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ORIGINAL RESEARCH

Infectious Disease

Rapid identification of sepsis in the emergency department

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Abstract

Objectives: Recent research has helped define the complex pathways in sepsis, affording new opportunities for advancing diagnostics tests. Given significant advances in the field, a group of academic investigators from emergency medicine, intensive care, pathology, and pharmacology assembled to develop consensus around key gaps and potential future use for emerging rapid host response diagnostics assays in the emergency department (ED) setting.

Methods: A modified Delphi study was conducted that included 26 panelists (expert consensus panel) from multiple specialties. A smaller steering committee first defined a list of Delphi statements related to the need for and future potential use of a hypothetical sepsis diagnostic test in the ED. Likert scoring was used to assess panelists agreement or disagreement with statements. Two successive rounds of surveys were conducted and consensus for statements was operationally defined as achieving agreement or disagreement of 75% or greater.

Results: Significant gaps were identified related to current tools for assessing risk of sepsis in the ED. Strong consensus indicated the need for a test providing an indication

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of the severity of dysregulated host immune response, which would be helpful even if it did not identify the specific pathogen. Although there was a relatively high degree of uncertainty regarding which patients would most benefit from the test, the panel agreed that an ideal host response sepsis test should aim to be integrated into ED triage and thus should produce results in less than 30 minutes. The panel also agreed that such a test would be most valuable for improving sepsis outcomes and reducing rates of unnecessary antibiotic use.

Conclusion: The expert consensus panel expressed strong consensus regarding gaps in sepsis diagnostics in the ED and the potential for new rapid host response tests to help fill these gaps. These finding provide a baseline framework for assessing key attributes of evolving host response diagnostic tests for sepsis in the ED.

KEYWORDS
consensus, Delphi study, diagnostic testing, sepsis

1 | BACKGROUND

Sepsis is one of the most common and costly medical conditions[1] and is a frequent cause of hospital admission and in-hospital mortality. In the United States, sepsis accounts for over 270,000 deaths and $38 billion in health care costs each year.[2] Many patients with sepsis initially present to emergency departments, where timely diagnosis and initiation of treatment are directly linked to reduced morbidity and mortality. Recognizing the critical importance of early recognition and treatment for patients with sepsis inspired the international Surviving Sepsis Campaign, as well as guidelines from numerous international medical organizations.[3–4] Despite these efforts, opportunities remain for improving outcomes,[5] particularly at the front-lines of medical care (EDs and ICUs).

2 | IMPORTANCE

One central and long-standing challenge in sepsis management is the absence of adequate rapid sepsis diagnostic tests to help identify which patients have sepsis and would benefit the most from rapid initiation of directed care. Given the importance of source control, initial research in developing sepsis diagnostic tests focused on direct pathogen detection methods.[6–7] Despite decades of research developing and applying these assays,[8–10] clinical use has failed to significantly improve sepsis-related outcomes.[11] As the understanding of sepsis has evolved, the target for sepsis diagnostics has shifted toward increased appreciation of the central role dysregulated host immune response plays.[12] This has led to focused research to identify biomarker assays that quantify the host response. Although early research in this arena focused on broad and non-specific biomarkers of organ dysfunction (such as lactate[13]), and inflammation (such as procalcitonin[14]), with potential value shown for improving patient management[15] limitations remain, including lack of assay specificity.[4,16]

3 | GOALS OF THIS INVESTIGATION

Recent progress in laboratory research coupled with a revolution in bioinformatics has helped define the complex biologic pathways in sepsis, affording new opportunities for developing a new set of diagnostic tests that leverage genomic, proteomic, and/or cellular targets.[17–20] Given recent advances in these technologies along different development trajectories, a group of academic investigators from emergency medicine, intensive care, pathology, and pharmacology came together to help define gaps and envision potential future use for emerging rapid host responses diagnostics assays for sepsis in ED settings. This group selected a modified Delphi method to identify areas of consensus and discordance to help inform sepsis research and clinical care.

4 | METHODS

4.1 | Study design

As with other similar projects, a 2-step modified Delphi approach[21–22] was undertaken with the specified goal of reaching consensus on defining (1) key unmet needs in sepsis diagnostics and (2) the potential utility for a future hypothetical rapid host response sepsis test for use in the ED setting. For purposes of this study, we introduced an operational definition and performance characteristics for a hypothetical rapid sepsis test to provide a concrete example for participants to consider as they contemplated potential applications for such a test. The following definition, along with the performance characteristics, were derived from consideration of host response tests under development or in clinical use, such as Monocyte Distribution Width (Beckman Coulter), SeptiCyte (Immunexpress), Triverity (Inflammatix), and IntelliSep (Cytovale).

The Bottom Line

Better measures are needed to identify sepsis in the emergency department. This consensus panel of 26 experts identified critical needs in sepsis diagnostics. These perspectives set the stage for the development of practical rapid sepsis diagnostic tools.

4.1.1 | Definition

A rapid sepsis test is defined as a blood test that, within 10 min, assesses host immune response to aid in identifying patients with sepsis or those at increased risk of developing sepsis within 3 days of hospital admission. Consider that per the Sepsis-3 consensus definition, sepsis is "life-threatening organ dysfunction caused by a dysregulated host response to infection.''

4.1.2 | Performance characteristics

In a population of patients presenting to the ED with signs potentially consistent with sepsis defined as 2 or more modified (systemic inflammatory response syndrome [SIRS]) criteria (with at least 1 being aberration of temperature or white blood cell count) and suspicion of infection defined as a clinician order for culture of a body fluid (eg, blood, urine, sputum, cerebrospinal fluid) with the following hypothetical performance characteristics:

1. Negative predictive value (NPV) of >95% for sepsis or for developing sepsis within 3 days of ED presentation, for patients who test "negative"
2. Positive predictive value (PPV) of ~50% for sepsis or for developing sepsis within 3 days of ED presentation, for patients who test "positive"
3. Area under the curve (AUC) of 0.84.

The modified Delphi method involved the following steps. First, a small steering committee defined 4 broad priority domains of interest in sepsis diagnostics for ED use through open discussion. The set of 4 domains included in the survey were (1) gaps and opportunities associated with sepsis diagnostics; (2) pretest probability for a hypothetical rapid host response sepsis test for ED use; (3) desired characteristics for a rapid host response sepsis test including turnaround time (TAT), and place in the ED workflow to best integrate; and (4) relative importance of key outcomes associated with use of a rapid host response sepsis test, including assessment of the importance of varied prognostication outcomes. The steering committee then generated lists of statements within each broad domain through open discussion, which were finalized through consensus voting. Next, the Round 1 survey generated by the steering committee was distributed via an electronic survey (using SurveyMonkey [surveymonkey.com]) to a larger expert consensus panel (see Table 1) with individuals privately voting on the discrete lists of statements for each domain. After the first round of voting the steering committee held a 1-hour virtual meeting to discuss the results of the consensus statements from the expert consensus panel and review the group input. For those statements in the Round 1 survey where consensus was not achieved, statement modifications were made by the steering committee based on free-text input provided by panelists via comment boxes embedded in the Round 1 survey. Lastly, a modified statement list was fielded to the panelists as the Round 2 (final) survey to the expert consensus panel from which additional findings were captured.

4.2 | Selection of Delphi panelists

This study involved 26 panelists, a number sufficient for a Delphi project of this type.[23] Representatives from a variety of selected specialties deemed key stakeholders in diagnosis and management of sepsis in ED settings were included in the group. Key stakeholders included representatives from 6 disciplines, including emergency medicine (56%), critical care medicine (22%), laboratory medicine (11%), infectious diseases (7%), and pharmacology (4%) (see Table 1 for expert consensus panel list).

Five key opinion leaders were selected to be a part of the steering committee based on a combination of prior involvement in sepsis-related research projects, sepsis-focused leadership within an academic center, and/or leadership within a recognized national professional medical organization with demonstrated interest and focus on sepsis and/or rapid diagnostics related topics. The steering committee members consisted of key thought leaders in emergency medicine (2: R.E.R. and W.S.), intensive care (2: T.R. and H.O.) and laboratory medicine (1: N.L.). The remaining Delphi panelists consisted of individuals similarly identified through involvement in sepsis and those identified by the steering committee as being leading voices in their respective communities or providing diverse perspectives related to practice facility, location or environment. In total, 26 panelists agreed to participate of 61 potential panelists approached. In addition to suggesting panelists, the steering committee reviewed background published materials that explained host responses sepsis diagnostic tests broadly, as well as published data from a series of studies from a specific precommercial diagnostic host response assay, IntelliSep, developed by Cytovale (https://cytovale.com/technology). This platform was selected as a prototype example for the panel to consider, as a hypothetical representative assay under the broader umbrella of host response sepsis assays.[20,24–25] An honorarium was provided by Cytovale, Inc. to each panelist who had committed to be involved in this study after the conclusion of the study.

4.3 | Data collection and analysis

Data from the initial and final web-based survey were gathered via SurveyMonkey. Before being fielded to the expert consensus panel, both the Round 1 and Round 2 surveys were pilot tested with a small number of panelists to ensure that statements being tested were clear

TABLE 1 Expert consensus panel

First name	Last name	Center	Specialty
Paul	Batmanis	Locum Work	Emergency medicine
Carey-Ann	Burnham	Washington University Medical Center	Laboratory medicine
Karen	Carroll	Johns Hopkins Medicine	Laboratory medicine/infectious disease
Debra	Goff	The Ohio State University College of Pharmacy	Pharmacy
Dan	Henning	University of Washington School of Medicine	Emergency medicine
David	Huang	University of Pittsburgh Medical Center	Critical care medicine
Hamad	Husainy	Helen Keller Hospital	Emergency medicine
Ryan	Jacobsen	University of Kansas Medical Center	Emergency medicine
Alan	Jones	University of Mississippi Medical Center	Emergency medicine
Chadd	Kraus	Geisinger	Emergency medicine
Nate	Ledeboer[a]	Medical College of Wisconsin	Laboratory medicine
Frank	LoVecchio	Arizona State University	Emergency medicine
Michael	Lyons	University of Cincinnati Medical Center	Emergency medicine
Simon	Mahler	Atrium Health Wake Forest Baptist	Emergency medicine
Larissa	May	University of California Davis Medical Center	Emergency medicine
Greg	Moran	University of California Los Angeles Medical Center	Emergency medicine
Jerod	Nagel	University of Michigan Medicine	Infectious disease
H. Bryant	Nguyen	Loma Linda University	Critical care medicine
Hollis	O'Neal[a]	Louisiana State University	Critical care medicine
Michael	Puskarich	Hennepin County Medical Center	Emergency medicine
Chanu	Rhee	Brigham & Women's Hospital	Critical care medicine/infectious disease
Todd	Rice[a]	Vanderbilt University Medical Center	Critical care medicine
Rich	Rothman[a]	Johns Hopkins Medicine	Emergency medicine
Wes	Self[a]	Vanderbilt University Medical Center	Emergency medicine
David	Talan	University of California Los Angeles Medical Center	Emergency medicine
Chris	Thomas	Our Lady of the Lake Medical Center	Critical care medicine

[a]Denotes steering committee members.

regarding intent. Statements that required rephrasing were refined until clarity was achieved by group consensus. Technical issues with survey access and navigation were also piloted and refinements made where necessary.

For both surveys, the expert consensus panel rated statements using a 5-point Likert scale[26–27] where 1 translated to "strongly disagree" and 5 translated to "strongly agree." The steering committee specified that ≥75% would be considered consensus for any given statement. Agreement was defined as ≥75% of panelists rating a statement either (4) agree or (5) strongly agree. Disagreement was defined as ≥75% of panelists rating a statement either (2) disagree or (1) strongly disagree. When consensus was not achieved, the statement was operationally defined as lacking evidence to reject or accept the statement, and the statement returned to the steering committee for further discussion, revision, or removal. After rating specific statements, respondents were given the opportunity to provide free-text input regarding their answers. After the first survey, the steering committee considered this free-text input as it made modifications to the next set of Delphi statements for testing in the second survey via a consensus process. If consensus (acceptance or rejection) was not reached on a statement after the final survey, no conclusions were drawn (see Figure 1). In addition to level of agreement questions, there

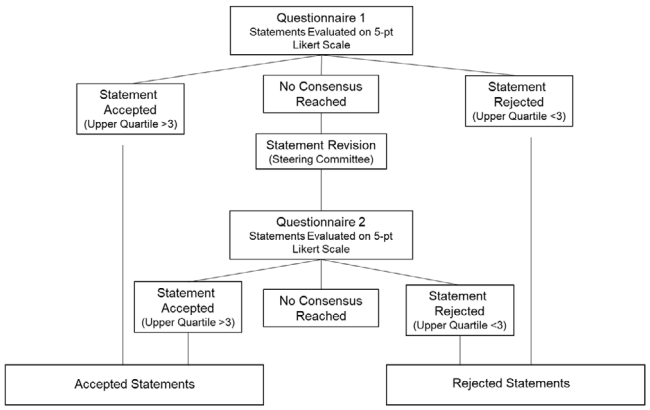

FIGURE 1 Flow chart of Delphi questionnaires, statement modifications, and determination of agreement and disagreement.

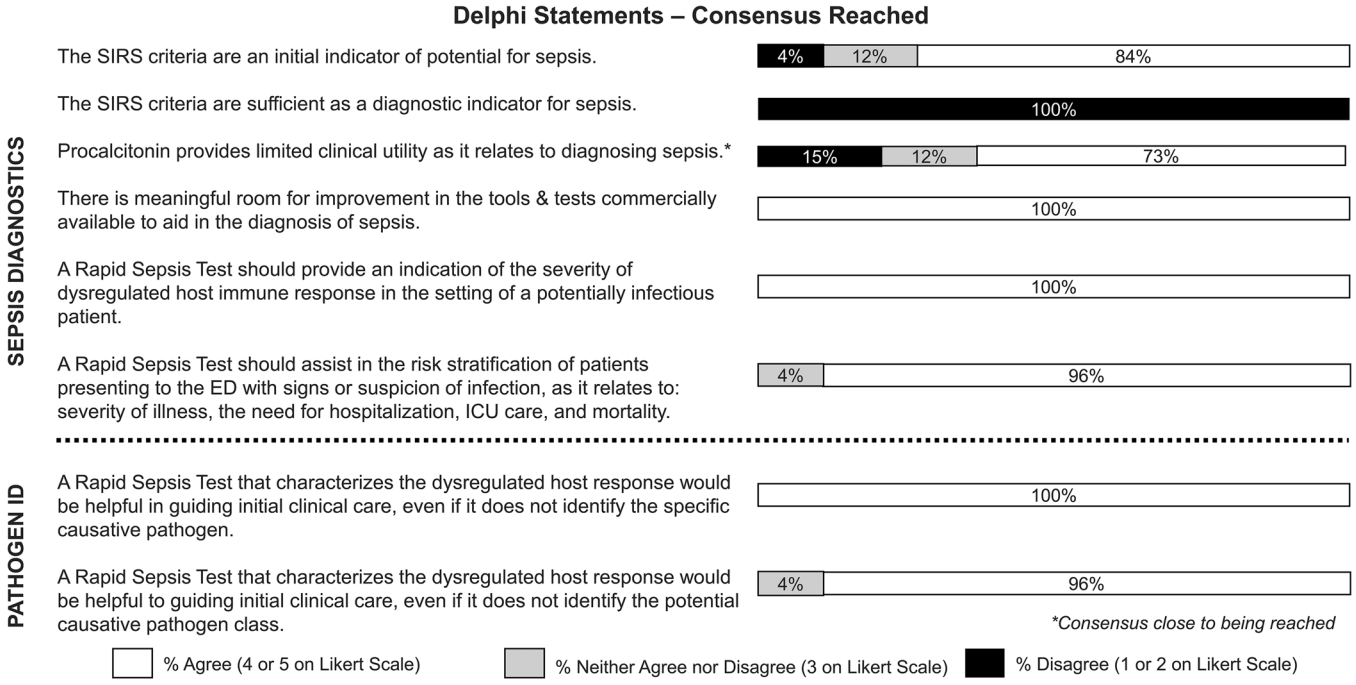

FIGURE 2 Rationale for a hypothetical rapid host response sepsis test for diagnosing sepsis and identifying the etiologic pathogen; statements captured are where consensus was reached between panelists (determined via the Likert scale approach) regarding sepsis diagnostics and pathogen identification tools. Abbreviation: SIRS, systemic inflammatory response syndrome.

was a smaller subset of statements (26%) where the expert consensus panel was asked to select either 1 or more prepopulated multiple-choice answers (see Supplement, Table S4). These multiple-choice statements were analyzed based on percentages of each response option.

The first and final surveys were shared with and completed by expert consensus in October–November 2021 and then November–December 2021, respectively, and each survey achieved 100% participation. Statement responses and results from the first survey were shared with the expert consensus panel before the final survey being fielded.

5 | RESULTS

Overall, 17 out of the 23 (74%) Delphi statements tested as part of the initial and final surveys achieved consensus within the expert consensus panel, 3 were rejected and the remaining 14 accepted. Findings for each domain are summarized in Figures 2–7.

For the first domain (ie, gaps and opportunities associated with sepsis diagnostics), 100% of panelists indicated that (1) there is room for improvement in the tests commercially available in the diagnosis of sepsis; (2) a test should provide an indication of the severity of dysregulation of the host immune response; and (3) a test that characterizes the dysregulated host response would be helpful even if it does not identify the pathogen (Figure 2). Importantly, 100% of panelists disagreed with the statement that the SIRS criteria are sufficient as an indicator of sepsis.

For the second domain (ie, pretest probability for a hypothetical rapid host response sepsis test for ED use), panelists were given performance characteristics of a hypothetical rapid host response sepsis test (NPV 95%, PPV ~50%; AUC 0.84) and then asked to indicate the pretest probability of sepsis where they believed such a rapid host response sepsis test would be useful in clinical practice. The mean minimum pretest probability threshold where the expert consensus panel deemed such a test would be useful was 25% (for a pretest probability for sepsis), and the mean maximum threshold where the expert consensus panel deemed such a test would be useful was 68% (Figure 3). Significant variability was observed among panelists' responses, however, and responses did not follow a clear pattern based on the medical specialty of the responding panelist.

For the third domain (ie, desired characteristics for a rapid host response sepsis test, including TAT, and places in the ED workflow to best integrate such a test), the majority of panelists (58%) indicated that the desired test TAT would be 30 min or less (Figure 4). Regarding the preferred time points/places for initially ordering a rapid host response sepsis test in the ED workflow (panelists were allowed to select multiple choices), 35% reported at triage, 62% reported when initial laboratory studies are ordered, and 65% reported during the initial clinical assessment (Figure 5; panelists were allowed to select multiple time points).

Finally, for the fourth domain (ie, relative importance of key outcomes associated with use of a rapid host response sepsis test, including assessment of importance of varied prognostication outcomes) the top 2 outcomes/metrics favored by the panelists (panelists were allowed to select multiple choices) were (1) "Improvement in

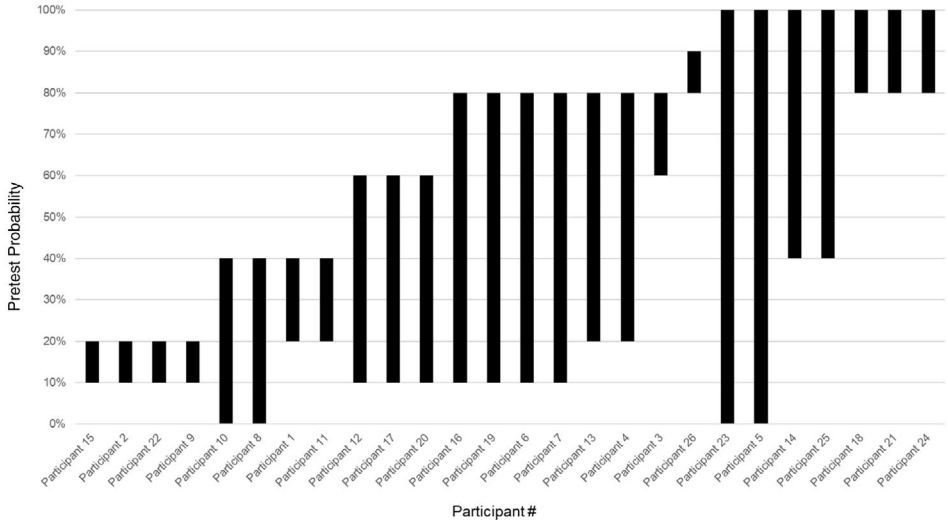

FIGURE 3 Pretest probability threshold to use a hypothetical rapid host response sepsis test; respondents were asked to respond to the following question: "At what pretest probability for sepsis would you utilize a Rapid Sepsis Test, with performance characteristics as described above?" (see performance characteristics noted earlier). Note: Respondents were asked to select pretest probability ranges from <10% to 90%; response selections provided in contiguous 10% intervals.

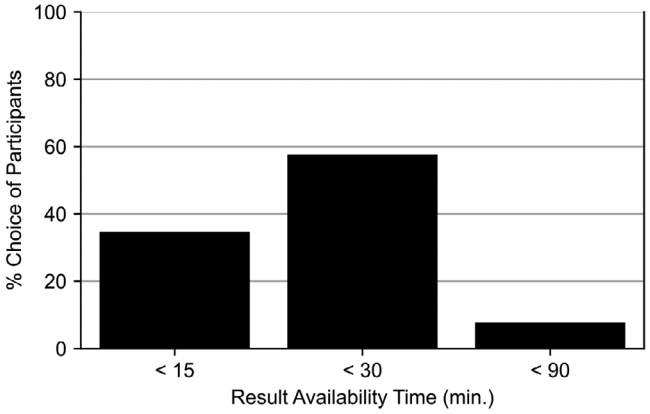

FIGURE 4 Desired rapid host response sepsis test characteristics: desired TAT for a hypothetical rapid host response sepsis test; panelists were asked to respond to the following question: "A Rapid Sepsis Test would provide clinical utility if results were available in (select one): 15 min or less, 30 min or less, 90 min or less." Abbreviation: TAT, turnaround time.

overall sepsis outcomes at my facility" (73% of panelists), (2) "Reduction of rates of unnecessary antibiotic use" (65% of panelists). Four outcome statements were tied for the third position: "Improvement of median time to activate immediate, aggressive sepsis care", "Improvement of appropriate ICU utilization", "Improvement of Emergency Department throughput" and "Improvement in Emergency Department discharge rates (with no compromise on quality of care)," each receiving 54% of panelists' votes. Lower ranking outcomes/metrics were "Reduction in variability of care across clinicians/shifts" (35% of panelists) and "Improvement in average patient length of stay" (31% of panelists). With respect to patient care outcome prognostication, mortality was cited as the most important outcome (Figure 6); however, when asked which aspect of prognostication a hypothetical host response rapid sepsis test could influence (panelists were allowed to select multiple choices), ICU admission was rated highest, with hospital admission and mortality following behind (Figure 7).

Detailed findings for other Delphi statements further addressing sepsis diagnostics, test impact, and workflow are shown in Tables S1–S3.

6 | LIMITATIONS

This study has several limitations. First, expert opinion can be biased by perspectives and clinical experiences of the panel. The assembled panelists were intended to represent a range of stakeholders involved in sepsis care, including emergency physicians, critical care physicians, laboratory medicine specialists, and infectious diseases specialists. Each of these panelist groups brings unique perspectives on sepsis diagnostics, as well as variability within specialties based on individual clinical practice experiences and practice settings (ie, community vs. academic). Further, despite the attempt to recruit panelists with deep knowledge and experience in the area, the construct of the study as a collection of expert opinion has intrinsic limitations. Second, the study was conducted at the height of the COVID-19 pandemic, which could have influenced panelists' responses to the ideal characteristics of a rapid sepsis test, particularly given the diagnostic uncertainties surrounding sepsis in patients with COVID-19. Third, the study relied on panelist background in the area of sepsis and a small amount of information about potential sepsis tests to provide a foundation for input. This level of information may have limited the panelists' abilities to provide broader more informed perspectives given we relied on the panelists' prior background knowledge and expertise. Lastly, how to best define sepsis remains a complex question with an evolving

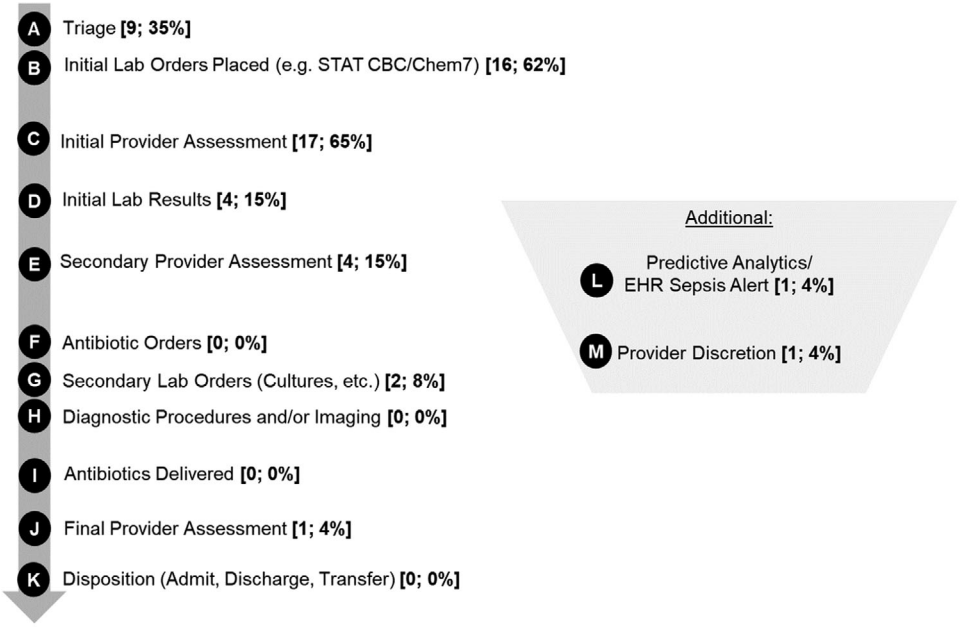

FIGURE 5 Desired rapid host response sepsis test characteristics: time point(s)/place for first ordering a hypothetical rapid host response sepsis test along a typical patient journey—panelists were asked to respond to the following question, using the provided image as a guide: "The most appropriate time point(s) for first ordering a Rapid Sepsis Test along a prototypical patient journey is/are (select at minimum 1 letter, max 3)." Abbreviation: EHR, electronic health record.

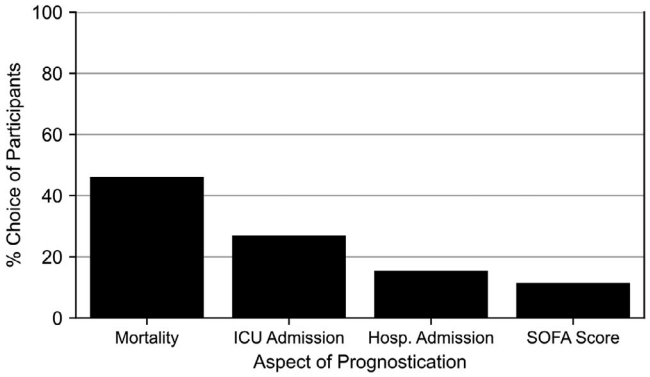

FIGURE 6 Patient outcome prognostication for a hypothetical rapid host response sepsis test: the aspect of prognostication that is most important to you—Panelists were asked to respond to the following question: "What aspect of prognostication is most important to you? Select one."

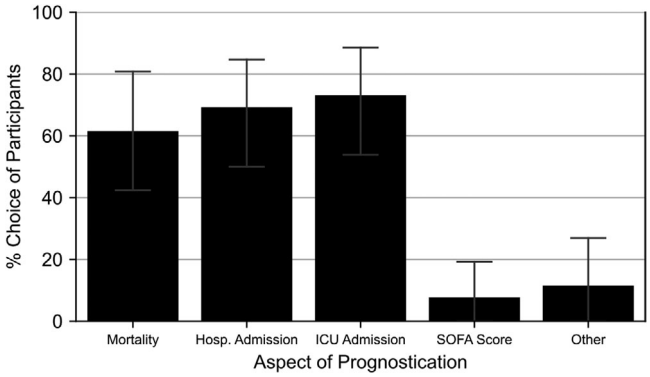

FIGURE 7 Patient outcome prognostication for a hypothetical rapid host response sepsis test: the aspects of prognostication that would be most impactful (not mutually exclusive; % out of total panelists who selected aspect). Panelists were asked to respond to the following question: "Which aspects of prognostication would be the most impactful for a Rapid Sepsis Test to influence? Select all that apply."

definition, which in practice may be influenced by context. The latest pathobiological perspective and the need for a definition that offers utility in a clinical setting are not always compatible.

7 | DISCUSSION

Multiple regulatory bodies and medical specialty societies have highlighted the importance of early recognition and treatment of sepsis. Although hospitals have made large investments to satisfy these guidelines, clinicians at the bedside continue to be challenged in identifying which patients require urgent sepsis evaluation and treatment. Academic and industry groups have also made significant investments in developing new and innovative diagnostic assays.[11] Given the potential for evolving diagnostics to affect patient care in the ED, a deliberate and disciplined approach to defining existing clinical needs and gaps that rapid host response sepsis tests could fill are needed. The expert consensus panel in this study identified some key gaps and opportunities along 4 domains related to sepsis diagnostics. These findings both reinforce themes that appear in the existing literature and identify key

challenges and uncertainties associated with practical use of rapid host response sepsis testing in ED clinical practice.

Related to the first domain, the panelists agreed that there are opportunities for the development of tests for the diagnosis of sepsis to fill current gaps in care. SIRS criteria were unanimously seen as inadequate as the initial indicator of potential sepsis, leaving room for improvement. There was also uniform agreement that rapid sepsis tests should provide insights into dysregulated host response, even if identification of the specific pathogen causing the response is not part of the initial diagnosis. Thus, beyond the currently available tests, such as blood cultures for bacteremia, viral pathogen panels for respiratory pathogens, or markers of end organ hypoperfusion such as lactate, there appears to be significant demand for host response assays to support early clinical decision-making.[16]

In the second domain of "when" (ie, under what clinical circumstance) a rapid host response sepsis test should be used, considerable variability was observed among the expert consensus panel. The uncertainty of when a new diagnostic assay should be applied in practice likely reflects the relative lack of clinical experience with host response assays for sepsis in the real-world. One of the few currently commercially available tests in the broad category of host response assays from which experience can be drawn is procalcitonin, for which widespread adoption in EDs has not been achieved.[28] Further, recent systematic reviews point to shortfalls and lack of consensus on use of biomarkers for sepsis in the ED,[29] particularly because many are directed toward identifying bacterial etiologies only.[30]

Lessons for achieving clinical integration of new and evolving tests into patient care in the ED might be learned from experience with previous assay development related to other acute clinical syndromes, where successive refinements have resulted in achieving a critical level of diagnostic accuracy. For example, in the case of acute coronary syndrome, cardiac troponin assays are now widely used in clinical practice, but it has taken many years of intensive collaboration between academic investigators and industry to achieve this level of adoption.[31] Even with the broad adoption of cardiac troponins into clinical practice, how and when to best integrate the test into ED management of acute coronary syndrome remain the subject of ongoing research.[32–33] Similar to cardiac troponin and procalcitonin, a novel sepsis diagnostic test will need to undergo rigorous and extensive study even after introduction into clinical practice. Further, specific challenges unique to sepsis (vs. acute coronary syndrome) must be considered when considering how to optimize decision-making about it in which patients and when to use new tests such as the prototype assay discussed by this expert panel. The recent explosion of research on host response diagnostic assays for sepsis[17,18,20] will demand focused implementation research to aid both ED administrators and clinicians with decisions related to their most effective use, whether for broad screening purposes or more targeted testing.

In the domain of workflow and TATs (ie, where to use the test in the course of clinical care), most expert panelists desired a TAT of 30 min or less, reflecting the time-sensitive nature of identifying sepsis for initiating aggressive therapeutics that are known to affect patient outcomes. This expert panel agreed that the ideal place to integrate a rapid host response sepsis test could be very early during clinical evaluation, with strongest preference given to triage, followed by during initial laboratory testing, or initial assessment by the treating clinician. This result is consistent with most other tests for time sensitive conditions, such as the ECG and troponin for the evaluation of acute coronary syndrome. It also highlights the necessity of a rapid host response sepsis test to be readily available within the context of existing ED workflows and processes. This is consistent with prior literature from both guidelines' committees and expert panels, which reported a need for more accurate risk stratification information early in the triage process.[4,16]

Finally, panelists identified several key outcomes and prognostic end points that a rapid host response sepsis test should facilitate. Mortality was the most important outcome identified by the expert panel; however, the panel concluded that the rapid host response sepsis test also has the potential to influence disposition decisions such as hospitalization and ICU admission (Figures 6 and 7). This is consistent with improvements sought during the rollout of other rapid tests for other emergent conditions such as myocardial infarction.[34] These results highlight the need for rapid tests for sepsis, which could greatly aid ED sepsis care. Although single or multiplex direct detection assays have not dramatically influenced ED care for patients with suspected sepsis, identifying dysregulated host immune response represents an interesting next step in the evolution of diagnostics for sepsis. A personalized approach to sepsis diagnosis that relies on host response may inform early care and permit a more tailored and targeted approach and more effective and directed use of resources. Indeed, nearly two thirds of panelists indicated that reduction of rates of unnecessary antibiotic use is an important potential outcome related to use of rapid host response sepsis test, which aligns with increasing attention and emphasis for ED clinicians to attend to antibiotic stewardship in sepsis management.[35]

Overall, in this modified Delphi study, the expert panel expressed a strong consensus regarding major gaps in sepsis diagnostics in the ED setting, as well as hope for the potential for rapid host response testing to fill these gaps. The findings from this expert panel provide a baseline framework for assessing key attributes of evolving host response tests for sepsis in the ED.

AUTHOR CONTRIBUTIONS

Kraus: Data analysis and presentation; Nguyen: Data analysis and presentation; Jacobsen: Data analysis and presentation; Ledeboer: Devised the study, developed survey questions; May: Data analysis and presentation; O'Neal: Devised the study, developed survey questions; Data analysis and presentation; Puskarich: Data analysis and presentation; Rice: Devised the study, developed survey questions; Self: Devised the study, developed survey questions; Rothman: Devised the study, developed survey questions; Data analysis and presentation. All authors contributed to writing and revision of manuscript and accept responsibility for the content of the manuscript.

CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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