

Distinguishing bacterial infections using a host signature: PERFORM- DIAMONDS studies

Dr Jethro Herberg, Imperial College London

Diagnosis of infectious and inflammatory illness continues to be a major obstacle in the provision of timely and targeted clinical care to febrile children. Only a small proportion of children attending hospital with fever have a bacterial infection, but many are treated with antibiotics. Pathogen diagnostic tests are often too slow to influence initial management decisions, or lack diagnostic accuracy. Furthermore, an increasing proportion of febrile children have an inflammatory illness, but specific diagnostic tests that would allow rapid initiation of anti-inflammatory treatment are lacking.

The PERFORM study (2016-2021) identified the pattern of genes and proteins activated by the host in response to infection, to identify a “host-gene signature” distinguishing bacterial from viral infection. A biobank of samples was generated from 6,000 children attending Hospitals across Europe, the Gambia, Nepal and Taiwan, and detailed molecular pathogen diagnostics were run in parallel with gene expression studies, using a prototype FilmArray device to measure a small host-transcript signature of bacterial and viral illness, and the results highlight the potential for gene expression-based diagnostics. Alongside biomarker discovery and validation work, analysis of clinical data from 38,000 children presenting to ED with fever generated insights into how children with fever are managed across Europe, including antibiotic usage, and identified clinical features that predict serious illness.

The DIAMONDS study (2020-2025, www.diamonds2020.eu) builds on PERFORM, and aims to revolutionise the diagnostic process for infectious and inflammatory diseases by bringing into clinical use diagnosis based on host molecular signatures. DIAMONDS will first expand the range of diseases for which we have diagnostic RNA signatures, to encompass all common infectious and inflammatory diseases and including presentations related to SARS-CoV-2. DIAMONDS will make these signatures available to researchers and clinicians worldwide as a resource for understanding infectious and inflammatory diseases by establishing a European Diagnostic Transcriptomic Library. By the end of the study, DIAMONDS aims to have developed a small molecular signature that enables individual common and important infectious and inflammatory diseases to be distinguished from each other in a single step (Personalised Molecular Signature Diagnosis), together with a test device for PMSD that can be used in the clinic. Together this work aims to provide evidence that a new diagnostic approach using RNA molecular signature diagnosis has clinical value, and is cost-effective.