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Turning a new page in sepsis molecular diagnostics necessitates generalizable biomarkers

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Keywords

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We thank Drs. Scicluna and van der Poll for their letter and congratulate them on the FAIM3/PLAC8 ratio(2), which we have shown has potential broad applicability beyond its initial intended clinical scenario(3). We first wish to correct one misstatement of theirs: the Sepsis MetaScore (SMS) has been validated using the NanoString nCounter platform,an independent targeted gene expression technology, in an independent cohort of 96 critically ill children(4). Further, we whole-heartedly agree that discovery datasets are biased towards their classifiers; we therefore reported performance statistics both with and without their inclusion(3).

We believe that there is a need for generalizable (not context-specific) biomarkers in sepsis for two reasons. First, the clinical question that underlies the FAIM3/PLAC8 ratio or any other sepsis biomarker is largely whether a critically ill patient needs antibiotics—and here generalizability is key to a successful tool. If we use *reductio ad absurdum*, the context specificity that Drs. Scicluna and van der Poll champion would lead to separate tests for pneumonia, skin and soft tissue infections, urinary tract infections, abdominal infections, etc.—and then separate versions of each test for the emergency department, ward, and intensive care unit. Validating and translating dozens of separate biomarkers would, of course, be unfeasible and unhelpful. Instead, what is needed is a non-context-specific, highly generalizable diagnostic that can discriminate whether patients with systemic inflammation have bacterial infections(4, 5). Our manuscript conclusively shows that the FAIM3/PLAC8 ratio is *not* specific to the clinical question of community-acquired pneumonia vs. non-infectious respiratory distress. It is clear from the data that the FAIM3/PLAC8 ratio is strongly induced for all of the types of infections represented in the 39 datasets and 2,604 patients included in our study(2). Thus, we have little confidence that a patient with an extra-

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pulmonary source of infection concomitant with respiratory systems would not be misclassified as ‘pneumonia’ in the narrow binary context of pneumonia vs. non-infectious respiratory distress. But isn't that a benefit? The critical need for early antibiotics in patients with sepsis from any source (6) suggests that a generalizable biomarker for bacterial infection would fit best into clinical workflows.

Second, it is of course true that a targeted study of gene expression is better than a microarray study; however, high-fidelity gene expression studies done for validation of a diagnostic in a population not significantly different from the discovery population (i.e., same inclusion/exclusion criteria, same enrolling site) are not a guarantee of generalizability. Performing multiple trials across a broad range of patient types from different centers is the only way to ensure the validity of a diagnostic test. Leveraging the existing clinical microarray data is an excellent way to rapidly test a diagnostic across multiple patient groups. There may even be an ethical argument that not to do so would risk harm to new trial participants in ‘reinventing the wheel’, while not making full use of the contributions of existing trial participants(7). In any case, we find it hard to understand any argument against widespread testing of proposed interventions for a problem as difficult and urgent as improving sepsis care.

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References

1. Scicluna BP, van der Poll T. Turning a new page in sepsis molecular diagnostics necessitates context-specific biomarkers. Crit Care Med. 2017 in press.
2. Scicluna BP, Klein Klouwenberg PM, van Vught LA, et al. A molecular biomarker to diagnose community-acquired pneumonia on intensive care unit admission. Am J Respir Crit Care Med. 2015; 192(7):826–835. [PubMed: 26121490]
3. Sweeney TE, Khatri P. Benchmarking Sepsis Gene Expression Diagnostics Using Public Data. Crit Care Med. 2016
4. Sweeney TE, Wong HR, Khatri P. Robust classification of bacterial and viral infections via integrated host gene expression diagnostics. Sci Transl Med. 2016; 8(346):346ra391.
5. Sweeney TE, Shidham A, Wong HR, et al. A comprehensive time-course-based multicohort analysis of sepsis and sterile inflammation reveals a robust diagnostic gene set. Sci Transl Med. 2015; 7(287):287ra271.
6. Gaieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med. 2010; 38(4):1045–1053. [PubMed: 20048677]
7. Bauchner H, Golub RM, Fontanarosa PB. Data Sharing: An Ethical and Scientific Imperative. JAMA. 2016; 315(12):1237–1239. [PubMed: 27002444]