2019. Host Gene Expression Signatures for Diagnosis of Acute Respiratory Infections in the Elderly
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Session: 229. Diagnostics: Biomarkers and Novel Approaches
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Background. Despite advances in molecular techniques the etiology of acute respiratory infections (ARIs) is often difficult to determine both at the point of care and/or at the laboratory. Unlike younger individuals aged 25 and 60 years old, viral ARI gene expression in peripheral blood was measured with Affymetrix microarrays. Published viral and bacterial signatures were applied to the data and Bayesian approaches were used to develop novel discriminative models.

Results. We noted a marked decline in signature performance between younger and older individuals in both viral (AUC 0.90 vs. 0.64) and bacterial (AUC 0.91 vs. 0.50) infections. Incorporation of age-related genomic changes was able to restore much of the signature performance in older individuals. When examining the genomic differences driving the drop in signature performance, we found marked perturbations in expression of immunoglobulin genes and pathways driving pathogenic regulatory mechanisms that provide novel insights into an age-related decline in ARI-focused immunity.

Conclusion. Pathogen class-specific host-based gene expression signatures offer great promise as diagnostic tools. However, altered immune responses in vulnerable populations such as the elderly are also manifested at the genomic level and can affect diagnostic signature performance. Age-specific alterations in the components of a diagnostic signature can minimize much of this effect, however this work highlights the need to consider age during biomarker development.

Disclosures. All authors: No reported disclosures.

2020. Concordance of Direct vs. Indirect Pathogen Detection Using the BioFire System
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Background. Polymerase chain reaction (PCR) is a highly sensitive and specific method for pathogen detection. While direct methods enable rapid identification, they are limited by pathogen titer, available assays, or sample matrix. Transcriptomic analysis addresses these limitations by measuring systemic host gene expression changes to infections. The BioFire System uses sample-to-answer multiple PCR that was adapted to detect 42 transcripts differentially expressed during viral and bacterial infections. Here we report concordance between indirect detection of viral respiratory pathogens and the FDA-cleared BioFire Respiratory Panel 2 (RP2).

Methods. Paired nasal pharyngeal swabs and blood samples were obtained by informed consent from patients with suspected acute respiratory illness. Swabs (COPAN FLOQSwab) were collected and stored in viral transport media (BD) for BioFire RP2 testing and peripheral blood samples were collected in PAXgene tubes (Qiagen) for testing with the use of only human response (HR) panel. A logistic regression model was developed to classify viral and nonviral positive samples using normalized quantification cycles for each assay. Probabilities of viral infection for each
2021. An Ultra-Rapid Host Response Assay to Discriminate Between Bacterial and Viral Infections Using Quantitative Isothermal Gene Expression Analysis

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Background. Accurate diagnosis and treatment of bacterial infection is critical for improving patient outcomes. However, over-expression of antibiotics has contributed to C. difficile-infections and to the emergence of antimicrobial resistance. As assessing bacterial infection by culture is slow and molecular pathogen detection is limited in scope, an unmet need remains for a rapid test to differentiate between viral and bacterial infections. We have previously identified a set of 7 host response biomarkers demonstrating an AUROC of 0.91–0.93 for separating bacterial from viral infections across multiple independent cohorts. A clinical in-vitro diagnostic test (IVD) using these markers must be very fast to integrate with physician workflows. Loop-mediated isothermal amplification (LAMP) represents a rapid amplification solution with the potential to meet these needs. We describe an ultra-fast LAMP assay designed to quantitate these markers for applications in point-of-care decision making.

Methods. LAMP primers for gene expression analysis of selected markers with a housekeeping control were designed for mRNA specificity by targeting FIP primers to splice junctions. Assay specificity, sensitivity and linear dynamic range were evaluated using serial dilution of control material. RNA extracted from preserved patient samples was evaluated by LAMP for concordance with Nanostring nCounter data (nCounter).

Results. Iterative optimization of primer design resulted in RT-LAMP assays that selectively amplify target mRNA. Assays demonstrate a linear dynamic range spanning 6 orders of magnitude and a quantitative LOD of about 10 copies. Quantitation of relative expression levels showed good concordance with nCounter data in 10 healthy, 6 viral and 6 bacterial patient samples, with average threshold times of <15 minutes.

Conclusion. Accurate discrimination of bacterial and viral infection can be achieved with a rapid assay. This LAMP strategy could be used on a standard thermal cycler or any quantitative molecular instrument that allows to measure at least eight targets. An IVD test distinguishing between bacterial and viral infections could aid in antimicrobial treatment decisions and thereby minimize over-prescription of antibiotics.

Disclosures. D. Rawling, Inflammatix Inc.: Employee, Salary. W. Nie, Inflammatix Inc.: Employee, Salary. M. Remmel, Inflammatix Inc.: Employee, Salary. M. Eshoo, Inflammatix Inc.: Employee, Salary. J. Romanowsky, Inflammatix Inc.: Employee, Salary. O. Lienfeld, Inflammatix Inc.: Employee, Salary. T. Sweeney, Inflammatix Inc.: Employee, Salary.