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Sepsis Diagnostics: From Discovery to Application*

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In 2015, the Sepsis-3 Consensus Conference proposed a new definition for sepsis and provided new clinical criteria for the early “recognition” of sepsis (1). Unfortunately, this definition suffers from many of the same limitations of the older definition, the reliance on less than adequate diagnostic testing to distinguish sterile inflammation from infection early in the clinical course. The clinical implications can be calamitous, since delaying antibiotic administration by even an hour increases the risk of mortality from sepsis (2), while the societal consequences of over administration of antibiotics are well known (3). In this issue of *Critical Care Medicine*, Sweeney and Khatri (4) have attempted to validate novel genomic biomarkers that can distinguish sepsis from sterile inflammation. Using genomic metrics that they (Sepsis MetaScore [5]) and others have developed (Fas apoptotic inhibitory molecule 3:placenta-specific 8 gene expression ratio [6] and SeptiCyt Lab [7]), the authors have conducted a meta-analysis of existing, publically available genomic datasets to retrospectively validate these three metrics and compare their ability to discriminate sepsis from noninfectious inflammation in different cohorts. Overall, the three diagnostics were able to distinguish noninfectious inflammation from sepsis with precision that in some cases was remarkably good. The MetaScore in particular proved highly sensitive in identifying sepsis.

Sweeney and Khatri (4) are to be commended for their innovative approach in this burgeoning new era of “precision medicine” where the goal is to improve treatment, diagnosis, and prevention of disease using massive repositories of “omics” data. The authors have moved the sepsis field forward by capturing terabytes of genomics and clinical data in the public domain originally created for other purposes. For example, much of the data in this meta-analysis came from the Glue Grant, which generated high-throughput genomic, proteomic, and observational clinical data in an effort to define the normal and pathologic human response to trauma and systemic inflammation (8). Using novel statistical and bioinformatics approaches, the authors were able to include 39 different clinical datasets from 2,604 patients into a single unified database that can be parsed for knowledge. Their

*See also p. 1.

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model allows for the combination of genomics data from multiple platforms while minimizing technical variation.

A significant limitation in the development of biomarkers, especially genomic, has been the inability to reproduce findings, and the failure to validate the initially identified metrics. The reasons are multifactorial but are common to small datasets, and range from differences in the analytical platform, to over-fitting of the data by the large number of variables collected. Using statistical approaches to minimize analytical bias, Sweeney and Khatri (4) have created a genomic metric (MetaScore) that appears sufficiently robust to maintain predictive ability across a variety of different clinical conditions using a number of different platforms. The authors are to be congratulated for providing to the public domain, a curated repository of these data and the tools for others to evaluate potentially new sepsis genomic biomarkers (<http://khatrilab.stanford.edu/sepsis>).

This study represents an outstanding beginning to an understandably long journey to its clinical use in the potentially septic patient. Nevertheless, this process presently remains discovery-driven and must transition to an application-driven approach to achieve its goal. The next steps will require prospective validation in a variety of patient populations to ensure reproducibility and, more importantly, to identify whether or not these diagnostic tools can impact patient management. Furthermore, the current genomic tests favor a high sensitivity at the cost of specificity, increasing the false positive rate. While we agree that a false negative, potentially not treating an infected patient, could have lethal ramifications, a high false positive rate or treating noninfected patients has its own consequences. The hope is that given the increasing rates of antibiotic resistance, the use of this genomic metric will reduce to some degree the use of antibiotics for patients correctly identified as not requiring antibiotics.

In order for a genomic biomarker to translate into clinical practice, the appropriate technology must also be developed, one in which sample turn-around time is measured in minutes and hours, not days as is currently required. This will necessitate a movement away from microarrays and sequencing, which are generally discovery based, to technologies more appropriate for application-based uses, such as those based on quantitative polymerase chain reaction or digital messenger RNA labeling (nanoString). Such technologies exist today and have proven their precision and accuracy in other clinical settings (9). Thus, some of the variability presented here may be due to inherent technical variation in the analyses, and we are intrigued to see what a prospective validation study with clinically optimized technologies will provide.

Severe infections leading to sepsis create a complex pro- and anti-inflammatory response with associated life-threatening organ dysfunction. Dysregulation of the inflammatory and host protective immune responses can lead to multiple organ failure and death, as well as to chronic critical illness and lifelong morbidity. Discovery-based studies have demonstrated different patterns of gene expression associated with viral and bacterial infections, trauma, and burns, as well as for differential clinical outcomes, and potentially response to therapeutic interventions (5, 9, 10). The current study by Sweeney and Khatri (4) in this issue of *Critical Care Medicine* provides a road map for the discovery and validation of

unique genomic biomarkers for a variety of clinical questions in the critically ill patient. It also births the question of whether we can use new bioinformatics and computational models to identify new genes that may contribute to a specific disease process. Enthusiasm for these genomic biomarkers must be tempered by the failure of numerous earlier protein biomarkers in sepsis (11). History tells us to remain skeptical that a single biomarker will be sufficient to prove clinically useful in such a complex phenotype as sepsis. Future diagnostic tests during sepsis may require a combination of existing and/or future biomarkers. However, Sweeney and Khatri (4) make a significant step forward and remind us that the massive amounts of public data collected since the inception of National Institutes of Health Gene Expression Omnibus in 2002 are an untapped source of knowledge (12). Future efforts will make the transition from discovery and validation to the clinical application of these and other tools more timely and cost-effective.

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