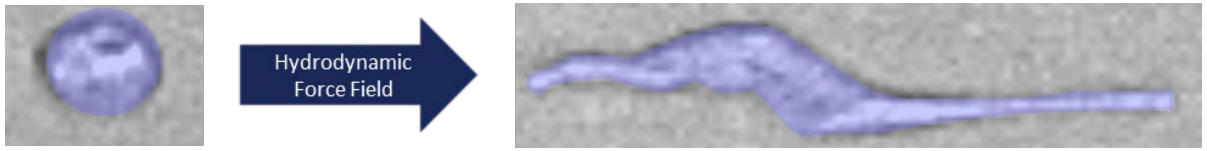
The dysregulated host response in sepsis results in broad activation of circulating leukocytes, upregulated transcriptional activity, and chromatin decondensation

Neutrophil Extracellular Trap (NETs) Formation



Brinkmann, J. Cell Biology, 2012

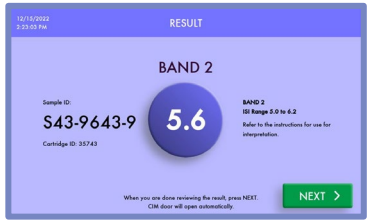
White blood cells from a septic patient

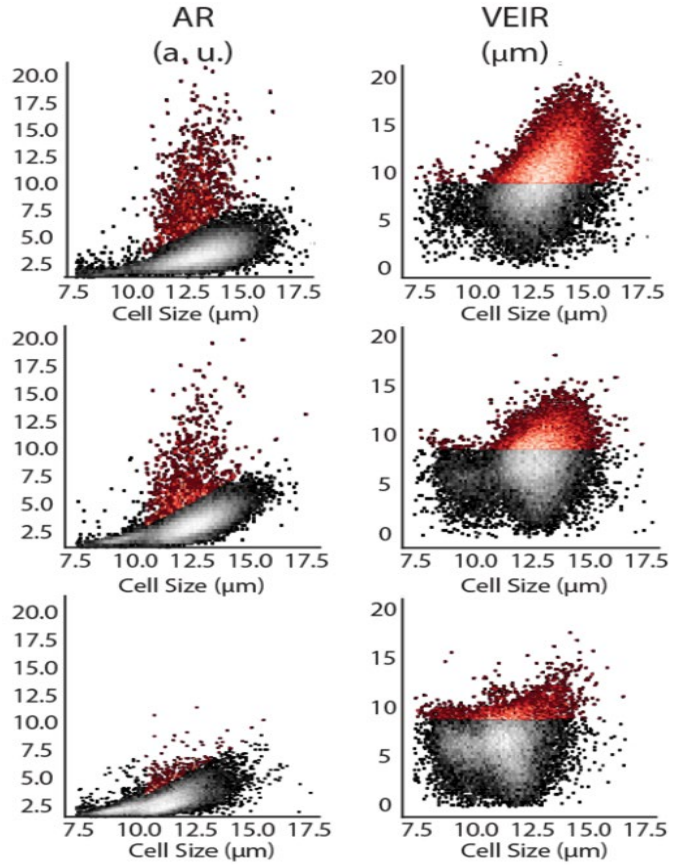


White blood cells from a non-septic patient

2 of the 6 Parameters Underlying the IntelliSep Index

IntelliSep Index





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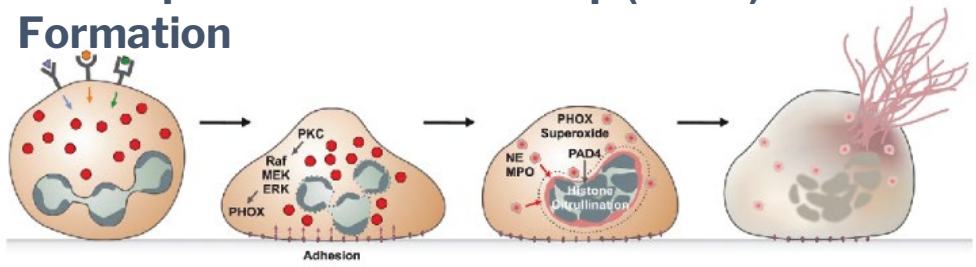

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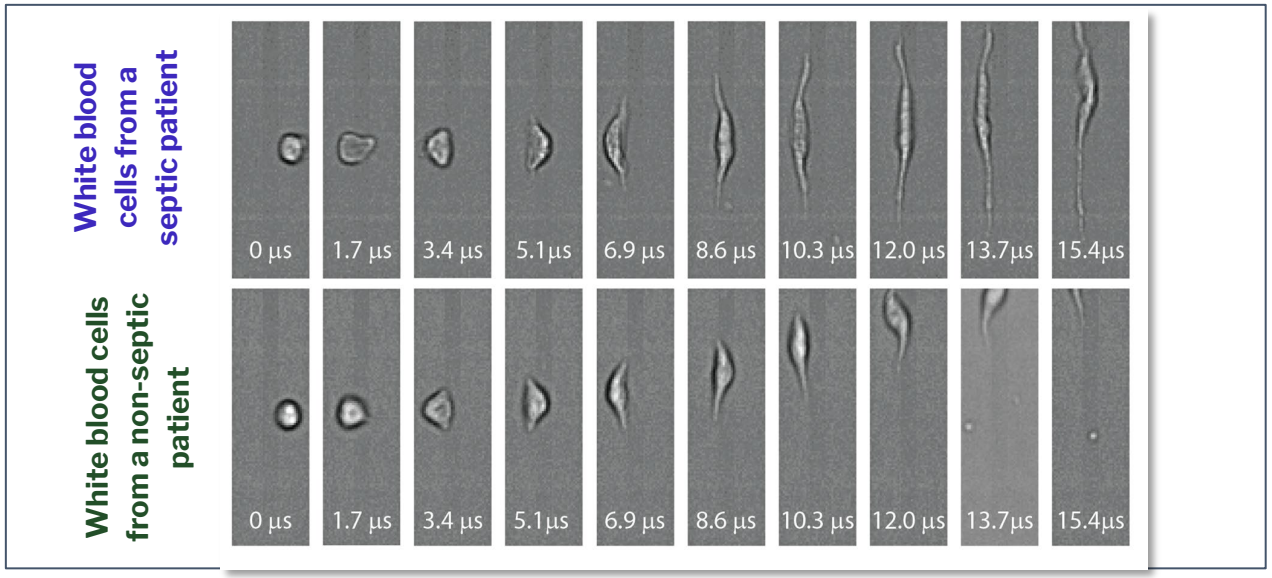

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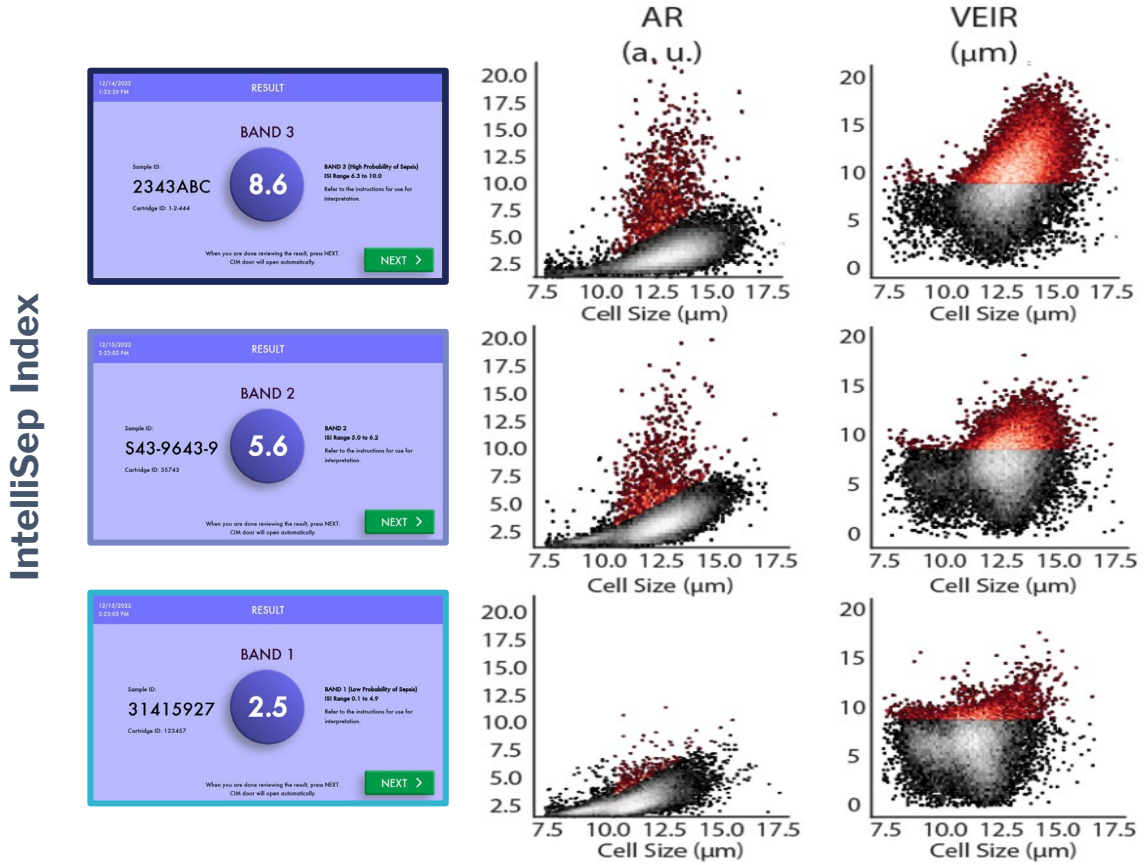


IntelliSep Measures the Dysregulated Immune Response

The Cytovale IntelliSep test is a **semi-quantitative** test that assesses cellular host response via deformability cytometry of leukocyte biophysical properties and is intended for use in conjunction with clinical assessments and laboratory findings to aid in the early detection of sepsis with organ dysfunction manifesting within the first 3 days after testing. It is indicated for use in adult patients with signs and symptoms of infection who present to the Emergency Department. The test is performed on an EDTA anticoagulated whole blood sample.

The IntelliSep test generates an IntelliSep Index value that falls within one of three discrete interpretation bands based on the probability of sepsis with organ dysfunction manifesting within the first three days after testing. The IntelliSep test represents the probability of the clinical syndrome of sepsis and is intended to be used alongside other clinical information and clinical judgement. It does not identify the causative agent of infection and should not be used as the sole basis to determine the presence of sepsis. The IntelliSep test is intended for in vitro diagnostic use.

The clinical performance has not been established in the following populations:

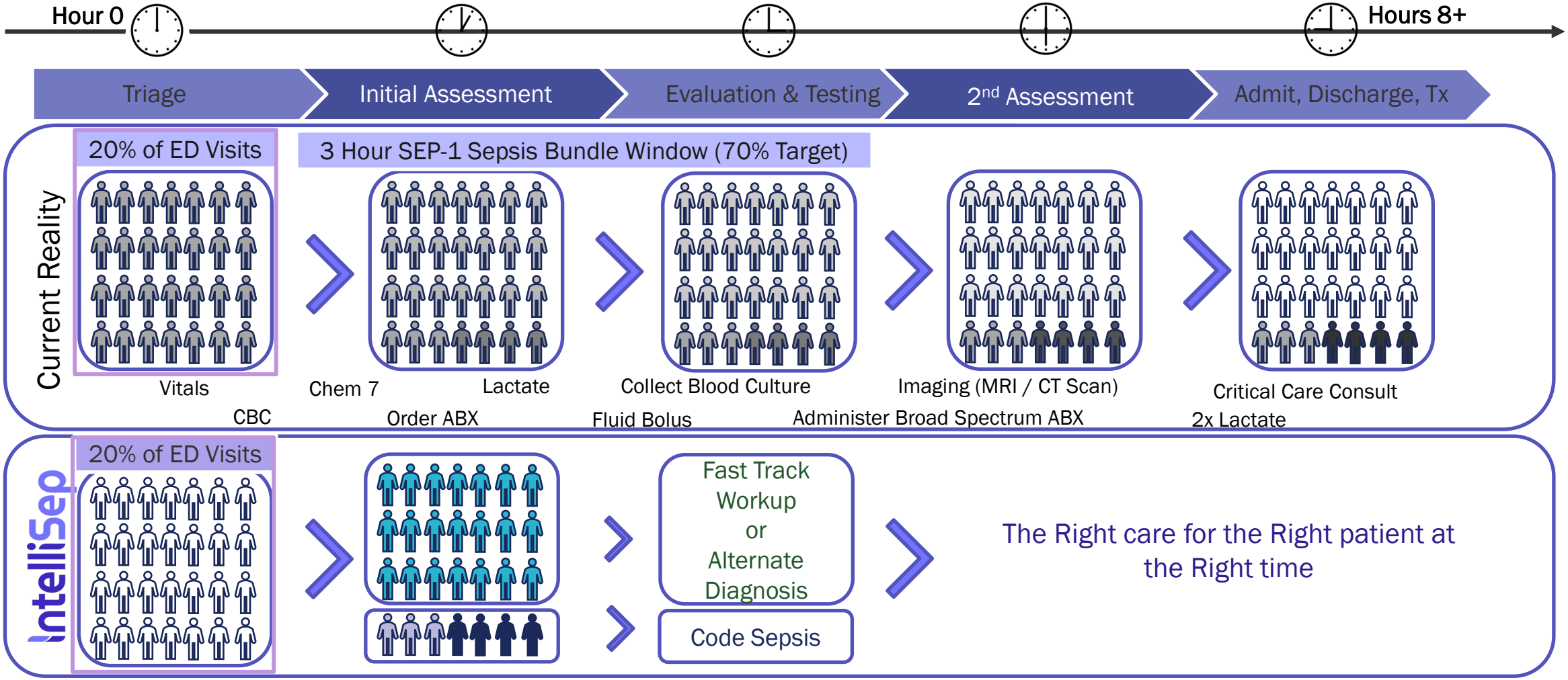
- Patients below 18 years of age.
- Patients with a history of a hematologic malignancy (any leukemia, lymphoma, or myeloma), myelodysplastic syndrome, or myeloproliferative disorder
- Patients who have undergone a hematopoietic stem cell transplant or any solid organ transplant
- Patients receiving a cytotoxic chemotherapeutic agent in the past 3 months
- Patients who are residents or patients of a hospital-based skilled nursing facility

IntelliSep

Fast	8 min Blood-to-Score
Workflow Fit	100uL from a standard ‘purple-top’ blood collection tube
Easy to Use	90 seconds of hands-on time
Low-cost Structure	Single use plastic disposable
Pathogen Agnostic	Host response approach covers all pathogens

IntelliSep Provides Objective & Actionable Clarity for ED Providers

Enables timely focus on high-risk patients & reduces effort (and losses) on low risk population



Cytovale System

System

3 ft bench space
1-day installation
No calibration required
PM every 90 days

CLIA Moderate

Enlarged View

Easily Integrated into Existing Lab Workflows

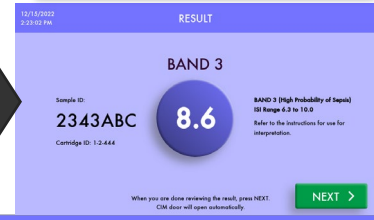
Cytovale System Specifications:

1. **Sample Preparation Module (SPM):** 16" wide, 15" tall, 18" deep, 40 lbs
2. **Cell Imaging Module (CIM):** 21.5" wide, 22.5" tall, 24" deep, 170 lbs
3. **Imaging Analysis Module (IAM):** 7.0" wide, 18.2" tall, 26.5" deep, 65 lbs
4. **Reagents**
5. **IntelliSep Cartridge (single-use)**

Process

<10 MINUTES TOTAL

Starts with a simple purple-top tube → Aliquot 100µl sample into preparation tube → Sample loaded into SPM → *90 seconds processing time*: White blood cells separated and suspended for analysis → Sample then transferred to the cartridge (contains precision microfluidics) for analysis → *~5 minutes processing time*: CIM captures images of cells under stress at high magnification, analyzed using ML algorithm → **IntelliSep Score Reported**



Running a Sample Through the Cytovale System:

Sample Preparation

90 seconds processing time

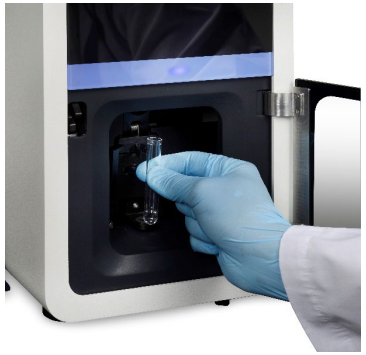
Cell Imaging

Image Analysis

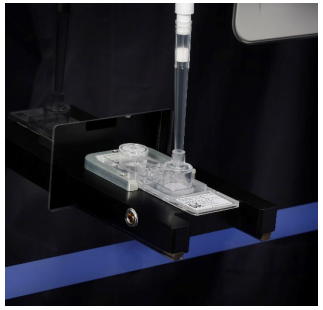
~ 5 minutes processing time

100µl whole blood sample aliquoted into preparation tube

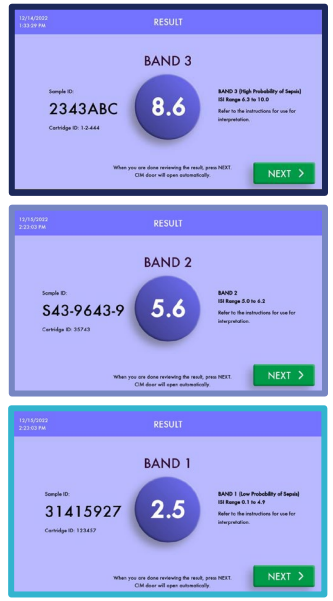
Operator Step 1:
Sample inserted into the Sample Preparation Module (SPM)



Operator Step 2:
Prepared sample transferred into cartridge for testing in the Cell Imaging Module (CIM)



ISI results displayed on touchscreen upon completion

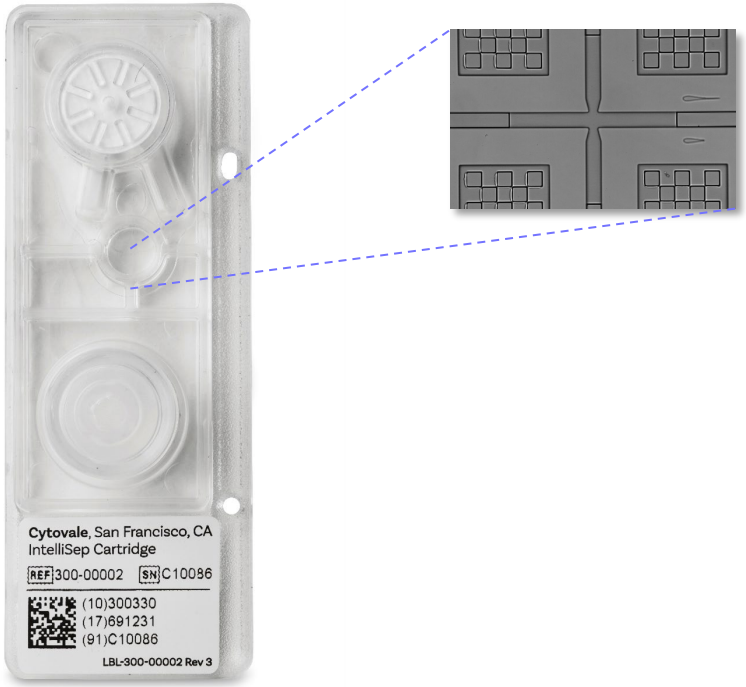


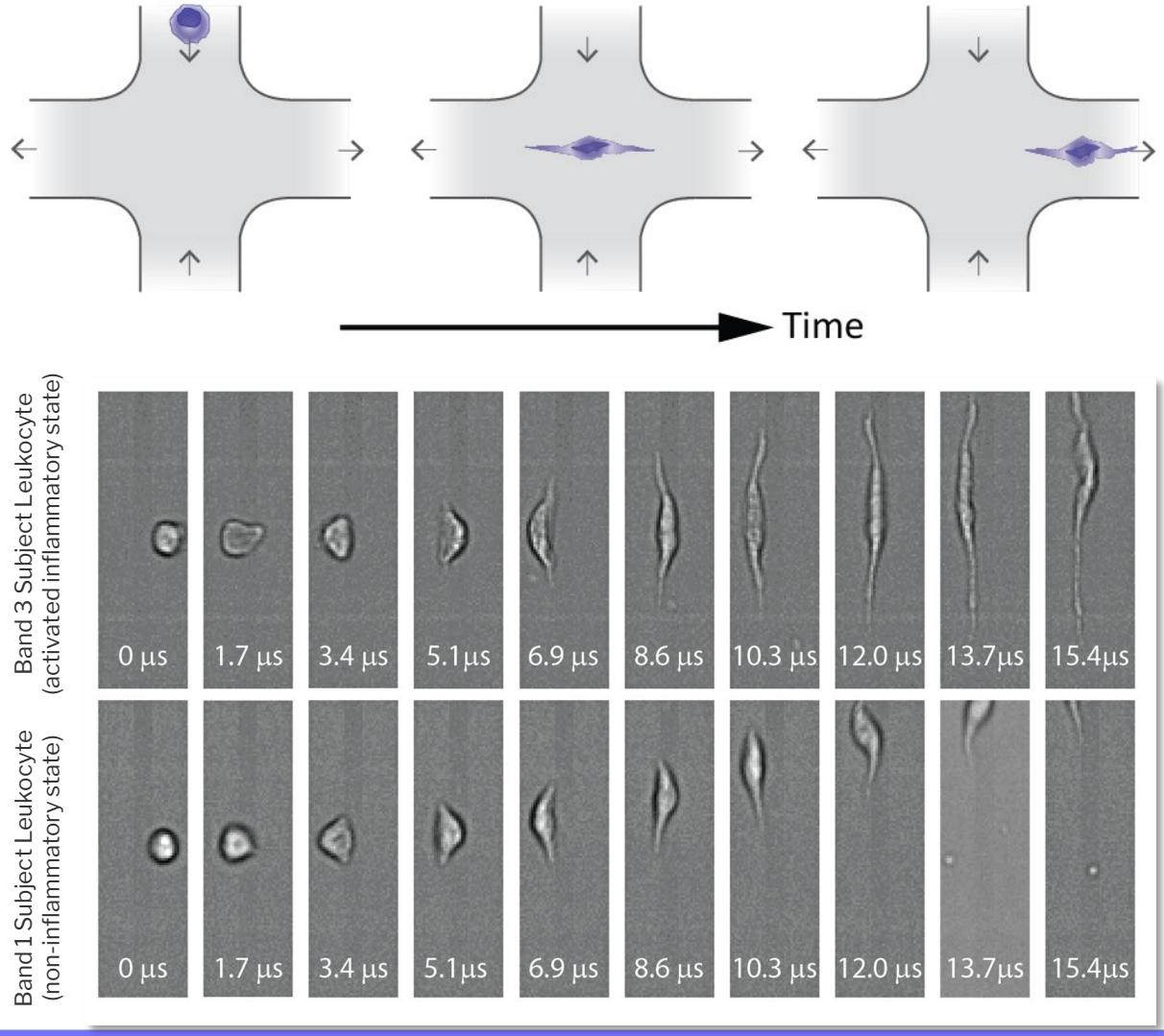
Hands-on time ~90 sec/sample

< 10 minutes

Fluid Juncture During Testing

Within the cartridge and during a run, cells are advanced towards a flow junction, where they are exposed to a controlled deformation process.





Cytovale Consumables

IntelliSep Quality Controls

- Stabilized whole blood for daily QC
- Manufactured by Streck for Cytovale
- 1 set (2 Levels) used per month

Cytovale Diluent & Cleanse

- Used in Sample Preparation Module
- Provides sample matrix for testing and cleans SPM, respectively
- 40-60 tests per set

Cytovale Reagents A & B

- Used in Sample Preparation Module
- Enables rapid RBC lysis
- 40-60 tests per set

IntelliSep Cartridges

- Provides fresh, clean microfluidic channel/window for each test
- 1 cartridge per test

Additional Materials:
K2 EDTA Tubes, Sample tubes (Corning PN:352052), Pipet Tips, Swabs

Clinical Studies To Date

SQuISH

Evaluate the system & initialize sepsis diagnostic algorithm

Population: Signs of infection & organ dysfunction - ED

(N = 307)

Adj. Sepsis/Infection = 23/33%

Key Findings:
- Sepsis: NPV = 96%
- Mortality: > 5-fold difference (Red/Green)
- Observed appropriate risk stratification in severity of illness and resource use

PLOS ONE

Guillou, Lionel, et al. "Development and validation of a cellular host response test as an early diagnostic for sepsis." PloS One 16.4 (2021).

LA-SQuISH

Locked algorithm applied to low-acuity population

Population: Signs of infection (HR, RR, Temp) - ED

(N= 94)

Adj. Sepsis/Infection = 6/15%

Key Findings:
- Sepsis: NPV = 100%
- Observed appropriate risk stratification in severity of illness and resource use

Be-SQuISH-ED

Locked algorithm applied to intended use population

Population: Signs or suspicion of infection - ED

(N = 255)

Adj. Sepsis/Infection = 17/40%

Key Findings:
- Sepsis: NPV = 97%
- Observed appropriate risk stratification in severity of illness and resource use

Critical Care Explorations — Society of Critical Care Medicine

O'Neal Jr, Hollis R., et al. "Assessment of a Cellular Host Response Test as a Sepsis Diagnostic for Those With Suspected Infection in the Emergency Department." Critical Care Explorations 3.6 (2021).

SQuISH-COVID

Locked algorithm applied to novel pathogen SARS-CoV-2

Population: Signs or suspicion of respiratory infection - ED

(N = 282)

Key Findings:
- Mortality: > 5-fold difference (Red/Green)
- Observed appropriate risk stratification in severity of illness and resource use

PLOS ONE

O'Neal Jr, Hollis R., et al. "Assessment of a Cellular Host Response Test to Risk-stratify Suspected COVID-19 Patients in the Emergency Department Setting." PloS One 17.3 (2022).

CV-SQuISH-ED

Locked algorithm applied to intended use population – Multi-center

Population: Signs or suspicion of infection - ED

(N = 572)

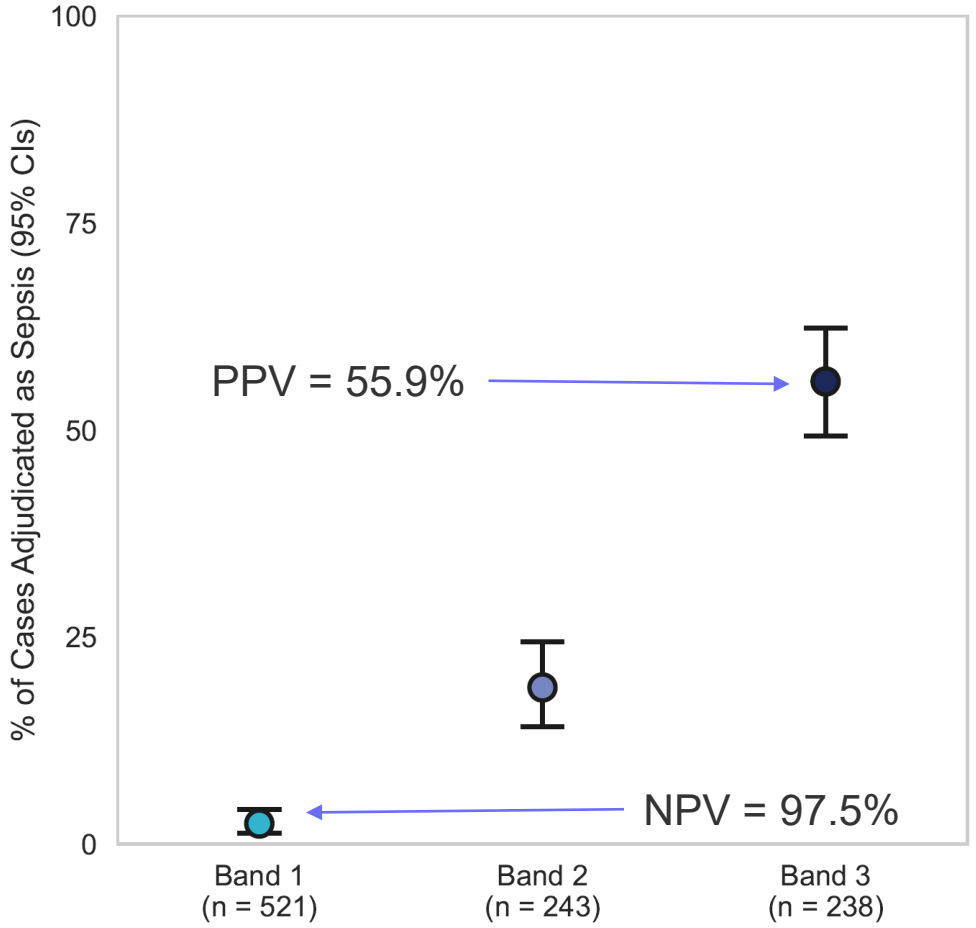
Adj. Sepsis/Infection = 27/50%

Key Findings:
- Primary, secondary, and tertiary endpoints all met and exceeded acceptance criteria
- Clinically actionable performance across all sepsis definitions

Manuscript under Review

Foundational science published in PNAS, Science Translational Medicine, American Journal of Respiratory and Critical Care Medicine

Consolidated Test Performance Across All Studies in Intended Use Population for Cases with High Confidence Adjudication (n = 1002)



Performance Characteristics - Value (95% CI)	
Population Size	1002
Sepsis Prevalence [%]	19.2%
AUC	0.87 (0.84 – 0.90)
Positive Percent Agreement (sensitivity): Band 1 vs. else	93.2 (88.7 – 96.3)
Negative Percent Agreement (specificity): Band 3 vs. else	87.0 (81.4 – 91.4)
Negative Predictive Value (NPV): Band 1 vs. else	97.5 (94.0 – 99.1)
Positive Predictive Value (PPV): Band 3 vs. else	55.9 (48.4 – 62.9)
LR+	5.34
LR- (1/LR-)	0.11 (9.1)

Adult patients with signs or symptoms of infection presenting to the ED (matching test intended use) enrolled prospectively in five discrete but similar cohorts at multiple sites in the US (Feb. 2016 – Oct. 2021; cases of high confidence retrospective physician adjudication per the Sepsis-3 criteria)

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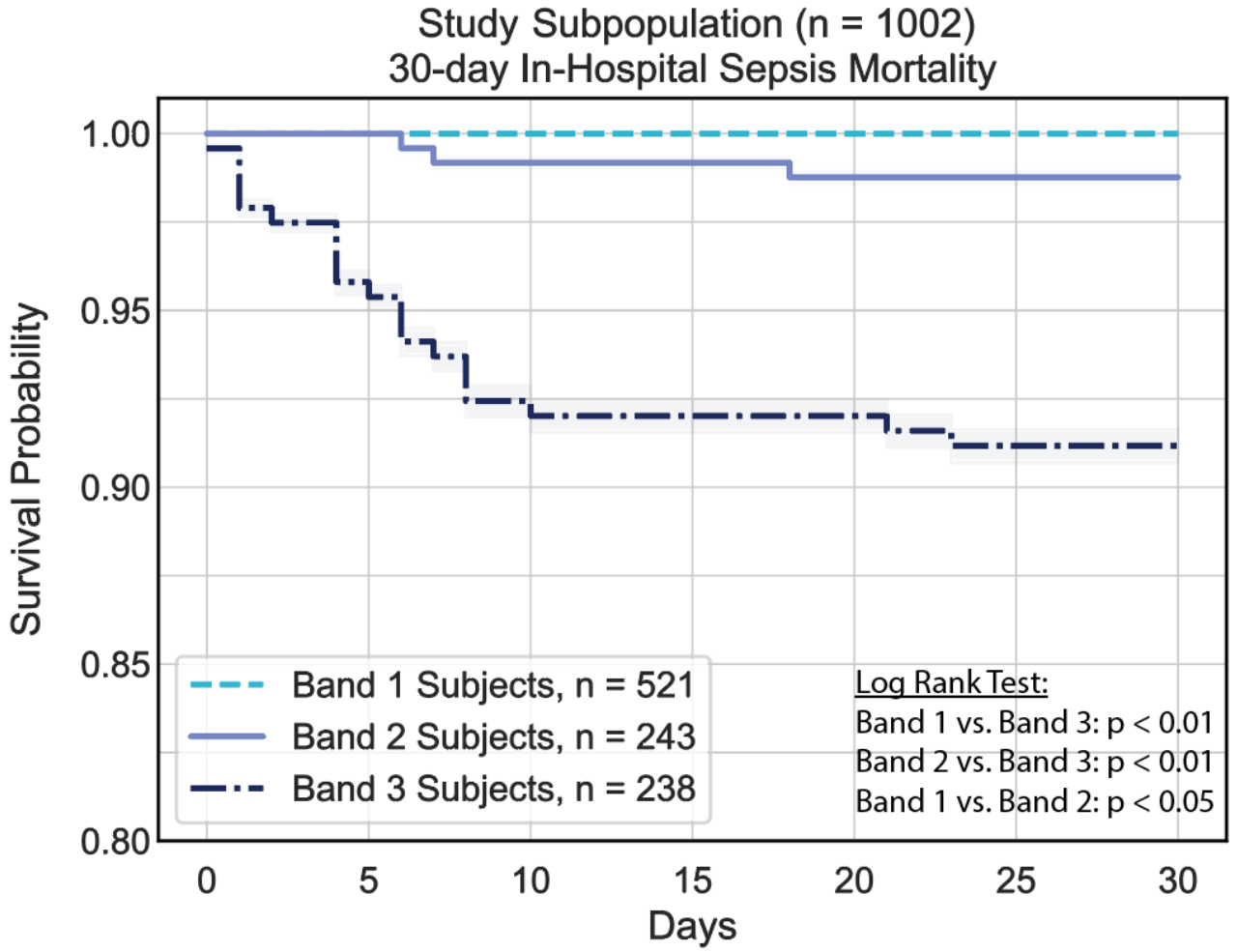

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Thank You

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