

REVOLUTIONARY DIAGNOSTICS – NONTRADITIONAL APPROACHES FOR DEVELOPING BREAKTHROUGH CAPABILITIES AGAINST EMERGING THREATS

A Universal ‘day Zero’ Infectious Disease Testing Strategy Exploiting Crispr-based Sample Depletion And Metagenomic Sequencing

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The lack of preparedness for detecting the highly infectious SARS-CoV-2 pathogen, the pathogen responsible for the COVID-19 disease, has caused enormous harm to public health and the economy. It took ~60 days for the first reverse transcription quantitative polymerase chain reaction (RT-qPCR) tests for SARS-CoV-2 infection developed by the United States Centers for Disease Control (CDC) to be made publicly available. It then took >270 days to deploy 800,000 of these tests at a time when the estimated actual testing needs required over 6 million tests per day. Testing was therefore limited to individuals with symptoms or in close contact with confirmed positive cases. Testing strategies deployed on a population scale at ‘Day Zero’ i.e., at the time of the first reported case, would be of significant value. Next Generation Sequencing (NGS) has such Day Zero capabilities with the potential for broad and large-scale testing. However, it has limited detection sensitivity for low copy numbers of pathogens which may be present. Here we demonstrate that by using CRISPR-Cas9 to remove abundant sequences that do not contribute to pathogen detection, NGS detection sensitivity of COVID-19 is comparable to RT-qPCR. In addition, we show that this assay can be used for variant strain typing, co-infection detection, and individual human host response assessment, all in a single workflow using existing open-source analysis pipelines. This NGS workflow is pathogen agnostic, and therefore has the potential to transform how both large-scale pandemic response and focused clinical infectious disease testing are pursued in the future.

A Universal Day Zero Infectious Disease Testing Strategy Leveraging CRISPR-based Sample Depletion and Metagenomic Sequencing

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