Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Host gene signature shows promise to distinguish bacterial and viral infections

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Determining the pathological cause of acute febrile illness is often considered the Holy Grail of infectious disease diagnostics. Diagnostic tests can lack sensitivity and take hours or even days to return conclusive results.[1] Consequently, antimicrobial therapy is often initiated before a definitive diagnosis, and inappropriate and overuse of antimicrobial drugs exacerbates the public health crisis of antimicrobial resistance.[2] Currently used biomarkers show variable sensitivity and specificity depending on the clinical scenario.[3] The COVID-19 pandemic has further demonstrated the variable performance of frequently used biomarkers such as C-reactive protein and procalcitonin.[4] Host-response transcriptional signatures have shown potential for substantial improvements over existing biomarkers in distinguishing bacterial from viral infections.[5,6] However, none are in common use in clinical practice.

In *The Lancet Digital Health*, Nannan Xu and colleagues[7] present a novel exploration of four host genes in patients with acute febrile illness using real-time PCR. Building on the past decade of research into host-immune response signatures, the investigators used existing gene microarray and RNA-sequencing datasets to shortlist candidate gene biomarkers. The authors compared RNA expression levels between patients with proven bacterial and viral infections in a screening group, and developed a logistic regression model in an additional discovery cohort with the two highest-performing genes (*IFI44L* and *PI3*).

The derived signature had exceptional performance in both internal (n=124) and external (n=78) validation cohorts, outperforming C-reactive protein and procalcitonin in diagnostic metrics (area under the curve, sensitivity, and specificity). The signature had variable performance on non-infectious inflammatory syndromes, with expression patterns in patients with systemic lupus erythematosus consistently similar to those with viral infections (19 patients in the internal validation group and 11 patients in the external validation groups). The signature reliably differentiated bacterial infections from combined cohorts of patients with viral infection or systemic lupus erythematosus, again outperforming traditional biomarkers.

A particular challenge for the use of biomarkers in acute febrile illness, particularly C-reactive protein, is a lag-time between symptom onset and measurable biomarker changes.[8] Subgroup analyses by Xu and colleagues[7] suggested their signature might be sensitive in early infection, with one patient identified as bacterial within 2 h of symptom onset. This early change is one potential explanation for the high performance compared with traditional biomarkers. Similarly, analyses between acute and convalescent samples suggested a potential role in monitoring treatment efficacy, adding to the health and economic value of such host-response signatures.

Despite these findings, many questions must be answered before any such signature will be confidently used in clinical practice. Perhaps the highest priority is the prospective evaluation of any biomarker in undifferentiated patients with acute febrile illness and other clinical syndromes. As with C-reactive protein, full blood count and other non-specific biomarkers, it is unlikely that any new infection biomarker will be restricted to a single clinical syndrome (eg, fever), and interpretability outside of these restricted syndromes is crucial knowledge for practitioners. Wider assessments must also include vulnerable populations, specifically immunosuppressed patients (eg, those with HIV or haematology/oncology), children, the elderly, and those with comorbidities. These patients account for substantial antimicrobial use and are at greater risk of developing antibiotic resistant infections; therefore, new diagnostics specifically targeting these groups are likely to have the most profound effects on clinical practice.[9]

The differential diagnosis of most patients with acute febrile illness is rarely limited to bacterial versus viral classification — other infections, mixed infections and non-infectious inflammatory syndromes all present significant barriers to the development of novel diagnostics. Non-binary signatures able to predict aetiology for various infectious and inflammatory disorders with high accuracy would have the greatest value. Such signatures will likely require more predictors (genes), and may have reduced sensitivity and specificity by virtue of diagnostic complexity.

Xu and colleagues[7] comment that trading some specificity for higher sensitivity might be needed to catch more bacterial infections, particularly in severely unwell patients. Diagnostic tests are never used in isolation, and the entire clinical picture is required to make safe decisions. The reported signature achieved very high diagnostic accuracy in both internal and external validation groups, with AUC 0·969 and 0·986, which suggests that application appropriate to clinical context could achieve exceptional diagnostic accuracy. Marginal gains of a few percentage points in sensitivity are therefore less important than appropriate integration with clinical assessment.

Potential future applications may benefit from combining routine demographic, clinical, and laboratory results with gene biomarker data. Soltan and colleagues[10] illustrated the power of training non-linear classifiers on routine clinical and laboratory data to screen for COVID-19 in the Emergency Department, and similar non-linear machine-learning techniques should be explored to maximise diagnostic performance. This could overcome common limitations of such studies, eg, limited ethnic diversity in study populations. However, care must be taken to avoid model bias. Ultimately, this approach may only be possible after such technology is in widespread use, due to the large sample sizes required. Bridging the gap between research and clinical practice will finally require randomised clinical trials assessing the real-world clinical usefulness of these novel signatures. Ambitious projects are now underway to bring the first generation of these gene-based diagnostic tools into clinical practice.

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