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Detection of respiratory pathogens using a novel plasma-based next-generation sequencing assay

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Background: Determining the etiology of lower respiratory tract infection is challenging. Blood cultures are positive in only 5-14% of patients with pneumonia and it can be difficult to distinguish colonization from infection among organisms identified in sputum or endotracheal cultures. The low sensitivity and specificity of current diagnostic tests results in empirical treatment, which leads to antibiotic overuse, particularly in the treatment of hospital-acquired pneumonia. There is a need for better diagnostics to aid in the management of respiratory infections.

Material/methods: We have developed a novel plasma next-generation sequencing (NGS) assay capable of detecting a wide breadth of bacteria, viruses and eukaryotic pathogens. Patients with positive respiratory microbiology tests were identified from a cohort of subjects with suspected infection who had blood culture and paired plasma NGS results. Plasma samples for NGS were obtained on the same day as the blood culture samples. DNA was extracted from plasma and NGS applied. After the removal of sequences associated with human DNA, the remaining reads were aligned to a pathogen reference-sequence database. Relative abundance of each individual microorganism was estimated, and pathogens present at high statistical significance were identified.

Results: A total of 25 patients with a positive respiratory result between 5 days before and 1 day after blood culture were identified. Of these 25 patients, our assay resulted in eleven correct positive calls, identifying the same species as was found in the respiratory test. The results included the confirmation of *Enterobacter aerogenes* (3), *Escherichia coli* (2), *Enterococcus* sp (2), *Moraxella catarrhalis*, *Serratia marcescens*, *Staphylococcus aureus*, and Adenovirus. In contrast, only three patients had

positive blood cultures that matched the respiratory tests. The 14 remaining patients did not match respiratory tests (e.g. sputum or BAL cultures) and had a mix of gram-negative, gram-positive bacteria, and yeast.

Conclusions: We have developed a novel plasma-based NGS assay that can detect pathogen DNA from patients with microbiologically confirmed respiratory infections despite negative blood cultures. This open-ended plasma assay can detect both bacterial and viral causes of respiratory infection and may be a useful aid in the diagnosis of the etiology of lower respiratory tract infection.