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# #15764 A host gene signature for diagnosis and risk stratification of acute infection and sepsis at hospital admission: HostDx™ Sepsis

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## Background

Acute infections and sepsis, as leading causes of morbidity and mortality, represent a major burden to healthcare systems. In the UK and US, respectively, 3.5 and 15 million people are assessed annually for acute infection and sepsis in A&E and Emergency Departments.[1,2] Diagnostic procedures to evaluate patients with suspected acute infections or sepsis in the ED are inaccurate or slow.[3] Analysis of host-response signatures using RNA expression has been described for both diagnosis and risk stratification of patients with acute infections or sepsis.[4-7] We here describe the development of HostDx™ Sepsis, a 30-host-gene PCR test that identifies i) the presence of an infection, ii) the type of infection (viral or bacterial), and iii) the severity of the infection using whole blood collected in PAXgene® RNA tubes. The HostDx Sepsis test is being developed as a cartridge-based, sample-to-answer, quantitative assay with turn-around time of less than 60 minutes (Fig. 1).

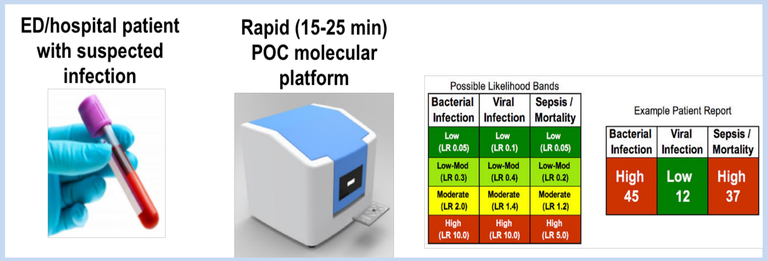


**Figure 1:** HostDx Sepsis workflow, sample processing using rapid POC molecular platform, and potential result readout

## Methods

The generation of validated generalizable gene signatures from heterogeneous microarray and RNAseq cohorts is described in Fig. 2.

Blood samples obtained in RNA-conserving medium (PAXgene) are processed using NanoString® nCounter standard to quantify target mRNAs for HostDx readouts. Rapid multiplex PCR tests are in development.

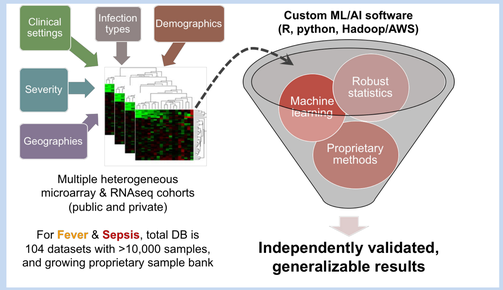


**Figure 2:** Analysis of publicly available microarray and NGS gene expression data sets from cohorts of children and adults with community- and hospital-acquired infection and sepsis allowed for identification of gene signatures that can distinguish between infections and non-infectious inflammation, between viral and bacterial infections, and that can predict the severity of infection.

## Results & discussion

**Presence of bacterial vs. viral infection.** The HostDx Sepsis clinical performance was validated in 38 independent cohorts. Performance for the presence of any bacterial infection in 20 pooled cohorts of 1,057 ED/ICU patients incl. kids/adults from all continents showed a 94% sensitivity and 60% specificity (99% negative predictive value at 15% prevalence) resulting in a negative likelihood ratio (LR-) of 0.1 (Fig. 3). In a prospective clinical study of 96 pediatric ICU subjects LR- was upheld at 0.15[5].

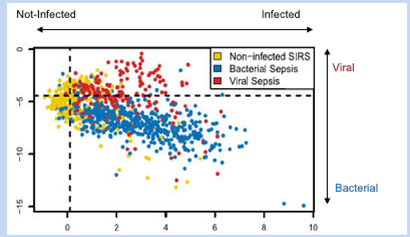


**Figure 3:** Distinction of infectious from non-infectious etiologies, and between bacterial and viral infections

The final HostDx Sepsis version will use a machine learning algorithm to output separate probabilities of bacterial and viral infections (Fig. 1), with expected better diagnostic performance than the initial validation shown here.

**Prediction of infection severity.** In 9 cohorts (471 patients admitted for sepsis/hospital-acquired sepsis) the mean area under the receiver operator characteristics curve (AUROC) was 0.88 for prediction of 30-day mortality, improving AUROCs for laboratory parameters and/or clinical scores including lactate and SOFA by an absolute 10%.

**Development of a PCR format assay.** To demonstrate proof of feasibility, a 7-gene subset signature distinguishing viral from bacterial infections was successfully converted into rapid multiplex PCR assays, with correlation of 0.95 to a NanoString standard based on digital detection and quantification of unique transcripts (Fever Metascores) (Fig. 4).

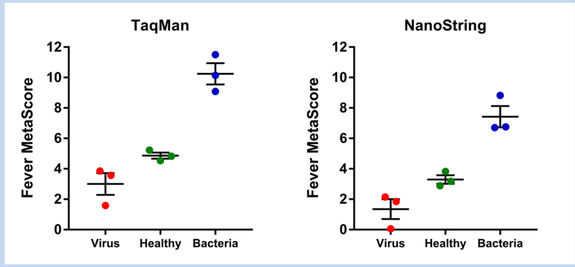


**Figure 4:** Correlation of results between TaqMan PCR (6 TaqMan assays divided into 2 multiplex reactions, one 5-plex/one 3-plex) and Nanostring standard in 9 blood samples of patients with viral or bacterial infections and controls. Correlation for 6-gene comparison: R=0.95

## Conclusion & perspectives

Emergency physicians rely on a battery of tests with low accuracy to diagnose acute infections and sepsis. Host-response signatures have demonstrated high diagnostic and prognostic accuracy. As a rapid (<60 min) triage assay on a molecular platform HostDx Sepsis allows for improved decision making for antibiotics, downstream testing, and level-of-care decisions. Emergency room physicians showed high interest in these tests (Poster #15170).

**References:**

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