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Point-of-care sensors for the management of sepsis

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Point-of-care sensors that enable the fast collection of information relevant to a patient's health state can facilitate improved health access, reduce healthcare costs and improve the quality of healthcare delivery. In the diagnosis of sepsis — defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection, and the leading cause of in-patient death and of hospital readmission in the United States — predicting which infections will lead to life-threatening organ dysfunction and developing specific anti-sepsis treatments remain challenging because of the significant heterogeneity of the host response. Yet the use of point-of-care devices could reduce the time from the onset of a patient's infection to the administration of appropriate therapeutics. In this Perspective, we describe the current state of point-of-care sensors for the diagnosis and monitoring of sepsis, and outline opportunities in the use of these devices to dramatically improve patient care.

Sepsis is the life-threatening dysfunction of organs, caused by a dysregulated immune system that is fighting an infection. Globally, 31.5 million people develop sepsis each year. Of these, 19.4 million experience severe sepsis and 5.3 million die[1]. Estimates suggest an incidence of 3 million cases of sepsis worldwide per year in neonates and 1.2 million cases per year in children, with mortality rates of 11–19%[2]. Furthermore, more than 75,000 women die each year due to puerperal sepsis around the world[3]. In hospitals in the United States, sepsis is not only the most expensive condition to treat but also the leading cause of death, with some reports estimating as many as 3.1 million cases at a cost of US$24 billion per year[4,5] and mortality rates between 20% and 50%[5].

Frustratingly, little progress has been made in the past three decades of development of diagnostics and therapeutics for sepsis. Perhaps the main reason for this lack of progress is the vast heterogeneity in the immune response of septic patients, which has made difficult the development of effective immunotherapies and the prediction of which infection cases will lead to life-threatening organ dysfunction. The current treatment strategy in the clinic is focused on antibiotics, fluid resuscitation and vasopressors. Many studies have shown improved patient outcomes with the early identification of sepsis cases and subsequent rapid treatment[6]. However, some studies have shown that early treatment with antibiotics led to no significant improvement (compared with the control patient cohort), further highlighting the heterogeneity of the disease and the need for personalized monitoring and treatment[7]. Point-of-care (POC) devices could enable the convenient acquisition of both pathogen information and host-response information almost anywhere with rapid turnaround times, and have the potential to transform sepsis care in two main ways: first, in instances where optimized care is started late, POC devices could accelerate the process, potentially improving outcomes; second, POC devices measuring many entities (pathogens, plasma proteins and cell-surface proteins) descriptive of the host response combined with sophisticated data analytics could help stratify septic patients into different endotypes to predict which patients will deteriorate. Such stratification could eventually enable the precise targeting of patients who would benefit from escalated care.

Current state of POC diagnostics in sepsis management

Sepsis has been recently re-defined as life-threatening organ dysfunction caused by a dysregulated immune response to infection. This definition underscores the need to integrate pathogen information and the monitoring of the host response, for patient stratification. In the following, we overview the current state of the art of POC diagnostic technologies for sepsis management.

POC technologies for acquiring pathogen information. When a patient is suspected of sepsis, there are two questions related to the infection that are most urgent to a physician. First, is an infection present? If an infection is suspected in hospital environments, broad-spectrum antibiotics are usually prescribed immediately, a trend that will not be sustainable in the fight against antibiotic resistance. Second, if an infection is suspected, are broad-spectrum antibiotics the optimal treatment, or should the antibiotics be tailored to a certain species? To answer these questions, three tests are performed in series: a test for the presence of bacteria (typically by bacterial culture and growth), a test for pathogen identification (sometimes preceded by Gram staining) and antibiotic susceptibility testing (AST). Figure 1 illustrates today's clinical workflow for sepsis care and management.

The three tests are typically performed in a clinical laboratory instead of at the POC. This is mostly because of the need for a blood culture, which typically takes 1–5 days[8]. This first step makes unnecessary both the identification of the pathogen and AST at the POC when these need prior culture or bacterial amplification. Some non-POC devices can detect pathogens directly from blood without the culture step in 3–5 hours by using magnetic-particle-based concentration[9] (T2 Biosystems' T2Candida Panel, approved by the United States Food and Drug Administration (FDA); or DNAe's

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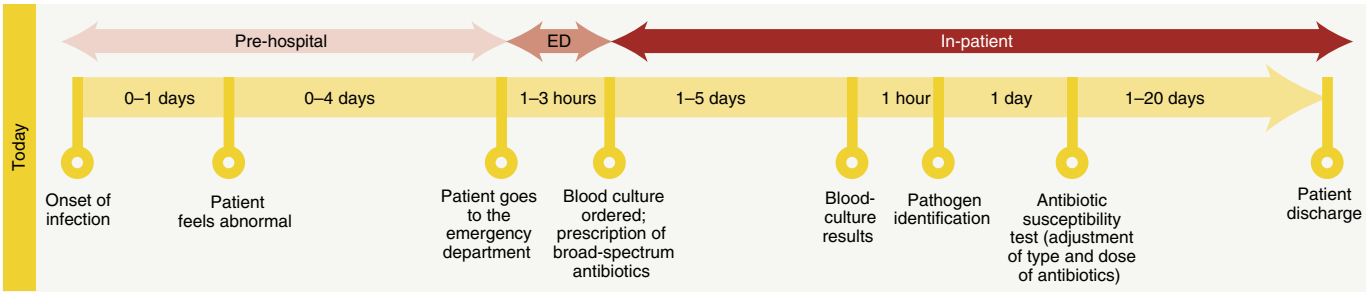

Fig. 1 | Current clinical workflow for the management of sepsis. Pre-hospital events can occur in the home, in the nursing home, in the physician's office or in ambulatory care. ED, emergency department.

immunomagnetic pathogen capture system) or DNA extraction and amplification steps (Roche's LightCycler SeptiFast, only for European use). The company ImpeDx has demonstrated automated electrical detection of bacterial growth earlier than the standard culture approaches[10,11]. Similarly, Qvella's FAST technology[12] and DNAe's LiDia instrument[13] are capable of fast and automated identification of blood infections directly from whole-blood samples. The Accelerate Pheno system (from Accelerate Diagnostics) provides pathogen identification and AST results in less than 9 hours directly from whole blood, and is FDA approved[14]. Most pathogen identification systems use nucleic acid testing technologies based on the polymerase chain reaction (PCR)[15], and there are many commercially available systems today that can perform multiplexed pathogen identification from blood-culture bottles within 1 hour (after bacterial culture). These include Biofire's FilmArray, GenePOC, Nanosphere's Verigene and Roche's Septifast. There are also many tests for viral and fungal pathogens, mostly based on magnetic bead-based capture and subsequent PCR. For example, the T2Candida Panel for fungal detection is commercially available and can identify different species of *Candida* directly from whole blood within 3–5 hours, without prior culture steps.

It is useful to reflect on the rationale behind the standard treatment strategy for sepsis. Should physicians really be concerned only as to whether or not a bacterial infection is present? It is normal for healthy people to acquire infections, but in most cases asymptomatic transient bacteremia and other community-acquired bacterial or viral infections are not life-threatening and do not require treatment. Conversely, many non-bacteremic infections can also cause life-threatening sepsis. In view of the latest international Sepsis-3 definition[16], it seems more relevant to consider whether or not there is an infection that has a reasonable probability of leading to organ dysfunction, especially if it will be life-threatening. This represents a shift in thinking away from acquiring only pathogen information and towards acquiring information also about the personalized state of the immune system of the patient, or about the host response to the infection that leads to sepsis.

POC technologies for the monitoring of immune biomarkers. Only a limited number of entities reflective of the immune system are measured clinically, including complete blood counts (CBCs, which measure total whole-blood cell count, platelets, immature granulocytes, immature polyps or bands, and other entities), lactate and procalcitonin (PCT). Most of these measurements can be carried out in clinical labs by using standard haematology analysers, biochemistry analysers and immune analysers. Solutions for measuring subsets of CBCs are commercially available at the POC (HemoCue, PixCell Medical), although these are not routinely used in most hospitals. POC lactate measurement is available (Abbott's I-STAT, Roche's Accutrend) and is routinely used in hospitals as a marker of altered tissue perfusion and to monitor the severity of sepsis. PCT and C-reactive protein (CRP) are plasma-circulating protein biomarkers that are FDA approved for the assessment of the progression to severe sepsis or to septic shock for patients in intensive-care units, to assess the 28-day risk of all-cause mortality[17], to aid in decisions for antibiotic therapy for some patients, and for the potential de-escalation of antibiotics for septic patients if tracked over time[17–21]. PCT is one of the most well-studied biomarkers for sepsis, with hundreds of published reports demonstrating correlation to sepsis and/or bacterial infections[22]. However, some studies reported that the clinical use of PCT alone does not translate to statistically significant improvements in outcomes or in prescribed antibiotics[22,23], lending credence to the growing belief that there will be no single biomarker for sepsis. No current devices are FDA approved for measuring PCT at the POC, although a few companies have developed such devices (Samsung's Labgeo IB10, Nanomix's e-Lab) and are currently seeking FDA approval.

Table 1 shows the current translational status of various sensing technologies for pathogen detection and host-response monitoring. It should be noted that, although POC technologies for blood-cell counts, circulating proteins and pathogen detection have already been introduced in clinical settings, no assay can measure multiple entities in an integrated device. POC technologies for bacterial growth, AST and cell-surface antigen expression are in the developmental phase. Moreover, technologies for other new biomarkers (such as cell stiffness, cell motility and microRNA (miRNA) from blood) that could be reflective of the host response are currently in the research phase, and further work is needed to evaluate their utility for the improved stratification of sepsis patients.

Opportunities for POC devices in sepsis management

There are two main diagnostic needs in sepsis management: pathogen information and host-response information (that is, the tracking of the patient's immune system). The main aspects of these two different paradigms of measurements are shown in Fig. 2a. Pathogen information primarily includes whether or not a pathogen is present in the bloodstream, the identification of the pathogen and the empiric determination of which antibiotic will effectively kill the pathogen. Host-response information can be gathered by measuring a variety of biomarkers, including but not limited to RNA, miRNA, plasma proteins, cell counts, cell-surface proteins, small molecules, and the mechanical properties, motility properties and other properties of cells. These biomarkers are involved in the progression of sepsis pathophysiology[18,24–31].

An ideal POC sensor would quantify all of the aforementioned biomarkers in a single assay from a small volume of blood, breath, urine, saliva, stool or nasal discharge. In reality, this task will probably be accomplished with several different devices, used in the scenarios where they offer the most value. Figure 2b shows a conceptual illustration of the ideal POC sensor, with most of the elements that would be necessary to measure all of the above-discussed entities. The ideal POC sensor would require small sample volumes, have a low cost per test, have a rapid turnaround time, be conveniently used in all necessary locations and require no training for its use. Developing a technology that can measure different entities is difficult and requires

Table 1 | Translational status of sensing technologies for acquiring pathogen information and for the monitoring of host responses

Clinical biomarkers and tests				Current test parameters			Translational or commercial status			
Technologies or biomarkers	**Is the test or biomarker FDA-approved?[a]**	**Clinical-test reimbursement (US$)[b]**	**CPT/ HCPCS codes**	**Current method**	**Blood volume (ml)**	**Time to result[c]**	**Translational status of the technology**	**Commercial entities (FDA approved or CLIA waived)**	**Commercial status[d]**	**Commercial entities (PoC/ minimal labour products)**
Bacterial growth	Yes	14.07	82803	Blood culture	15–20	1–5 days	Clinical	Standard blood culture[f]	Prototype	ImpeDx, BacterioScan, Curetis' Unyvero BCU[g]
Pathogen identification	Yes	26.87 11.00 17.06	87149 (NA probe) 87076 (chemical) 87143 (typing-glc)	DNA amplification, PCR	<0.05[e]	1–2 hours	Clinical	Roche SeptiFast[g], T2Biosystems T2Dx, FilmArray BioFIRE, MALDI Biotyper CA System, Genmark Dx: ePlex Panels, Accelerate Pheno system	Commercial	Molzym SepsiTest, T2Biosystems T2Dx, DNAe's LiDia, Qvella's FAST technology
Antibiotic susceptibility test	Yes	11.78	87186	Agar/broth dilution assay	<0.05[e]	1 day	Clinical	BioMérieux's Etest, BD PhoenixTM	Prototype	Liofilchem MIC Test Strip, BioMérieux's VITEK 2, Thermo Scientific Sensititre System
Enumeration of blood cells	Yes	10.59	85025	Haematology analyser	<5	30 minutes	Clinical	Sysmex XP-300, Beckman Coulter LH-780	Clinical	Orflo, CytoBuoy, NanoCellect Biomedical, Beckman Coulter DXH900
Circulating proteins	Yes	5.21 (CRP) 36.49 (PCT)	86140 (CRP) 84145 (PCT)	Immuno-analysers	<10	30 minutes	Clinical	BioMérieux's VIDAS 3, Roche's Elecsys BRAHMS (PCT only)	Clinical	Abbott I-STAT (Troponin only), Myraid RBM
Small molecules (lactate, gases)	Yes	21.39 (gases)	82803	Blood gas analysers	<10	<15 minutes	Clinical	Abcam L-Lactate Assay kit, Abbott I-STAT, IL's GEM Premier 5000	Clinical	Abbott I-STAT, Radiometer ABL800 FLEX, Roche Cobas b 221 Blood Gas system
miRNA	No	NA	NA	Nucleic acid tests	<10	1–2 days	Clinical	GeneXpert Cepheid, FilmArray BioFIRE,	Research	Excedr, MDx Biocartis, Enigma MiniLab
Cell antigen expression	No	NA	NA	Flow cytometry	<5	1–2 hours	Prototype	Beckman Coulter FCA-500 and Navios EX	Prototype	LeukoDx Accellix
Cell stiffness	No	NA	NA	Optical tweezers	NA	NA	Research	NA	Research	NA

[a]FDA-approved status is related to the approval status of a test and not to the POC status of the technology. [b]Clinical test cost is based on current procedural terminology (CPT) reimbursement codes, with 2016 fee schedule (60% of Medicare). [c]Time to result is the time to run a specific test in a clinical laboratory. It excludes times for sample draw, logistics, labelling and handling. Actual time from sample draw to results can be significantly higher, depending on the clinical settings and laboratory workflow. [d]Commercial status: research, technologies being researched in academia; prototype, start-up companies are developing products; commercial, products being sold by companies, but still require FDA approval or CLIA waiver; clinical, FDA-approved/CLIA-waived devices being sold by companies and used in clinical settings. [e]Input sample is the cultured product from whole blood. [f]Many FDA-approved blood-culture media are available with standardized protocols. [g]Product not available in the United States. HCPCS, healthcare common procedure coding system; NA, not applicable.

solving a variety of challenges, including fluid manipulation, parallelization, and the integration of single-sensing or multisensing mechanisms. It will most likely be highly advantageous for the design to be modular, so that the same system can use different components separately or together in various combinations, for maximum flexibility. Different tests may be critical in different situations. For example,

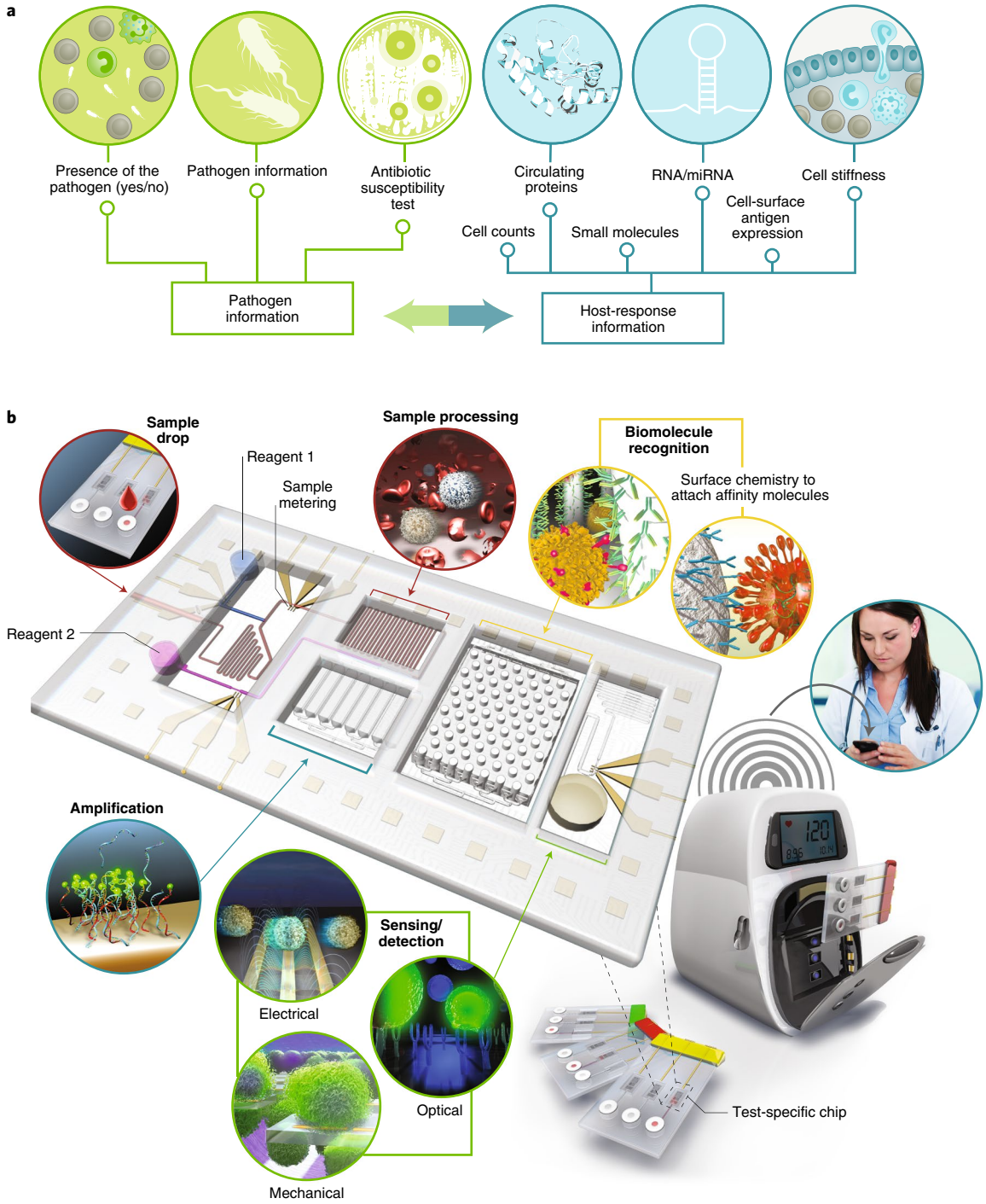

Fig. 2 | Diagnostic needs and the ideal POC sensor. a, Critical information regarding sepsis includes both pathogen information and host-response information. **b**, Concept for a modular POC biosensor that provides biomolecular identification of the pathogen and quantification of host-response biomarkers. Figure courtesy of Janet Sinn-Hanlon, The DesignGroup@VetMed, University of Illinois at Urbana-Champaign; image in blue circle in **b**: gpointstudio/iStock/Getty Images Plus.

certain biomarker panels might be most important in stages before organ dysfunction, whereas others might be more relevant during septic shock[18,24–30].

Tiered strategy for the development of POC devices

We believe that the future of POC-device development for sepsis care can divided into three tiers (Fig. 3a).

Tier-1 POC devices. Tier-1 devices would detect biomarkers currently being measured today in the normal clinical workflow for diagnosing sepsis. The first category of these devices is targeted at collecting pathogen information (replacing blood cultures, pathogen identification and AST). There are significant challenges that still prevent POC devices from replacing these steps. First, it is difficult to design a POC bacterial-identification technology directly from whole blood. This is because the fundamental requirements of bacterial growth are challenging for typical POC-device design specifications (small sample volumes and rapid time-to-result). Large volumes of blood (typically 10 ml) are usually drawn from patients for blood culture. However,

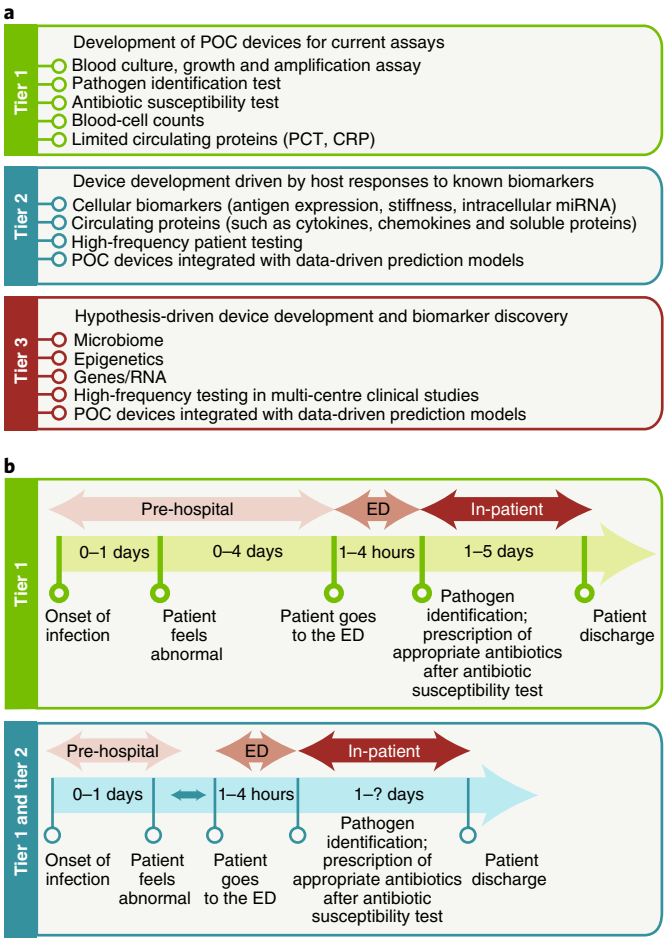

Fig. 3 | Tiered strategy for POC sensor development. a, Proposed strategy for the development of POC sensors. **b**, Impact of tier-1 and tier-2 sensor deployment on clinical workflows. Pre-hospital events can occur in the home, in the nursing home, in the physician's office or in ambulatory care. ED, emergency department.

because of the extremely low concentrations, it is still possible that not enough blood has been drawn to contain at least one bacterium, which is one factor that contributes to the high rate of false negatives in current blood cultures. For POC devices typically employing microfluidics, 10 ml of whole blood is challenging to analyse in a reasonable amount of time. In addition, isolation of a few bacteria from 10 ml of whole blood has been a challenge due to the low concentration, small size and heterogeneity of the entities present in whole blood. However, there have been recent advances in the development of microfluidic technologies for high-volume bacterial isolation that are based on sedimentation, hydrodynamic focusing and magnetic-bead capture. These are promising but have yet to be implemented in clinical workflows[32]. Similarly, microfluidic chips have also been developed for high-volume sample processing to sort circulating tumour cells from whole blood[33–35].

Because of these challenges, the need for POC devices for pathogen identification or AST in hospital settings is difficult to justify; if a 3–5-hour step is needed before using the POC device, then such a test could easily be run in the clinical laboratory itself. However, there is still an opportunity in this space for the development of superior bench-top detection technologies. Sample sparing is an important consideration in clinical settings and becomes especially important for the paediatric population (neonates and infants), for which blood is not available in high quantities. Developing POC devices that can provide pathogen identification using minimal blood volumes could be beneficial in these situations; with today's technology, enough blood to properly identify the pathogen may simply not be available. If somehow the current standard of bacterial growth and pathogen identification could be reduced from the current 1–5 days to less than 30 minutes, this would represent a breakthrough that would have significant impact on patient care. Hence, this remains a highly attractive opportunity that will require technology that can truly find a 'needle in a haystack'. Only recently such approaches are beginning to emerge; for example, the Accelerate Pheno system provides pathogen identification in less than 2 hours directly from whole blood[14]. Although it still requires 5–10 ml of whole blood, the reduced time-to-result is highly beneficial in most applications.

The second category of tier-1 devices would replace measurements of host response currently performed in the clinical laboratory. These could include wearables to acquire measurement of vitals, POC devices for measurement of blood cells and POC PCT devices. The use of these devices to improve sepsis care is limited because in most hospital scenarios where sepsis is the biggest concern, the turnaround time for vitals, CBCs or PCT is usually adequate for most applications. However, POC devices that could measure a total whole-blood count, platelet count, possibly immature granulocytes and bands, and PCT from a drop of venous blood in 10–15 minutes could still be valuable in ambulatory scenarios, outpatient facilities and for patient triage in emergency departments. Here, the goal is to identify patients with dysregulated immune responses caused by potential infections as soon as possible, to decrease the time until broad-spectrum antibiotics are administered. Although none of these entities from blood have ideal sensitivity and specificity for sepsis, if these values were available on arrival to the emergency department (in the case of POC testing in ambulatory or outpatient facilities) or soon after arrival (in the case of POC testing during patient triage in the emergency department), a population-based approach of prioritizing patients with elevated values could have an overall benefit. There are also potential benefits for the use of CBCs and PCT POC devices in physician offices to rapidly determine the probability of bacterial infection before the patient leaves the office, to help decide whether to place the patient on antibiotics and/or to escalate care.

In the United States, some tier-1 POC devices could include devices targeted at specific Center for Medicare and Medicaid Services sepsis bundles, for one-stop-shop access to all diagnostic-bundle information as well as for increased ease of bundle compliance. For example, a POC test could include a CBC, all blood-culture information and lactate values to help satisfy the Center for Medicare and Medicaid Services three-hour sepsis bundle.

The primary impact of tier-1 devices could be to reduce the time it takes to acquire important diagnostic information in the hospital (Fig. 3b). Instead of taking 1–5 days to perform blood culture, pathogen identification and AST, pathogen tier-1 devices would enable the same information to be available on the order of minutes to hours. Both pathogen and host-response tier-1 devices could be used in ambulances or non-acute care facilities so that important diagnostic information is available immediately when the patient enters the emergency department. Both types of tier-1 device could also reduce the time until the administration of broad-spectrum antibiotics, which has been shown to improve mortality[31]. If pathogen identification or AST could be performed directly from whole blood in 30 minutes, these devices could eliminate the need for blood culture, enable immediate tailored antibiotic treatment and eliminate the current blanket approach of application of broad-spectrum antibiotics. It has been shown that such an optimized treatment can directly translate to reduced length of stay, reduced mortality and improved patient care[4–6].

Tier-2 POC devices. Tier-2 devices would consist of POC devices for entities that have already been well studied in the research literature but that are not routinely measured in clinical practice. For the most part, these are host-response biomarkers such as cell counts[36,37], cell-surface receptors[38], plasma proteins[39–41], miRNA[42,43], RNA[42–44], the mechanical properties of cells[45,46] and small molecules[47]. In view of the large volume of literature showing the correlation of these biomarkers to sepsis, it is natural to question why almost none of them have made it into clinical practice. Although the answer to this question is complex, we believe that there are two primary factors: the lack of sufficient understanding of the enormously complex and heterogeneous pathophysiology of sepsis, and the lack of a gold standard to compare these biomarkers with. Furthermore, the heterogeneity of the immune response is now widely accepted. There is heterogeneity in the different pathways that can cause the progression of sepsis, among different patient immune systems, in the original causative infection, in treatment strategies and in many other factors. This has made it difficult to generalize the results of any particular biomarker study. Many studies have shown promising sensitivity, specificity and area under the receiver operating curve in limited populations[18–21], but nearly all efforts to scale these biomarkers to wider populations have failed. It is clear that without a better understanding of the underlying pathophysiology, which should include a way to better describe and stratify sepsis so that the endotype of any given patient at any given time can be identified, the results of these biomarker studies will most likely not be generalizable.

This lack of understanding also propagates into the lack of a gold standard. With the ever-evolving definition of sepsis, different clinical practices and the inherent heterogeneity of the disease and immune response of the host, there is a high degree of complexity preventing the standardization of the various stages of disease progression. Sensitivity, specificity and predictive power depend on having a metric with which to compare the biomarker, the biomarker panel or the model. In the literature, this metric is often 'independent adjudication' based on chart review of a certain number of physicians. However, it is now well known that the disagreement among adjudicators can be high when it comes to sepsis, which calls into serious question the validity of this method to generate a gold standard. With varying metrics to measure performance, it is not surprising that most biomarker studies cannot scale. An additional difficulty tied to this problem is that patients are assigned to specific 'no sepsis' or 'sepsis' categories when in reality there is most likely a continuous spectrum of patients between a healthy patient and a patient that is at risk for life-threatening consequences owing to infection. Once again, the constructs of sensitivity, specificity and predictive power are not equipped to handle the fundamental problem: to what degree the patient is septic, rather than whether a patient is septic. These problems have been described in detail in a debate following the Sepsis-3 definition[48].

With these problems in mind, we believe that more research is needed to elucidate the underlying pathophysiology of sepsis and to ultimately define which panels of biomarkers are clinically useful to measure, and at which time and for which patients. Most likely, instead of using a single-biomarker panel to diagnose sepsis for all suspected patients, it will be necessary to employ different biomarker panels for different patients at different times. In other words, the biomarkers measured for a patient should be specifically tailored to the patient's health condition. We propose that to accomplish this, researchers should track candidate combinations of biomarkers over time for groups of patients potentially at risk for sepsis, and then build associations of this data with relevant clinical outcomes, such as mortality, length of stay, antibiotic duration and readmission rates. To handle these complex multidimensional data, sophisticated machine-learning and predictive analytics should be brought to bear. The combination of time-series biomarker data, clinical outcomes and predictive analytics may reveal which biomarkers could be useful for which patients, and in which health states to decouple heterogeneous sepsis subpopulations from one another. Ultimately, clear strategies for the accurate estimation of the probability that a patient will deteriorate in health towards life-threatening organ dysfunction due to infection are needed.

The use of new panels of host-response biomarkers will be critical for personalized patient monitoring. These efforts themselves could benefit from the development of POC devices. For example, although cell-surface antigens or circulating proteins can be currently measured in hospital laboratories that are approved for standard clinical laboratory improvement amendments (CLIA), needs for high-frequency testing, desires to lower test costs and concerns of clinical-sample sparing in the paediatric population could justify measurements with POC devices. Moreover, certain host-response biomarkers cannot be quantified by using current standardized laboratory equipment available in CLIA-approved hospital laboratories and would require new-device development. Such biomarkers may include cell stiffness[46] and neutrophil motility[49], and would require the development of new devices. Furthermore, many important biomarkers are known to dramatically change as a function of environmental factors after the blood is drawn from the patient. For example, most cell markers, including monocyte HLA-DR (human leukocyte antigen–antigen D related; one of the anti-inflammatory sepsis markers), are known to drift significantly if the blood is kept at room temperature outside the body before measurement[50]. In these cases, POC devices could help increase the fidelity of measurement of such labile markers.

When it is possible to predict the probability of deterioration of health given certain biomarker inputs, tier-2 POC devices could be used to enable the measurement of these markers in pre-hospital environments and in hospital environments where turnaround time is important. Such environments could eventually include ambulances, out-patient facilities, physician offices, pharmacies, assisted-care facilities and homes.

When coupled with a better understanding of the precursors of the immune system before advanced sepsis, these devices could encourage patients to present themselves to a healthcare facility much earlier (Fig. 3b). Because of the nature of sepsis, it is probable that patients wait anywhere from hours to days after feeling abnormal before they decide to go to a hospital. In a recent study, this time was described as the 'patient delay' (and defined as the time between the onset of sepsis and a first emergency call[31]). It will also be important to perform studies correlating patient delay with outcomes, similarly to how downstream delays, such as total medical contact delay (the delay between when an ambulance arrives and the administration of antibiotics), have a significant impact on patient mortality.

Furthermore, high-frequency patient testing in longitudinal studies using POC devices, combined with the development of data-driven predictive systems based on machine learning, can provide new insights into the pathogenesis of sepsis. For example, a biochip that quantifies neutrophil motility from patient blood samples and a machine-learning-based predictive system for sepsis diagnostics[49] has provided new insights into the role of neutrophil motility in sepsis pathogenesis, especially at the early stages of inflammation. Similarly, a biosensor that quantifies leukocyte differentials and CD64 expression levels from whole blood, and the combination of this information with patient information from electronic medical records, have improved sepsis identification in longitudinal studies of septic patients[38]. Many other technologies that are being developed to quantify biomarkers such as RNA, the cells' mechanical properties and small molecules[45–47] have the potential to provide additional detailed insights into the pathogenesis of sepsis.

In future, as databases are built to validate biomarkers coupled with data analytics, the process and methodology to collect such

markers must be standardized, with unified gold standards, calibration standards and quality control systems. Only then should the data be used to perform high-quality data analytics. Building up such a database across different hospitals is a challenge that must be undertaken carefully and thoughtfully. And because of the patient heterogeneity and complexity of sepsis progression, a large number of biomarkers (biomarkers currently known and other promising biomarkers) would have to be collected, as there may never be a single biomarker for sepsis. The approach of combining and applying machine-learning analytics on large biomarker datasets could help address and develop such personalized approaches.

Overall, tier-2 devices combined with 'big data' predictive analytics could allow for the prediction of which patients will deteriorate significantly, and could encourage these patients to see a doctor to receive appropriate treatment much earlier. The trigger for these tests would depend on the environment. For example, the test could be performed on all patients in an ambulatory environment suspected of infection, on patients in higher-risk categories in nursing-home environments periodically, or on patients at home who feel abnormal yet are unsure of whether they should see a doctor. Careful optimization of the trigger of the test to maximize the difference between the benefit of true positives and the cost of false positives will be needed. The earlier in the disease state that testing is performed, the worse the true-positive-to-false-positive ratio is expected to be. Also, these systems could be used in hospitals to generate alerts for patients who are at risk of sepsis from hospital-acquired infections. Furthermore, the use of tier-1 and tier-2 devices throughout the course of the disease could allow for real-time feedback as to how the patient's underlying immune state is responding to treatment (such as antibiotics). This information could be used in real time to adjust and optimize treatment strategies, potentially assisting in the specific de-escalation of broad-spectrum antibiotics. In addition, as sepsis is viewed more as a chronic disease condition because of irreversible damage to the immune system post-sepsis, tier-1 and tier-2 devices could also be used for monitoring after hospital discharge to improve post-acute care.

Another important concern is that the route to obtain FDA approval can be complex and depends on the new claims attached to the device. For example, a device claiming 'equivalence to a previous assay' does not have as high a regulatory burden as a device being developed for a new clinical application. This requires a 510(k) premarket submission made to the FDA to demonstrate that the new device is effective and safe, and that it has substantial equivalence to a predicate device. This is typically a much faster and easier route than submitting entirely new clinical claims under a premarket approval process[51]. For sepsis, equivalence to a previously approved assay can be established for a new POC device to quantify CRP and PCT levels (because CRP and PCT are already approved for sepsis claims). Such devices will not have as high a regulatory barrier as a device that measures a new parameter (such as cell stiffness, miRNA or other previously non-approved biomarker measurements).

Tier-3 POC devices. Tier-3 devices would focus on new entities that require significant clinical proof-of-concept studies. Many hypothesis-driven research studies on biomarker discovery will need to be completed to further explore the pathobiology and pathophysiology of sepsis. These should include more investigations exploring the connections between sepsis and the microbiome[52–54], sequencing information, genetic predisposition and epigenetic alterations of specific genes during the course of sepsis progression[44]. Microbiota, in addition to maintaining the gut–barrier function, play a critical role in the modulation of the innate and adaptive immune responses of septic patients in response to infection[52]. Sepsis can also alter the composition of the gut microbiota, and this can subsequently result in organ failure[52,53]. Furthermore, the downregulation of certain genes has been associated with sepsis-related organ dysfunction. For example, the Tie2/Ang (angiopoietin receptor/angiopoietin) and VEGFR/VEGF (vascular endothelial growth factor receptor/vascular endothelial growth factor) pathways play a critical role in the regulation of microvascular endothelial function, and their downregulation during sepsis can result in microvascular leak[44]. And methylation is known to play a significant role in the irregular transcription of angiogenic genes[44]. These preclinical findings, which need to be extensively studied, may be relevant for clinical applications. Although tier-3 efforts should focus on hypothesis-driven biomarker discovery, these biomarkers need to be extensively investigated in longitudinal multi-centre clinical studies with high-frequency patient testing. Predictive computational models will need to be subsequently developed by integrating the newly hypothesized biomarker data with more traditional biomarker data for the increased understanding of sepsis pathogenesis and patient heterogeneity and to further shed light on the mechanisms of sepsis progression and organ dysfunction. The development of tier-3 POC devices should only begin when research has better validated these correlations.

The quest for improved knowledge of sepsis pathophysiology and for the optimization of state-of-the-art clinical protocols should drive the development of POC sensors. This highlights a 'need based' technological development approach. The technologies should be tested in multi-centre clinical trials and eventually be integrated into clinical workflows. Clinicians, data scientists and technology developers must collaborate to develop a systems-based approach for sepsis diagnosis and stratification. At the same time, basic-science researchers must continue to advance the fundamental knowledge in sepsis pathobiology to discover new opportunities for translational sepsis care.

A precision-medicine system

Primary bottlenecks for improving sepsis care are time-to-diagnosis and the identification of well-proven biomarker panels. The immediate clinical need is to develop devices for pathogen identification and AST that can reduce the time to obtaining pathogen information from days to a few hours. Monitoring the immune response of a patient to determine the progression of sepsis will most likely require a data-driven integration of many panels of biomarkers from the patient. The ever-evolving definition of sepsis, different clinical practices and the inherent heterogeneity of the disease all contribute to the complexity of standardizing sepsis, and call for an increasingly personalized monitoring of the patient's immune system via high-frequency biomarker measurements.

We believe that the future of sepsis care can be a model for systems medicine and precision medicine. Such a system would consist of: (1) training datasets for machine-learning algorithms; the datasets would incorporate high-frequency measurements of validated biomarkers from blood and other body fluids throughout the course of sepsis progression, independently of the location of the patients; (2) accompanying patient data, including vital measurements, laboratory values, past medical history, comorbidities and demographic information; (3) complex analytic models that are capable of de-convoluting inherent heterogeneity and of predicting the future health states of patients; and (4) POC devices capable of measuring the latest relevant data from patients in any location, and with cloud connectivity so as to directly input this data into the analytic models. Such a system could enable the early screening of sepsis cases, personalized treatment strategies and eventually the development of new drugs targeted at specific patient populations.

A call to action

There are many opportunities for POC devices to improve sepsis care by providing timely information on the pathogen and on the

host response. For pathogen information, one of the most critical needs is the development of a POC device that could directly identify the pathogens and provide antibiotic-susceptibility information from whole blood in minutes. For monitoring the host response, POC devices coupled to analytics and a better understanding of sepsis biology could enable the much earlier identification of possible sepsis cases in pre-hospital settings. Furthermore, quantifying host immune biomarkers on patient entry into emergency departments could be critical for the investigation of the state of the host's immune system and of organ dysregulation. This information could be used to strategically allocate resources to optimize care, by influencing the triage process, the need for admission into the hospital or intensive care unit and the use of various therapeutics. A careful evaluation of the advantages and trade-offs of POC devices is important in determining a step-by-step approach for the introduction of these devices into clinical workflows to maximize the benefits of these technologies for patients at risk of developing sepsis.

Sepsis is one of the most critical problems that hospitals face today. Especially considering the implications of the alarming trends in antibiotic resistance, much more effort must be focused on innovative solutions to improve sepsis management. This will most likely require massive multidisciplinary efforts incorporating clinicians, device developers, big-data and machine-learning researchers, basic-science researchers, and educational specialists. In 2013, the National Institutes of Health allocated US$88 million for sepsis research, which is less than 0.3% of the total National Institutes of Health research budget[55]. Furthermore, only US$458 is spent in federal funding per sepsis death, a much lower amount of spending than for other diseases such as cancer, HIV and cardiovascular pathologies[55]. Public awareness of sepsis also needs to be much improved, as fewer than half of US citizens are familiar with the term 'sepsis'[56]. An increase in awareness of sepsis by the general public can help with its prevention, early detection and subsequent treatment, and also with increased advocacy to close the gap between current federal and private funding and actual funding needs. Government agencies, foundations, charities and companies need to increase the number and strength of collaborations, dramatically ramp up efforts and create initiatives that improve the tools available to combat sepsis.

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Author contributions

B.R., U.H. and R.B. conceived and designed the article. C.S., T.S.I., D.C.A., L.Y., W.W., K.W. and A.V. helped in identifying the primary clinical needs in sepsis and provided intellectual input on the best solutions to these needs. B.R. and U.H. made the figures and table. All authors provided input and reviewed the article. B.R., U.H. and R.B. edited the manuscript.

Competing interests

B.R., R.B. and U.H. have financial interests in Prenosis Inc. The remaining authors declare no competing interests.

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