Evaluating Native and Prosthetic Joint Infections Using Novel Genomic Biomarkers (ELIJA)

Antony Rapisarda[1], Kevin Tetsworth[2], Andrew P Kurmis[3], Richard Hocking[4], William Lindsay Walter[5]
[1]OrthoDx, [2]Royal Brisbane Hospital, [3]Kurmis Orthopaedics, [4]Coral Coast Orthopaedics, [5]Royal North Shore Hospital

INTRODUCTION:

Joint pain is common. In Australia alone there were over 165,000 such emergency department (ED) presentations in the 2019-20 clinical year. Confidently differentiating infective from aseptic causes can be a challenge with conventional methods often invasive and grossly inaccurate. While delays to 'final' diagnosis often result in unnecessary bed occupancy and resource utilization, errors in diagnosis can be catastrophic and costly. What has been lacking is a reliable, highly accurate, and rapid turn-around diagnostic test to aid such patient evaluation.

The current work represents an entirely novel approach to differentiating infective and non-infective causes of acute joint pain utilizing cutting-edge genomic technology. A proof-of-concept study (phase 1) was performed using synovial specimens of 60 patients in 4 even groups designated 'native non-infective,' 'native infected,' 'prosthetic non-infective,' and 'prosthetic infected' as per conventional diagnostic standards. PCR- based analysis permitted identification of distinctive genomic signatures allowing highly-accurate blinded differentiation of the 4 groups. Phase 2 of the study involved a national multi-center trial deliberately recruiting a highly diverse and heterogenous patient cohort to test the novel diagnostic signatures under 'real world' conditions. Adult patients were included from metropolitan, regional, and rural hospitals to mitigate location bias. There were no exclusion criteria based on patient comorbidities

METHODS:

Reference method: standard-of-care diagnosis of joint pain (i.e., 'native non-infective,' 'native infected,' 'prosthetic non-infective,' and 'prosthetic infected') made at initial ED presentation we obtained, as was the 'final' diagnosis recorded at patient discharge. Both diagnoses were made utilizing clinical data available at the time including clinical observations, pathology/blood testing, imaging, and microbiology (i.e., cultures).

Independent discharge evaluation: was provided by study clinicians separate from the index treating team, with access to all available clinical details – this may or may not have shown concordance with the recorded discharge 'final' diagnosis. Where relevant, the MSIS (Musculoskeletal Infection Society) scoring2 matrix was used to evaluate the likelihood of prosthetic joint infection (PJI). For study purposes, this retrospective diagnosis was deemed the 'gold standard' for test comparison.

Genomic Signature Evaluation: our RT-qPCR-based test allows quantification of the expression of 7 distinct gene signatures associated with the host immune response to infection and inflammation. Analysis allows determination of a binary likelihood of infection correlating with a very high (>95%) negative predictive value (NPV) (result 1) or a lower (>85%) positive predictive value (PPV) (result 2).

RESULTS:

Our results show highly accurate and reliable discrimination between 'infective' and 'non-infective' drivers for acute joint pain. Figure 1 shows the genomic signature analysis of each of the 4 cohorts showing highly statistically significant diagnostic capacity. When pooled into 'infectious' versus 'inflammatory' etiologies, Figure 2 shows the genomic signature analysis results showing signature diversity for infected cases (this highlights the poor pre-test probability assessment of conventional standards).

Our findings shown that initial (i.e., ED presentation) diagnoses and subsequent episode-of-care 'discharge' diagnoses using conventional diagnostic approaches are grossly inaccurate and unreliable. The impact on patients and healthcare resource allocation of delayed or incorrect differentiation between infective and inflammatory causes of acute joint pain can be considerable. With the accepted gold standard of aspirate-derived cultures having high false negative rates and lengthy processing times (sometimes up to 2 weeks for 'final' culture results) the novel test – with definitive diagnosis achievable within hours – has immediate clinical appeal. These results suggest that SynvIchor can offer markedly increased diagnostic accuracy, with rapid result availability, potentially allowing early instigation of definitive treatment and/or bed utilisation.

DISCUSSION AND CONCLUSION:

Based on state-of-the-art PCR genomic analyses, the novel genomic signature test provides a rapid diagnostic differentiation between infective and inflammatory (i.e., non-infective) causes of acute joint pain – for both native and prosthetic joints. The results of phase 1 and 2 studies suggest levels of accuracy and predictive values far exceeding conventional (unreliable) diagnostic standards which rely on interpretation of a difficult constellation of clinical and biochemical parameters. Application of this technology to diagnostic pathways for adult patients shows considerable promise with regard to time and resource savings, avoidance of unnecessary ED bed block and hospital admissions – all above and beyond a reduced patient burden permissible through accurate and early definitive diagnosis.

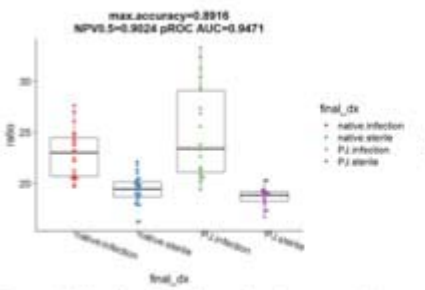

Figure 1: ELIJA cohort divided into each subgroup evaluating infectious vs non-infectious joint inflammation

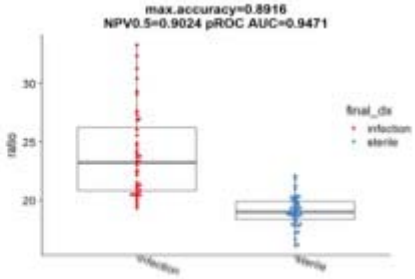

Figure 2: ELIJA cohort combined to pool infective and non-infectious vs non-infectious joint inflammation