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Correcting the mischaracterization of the current utility nucleic acid-based

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The recent JBJS article by McLure et al. “Application of Nucleic Acid-Based Strategies to Detect Infectious Pathogens in Orthopaedic Implant-Related Infection” reflects on the inadequacy of culture techniques for the diagnosis of infection and reviews DNA/RNA detection molecular techniques which have much higher sensitivity for microbial pathogen identification. The authors cite key statistics on failure for current standards of care to manage infection, especially relating to culture-negative infection, in a variety of orthopedic contexts (e.g., implants, periprosthetic joint and fracture-related infection). A central argument made by the authors is that nucleic acid (NA) based methods can improve our capability to detect pathogens and, presumably, be used to improve patient outcomes impacted by infection. However, a primary message from the remainder of the article is that nucleic acid (NA) approaches should not be used because their sensitivity may result in false positives (operating room/laboratory contamination/non-infecting species present in the joint) and because clinicians first need to have a detailed technical understanding of the process leading to molecular-based clinical reports, to which guidelines are proposed wide in scope yet limited in depth.

Given the high culture negative rates cited (e.g., as high as 30-50% in infected cases) and associated poor outcomes, it is difficult to understand the apparent call to embargo NA molecular approaches in fear of false positives and when there is such a large margin for improvement in failure rates. In particular, the authors take aim at poorly defined ‘black-box’ methods and advise against commercial entities operating in the space. Representing MicroGenDX and concerning authors proposed guidelines for NGS, it is paramount to recognize that laboratories such as ours operate under College of American Pathologist (CAP) accreditation and Clinical Laboratory Improvement Amendments (CLIA) certifications. CLIA certification requires the implementation and inspection of technical approaches to ensure accurate reporting based on molecular approaches (e.g., inclusion of controls, defined thresholds for reporting, database curation, reproducibility). Furthermore, our CAP Proficiency Scores have averaged 99.6% over the past 12 years. By failing to discuss these rigorous validations, the article mischaracterizes the quality of molecular diagnostics commercially available.

The article states that molecular methods should not be used as “there are important technical and logistical hurdles involving the infrastructure needed for the analysis of NA-based diagnostic tools, particularly NGS. Furthermore, the time required from the operating room to the data analysis and robust interpretation needed to inform clinical decision-
"Making is currently impractically long.” This statement is simply incorrect for a few reasons: first, it again ignores that commercial infrastructure is already in place and compliant with CAP and CLIA validation standards. Second, the time required from operating room to clinical decision-making is not currently impractically long. We routinely provide qPCR results within 24 hours of receiving samples and 3 days for comprehensive NGS testing. This should be compared to culture diagnostics which may range from 2-14 days to obtain an actionable or final negative result. Lastly, NGS is increasingly affordable at scale and, from an economic standpoint, is likely now cheaper than hospital-based culture. While we are certainly interested in further improving the turn around time and interpretability of our findings, the article does not well acknowledge that many of these technical and logistical hurdles are readily solved through the use of a central laboratory.

Finally, recommending that clinicians become trained in the myriad of subject areas surrounding microbial sequence-based profiling including laboratory processes, sequencing applications, bioinformatic and statistical procedures so they can interpret the molecular data is simply unrealistic given clinician time constraints and, again, negates the benefits afforded by validated high complexity tests. The unfounded recommendations against using NGS in clinical practice presented in this article will setback treatment advances which can reduce the devastating impacts of failed infection management.

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Conflict of Interest:

The authors of this letter are consultants or employees of MicroGenDX.