Diagnosis of Periprosthetic Joint Infection: The Potential of Next-Generation Sequencing

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Background: Next-generation sequencing is a well-established technique for sequencing of DNA and has recently gained attention in many fields of medicine. Our aim was to evaluate the accuracy of next-generation sequencing in identifying the causative organism(s) in patients with periprosthetic joint infection.

Methods: In this prospective study, samples were collected from 65 revision arthroplasties (39 knees and 26 hips) and 17 primary arthroplasties (9 hips and 8 knees). Synovial fluid, deep tissue, and swabs were obtained at the time of the surgical procedure and were shipped to the laboratory for next-generation sequencing. Deep-tissue specimens were also sent to the institutional laboratory for culture. Sensitivity and specificity were calculated for next-generation sequencing, using the Musculoskeletal Infection Society (MSIS) definition of periprosthetic joint infection as the standard.

Results: In 28 revisions, the cases were considered to be infected; cultures were positive in 17 cases (60.7% [95% confidence interval (CI), 40.6% to 78.5%]), and next-generation sequencing was positive in 25 cases (89.3% [95% CI, 71.8% to 97.7%]), with concordance between next-generation sequencing and culture in 15 cases. Among the 11 cases of culture-negative periprosthetic joint infection, next-generation sequencing was able to identify an organism in 9 cases (81.8% [95% CI, 48.2% to 97.7%]). Next-generation sequencing identified microbes in 9 (25.0% [95% CI, 12.1% to 42.2%]) of 36 aseptic revisions with negative cultures and in 6 (35.3% [95% CI, 14.2% to 61.7%]) of 17 primary total joint arthroplasties. Next-generation sequencing detected several organisms in most positive samples. However, in the majority of patients who were infected, 1 or 2 organisms were dominant.

Conclusions: Next-generation sequencing may be a useful adjunct in identification of the causative organism(s) in culture-negative periprosthetic joint infection. Our findings suggest that some cases of monomicrobial periprosthetic joint infection may have additional organisms that escape detection when culture is used. Further study is required to determine the clinical implications of isolated organisms in samples from patients who are not thought to be infected.

Level of Evidence: Diagnostic Level I. See Instructions for Authors for a complete description of levels of evidence.

Periprosthetic joint infection is a serious complication following total joint arthroplasty, with broad implications[1-4]. Perhaps the most challenging facet of managing periprosthetic joint infection is reaching a prompt and definitive diagnosis, with identification of the causative organism[5,6]. In up to 50% of periprosthetic joint infection cases, cultures fail to isolate the infecting organism[7-11]. Negative cultures pose a challenge as the lack of identity of the infecting organism leads to the use of empiric antimicrobial therapy, with the potential to miss covering the true infecting pathogen, and negative cultures have been associated with a 4.5 times increased risk of reinfection in comparison with culture-positive cases[6,12].

We have a long-standing interest in employing molecular techniques for the diagnosis of periprosthetic joint infection[13]. Our initial studies using multiplex polymerase chain reaction (PCR) revealed that the molecular techniques for isolation of the infecting organism held potential[14]. However, this technique demonstrated a false-positive rate of 88%, and in other studies, it did not outperform culture, with a sensitivity of 81%[14,15]. Other techniques such as broad-range PCR are limited

Disclosure: There was no external funding received for this study. One author of this study (J.P.) has ownership interest in MicroGen Dx, the laboratories that were used for next-generation sequencing of samples. On the **Disclosure of Potential Conflicts of Interest** forms, *which are provided with the online version of the article*, one or more of the authors checked "yes" to indicate that the author had a relevant financial relationship in the biomedical arena outside the submitted work and "yes" to indicate that the author had a patent and/or copyright, planned, pending, or issued, broadly relevant to this work (http://links.lww.com/JBJS/E507).

in the output that they can produce, as 70% of the amplicons (the fragment of DNA that is amplified as the result of a PCR) must be of a single sequence to generate a meaningful result. Additionally, only 1 organism can be detected at a time, unless sequencing of several clones is to be performed[16]. Broad-range PCR has also shown a limited sensitivity ranging from 67.1% to 73.3% and hence does not hold a clear advantage over culture[9,17,18].

Next-generation sequencing is capable of sequencing all DNA present in a given sample, giving a more complete picture of the microbial profile present[19]. Next-generation sequencing has been shown to identify pathogens in patients with neurological infections and systemic sepsis[20,21]. To our knowledge, there have been no studies evaluating next-generation sequencing for identifying infectious organisms in periprosthetic joint infection. In recent years, with the rapid decline in the cost of sequencing, we have been exploring the role of next-generation sequencing in diagnosing periprosthetic joint infection. A prospective study was designed to evaluate the role of next-generation sequencing in diagnosing periprosthetic joint infection, and culture-negative periprosthetic joint infection in particular.

Materials and Methods

Following institutional review board approval, consecutive patients undergoing revision arthroplasty from June to November 2016 by a single surgeon were prospectively enrolled in this study. All patients undergoing revision total knee arthroplasty or revision total hip arthroplasty were eligible for recruitment. In addition, a cohort of patients undergoing primary arthroplasty was also included, provided that there had been no previous surgical procedure performed in the index joint.

Preoperative Assessment

Patients undergoing revision arthroplasty were screened preoperatively according to institutional protocols, including obtaining blood for measurement of the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)[22]. Joints were aspirated at the discretion of the treating surgeon, if it was thought that a definitive diagnosis had not been reached. In these cases, synovial fluid was assessed for white blood-cell count, white blood-cell differential, and leukocyte esterase, and culture results. Preoperative antibiotics were withheld 2 weeks prior to the surgical procedure until samples were collected for culture and next-generation sequencing in all revision arthroplasty cases.

Intraoperative Sample Collection

Synovial fluid, deep-tissue specimens, and swabs from the medullary canals were obtained for all patients at the time of the surgical procedure. Synovial fluid was obtained in a sterile fashion, using an 18-gauge needle prior to arthrotomy. Deep-tissue specimens were taken from the synovium and medullary canals. Swabs of the acetabulum and the medullary canal of the femur were obtained from hips, and swabs from the medullary canal of the femur and tibia were obtained in knees. All samples were promptly stored in sterile containers and were shipped overnight at an ambient temperature to the laboratory (MicroGen Dx Laboratories) for next-generation sequencing. Deep-tissue specimens were also sent to the institutional laboratory for routine culture, including aerobic and anaerobic bacterial cultures, fungal cultures, and acid-fast bacillus cultures. Samples for culture were not collected from primary arthroplasty cases.

Next-Generation Sequencing

Upon arrival at the laboratory, the first step was DNA extraction and performance of a quantitative PCR to determine the bacterial burden present in the sample (see Appendix). The second step was the next-generation sequencing assay. Initially, the DNA was amplified via PCR using forward and reverse primers flanking the region of interest. For the detection of bacterial and fungal species, the 2 regions of interest are the 16S and internal transcribed spacer regions, which are highly conserved regions of the ribosomal ribonucleic acid (rRNA) gene in bacteria (16S) and fungi (internal transcribed spacer)[23,24]. Following the amplification process, the amplified DNA was pooled on the basis of amplification strength. Sample DNA was then loaded onto beads for the emulsion polymerase chain reaction. Emulsion PCR was then carried out to generate high levels of the sample DNA for next-generation sequencing. The sample was then sequenced on the Ion Torrent Personal Genome Machine (PGM) system sequencing platform (ThermoFisher Scientific). The Ion Torrent sequencer relies on the principle that a hydrogen ion is released each time that a nucleotide is incorporated into the DNA, thus generating a change in pH. This change in pH corresponded with the number of nucleotides incorporated into the growing sequence, which was then detected by the sequencer. The final step before data analysis consisted of denoising, to remove short sequences that may interfere with the interpretation of the data generated[25]. The sequence reads generated were then compared against a curated National Institutes of Health (NIH) GenBank database. The comparison with the database was performed using USearch 7, and an agreement of at least 90% between the sequence reads and the database was necessary.

Antimicrobial Therapy

For all patients with a positive culture at the time of the surgical procedure, antimicrobial therapy was administered intravenously to cover organisms in accordance with culture results. For patients with culture-negative periprosthetic joint infection, intravenous antimicrobial therapy was initiated and was continued. Our infectious disease physicians considered the findings of the next-generation sequencing and tailored the antimicrobial therapy on the basis of the next-generation sequencing findings. The outcome of all patients with regard to infection control was evaluated.

Data and Statistical Analysis

Power analysis was conducted to determine the sample size. Using prior institutional data on molecular techniques[14], we

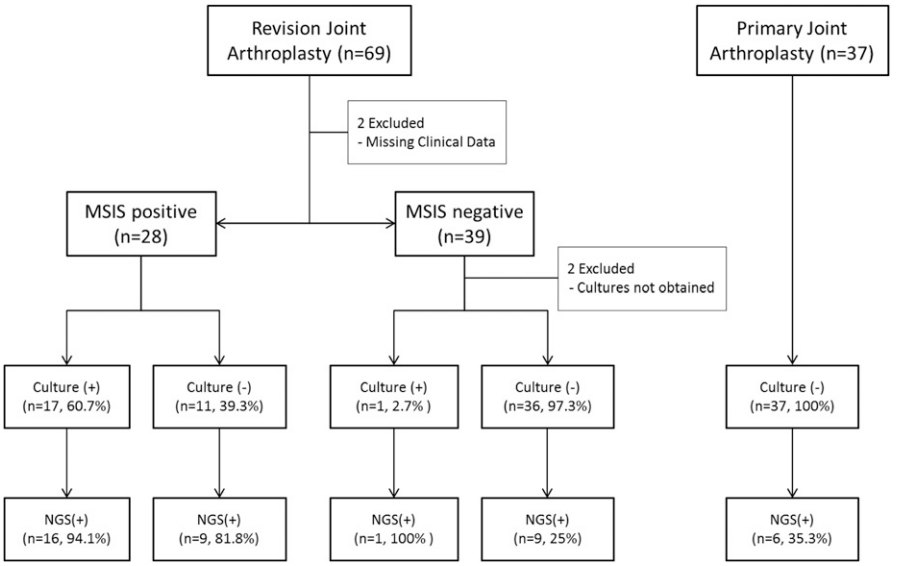

Fig. 1

Flowchart detailing the procurement of patient samples. Culture (+) = culture-positive, culture (-) = culture-negative, and NGS(+) = next-generation sequencing-positive.

used a 30% difference in sensitivity between next-generation sequencing and culture, a power of 80%, and an alpha error of 0.05, and a sample size of 55 patients was determined.

Patients were categorized as infected or aseptic using the Musculoskeletal Infection Society (MSIS) criteria[26]. These 2 groups were further subdivided on the basis of whether culture results were positive. The Student t test was used to calculate differences in continuous variables between groups, and chi-square analysis was used to measure differences in categorical variables. Sensitivity and specificity were calculated and were compared between next-generation sequencing and culture using the McNemar test. We examined the peak percentage of

TABLE I Demographic Characteristics and MSIS Criteria for Revision Cases Included in the Study (N = 65)*

Characteristic	MSIS-Positive (N = 28)	MSIS-Negative (N = 37)	P Value
Age* *(yr)*	63.3 ± 11.2	64.7 ± 10.4	0.62
Sex†			0.79
Male	19 (67.9%)	23 (62.2%)	
Female	9 (32.1%)	14 (37.8%)	
Body mass index* *(kg/m²)*	32.6 ± 7.0	30.1 ± 6.2	0.14
Joint†			0.45
Knee	15 (53.6%)	24 (64.9%)	
Hip	13 (46.4%)	13 (35.1%)	
MSIS criteria			
Major†			
Sinus tract	4 (14.3%)	0 (0.0%)	0.03
2 culture-positive	17 (60.7%)	0 (0.0%)	<0.0001
Minor*			
Serum ESR *(mm/hr)*	66.0 ± 29.6	20.5 ± 15.3	<0.0001
Serum CRP *(mg/dL)*	8.6 ± 8.9	0.6 ± 0.8	<0.0001
Synovial fluid white blood-cell count *(cells/μL)*	45,201.2 ± 68,766.3	1,379.3 ± 1,952.2	0.03
Synovial fluid polymorphonuclear neutrophils *(%)*	89.2 ± 8.5	38.4 ± 15.8	<0.0001

*The values are given as the mean and the standard deviation. †The values are given as the number of cases, with the percentage in parentheses.

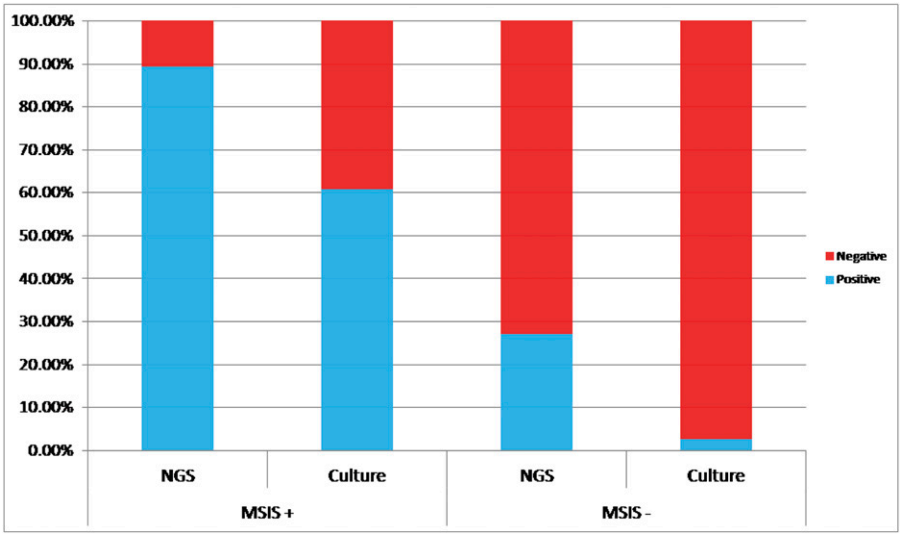

Fig. 2

Bar graph showing the comparison between next-generation sequencing (NGS) and culture results based on MSIS criteria. + = positive, and - = negative.

an individual organism in a next-generation sequencing sample as a predictor for infection using the area under the receiver operating characteristic (ROC) curve (AUC). Concordance between culture and next-generation sequencing was also examined, and all cases with at least 1 positive intraoperative culture were considered culture-positive. Given that next-generation sequencing detects all organisms in a given sample, the detection of multiple species is not an infrequent occurrence. Complete concordance was defined as next-generation sequencing picking up all organisms identified on culture. If culture detected multiple organisms that were undetected on next-generation sequencing, then any overlap with regard to organisms identified was considered to be partial concordance. If next-generation sequencing and culture identified completely different bacteria, this was considered discordant.

Results

Overall, samples were obtained from 78 patients undergoing 86 procedures. Two patients were excluded because of insufficient data to allocate them as infected or aseptic. Another 2 patients were excluded because a culture had not been obtained. Sixty-five revision arthroplasties (39 knees and 26 hips) and 17 primary arthroplasties were included in the analysis (Fig. 1). Overall, 28 samples were classified as infected and 37 were considered aseptic (Table I). Cultures were positive in 17 infected cases (60.7% [95% confidence interval (CI), 40.6% to

TABLE II Infection Status of All Patients at a 6-Month Follow-up According to the Next-Generation Sequencing Result*

Infection Status	No. of Patients			
	Infection-Free	Retained Spacer	Reinfection	Lost to Follow-up
Culture-positive infections (n = 17)				
Positive next-generation sequencing	7	5	3	1
Negative next-generation sequencing	0	0	0	1
Culture-negative infections (n = 11)				
Positive next-generation sequencing	5	3	1	0
Negative next-generation sequencing	1	0	1	0
Aseptic revisions (n = 37)				
Positive next-generation sequencing	9	NA	1	0
Negative next-generation sequencing	23	NA	4	0
Primary arthroplasties (n = 17)				
Positive next-generation sequencing	6	NA	0	0
Negative next-generation sequencing	11	NA	0	0

*NA = not applicable.

78.5%]) and in 1 aseptic revision (2.7% [95% CI, 0.1% to 14.2%]). Next-generation sequencing was positive in 25 infected cases (89.3% [95% CI, 71.8% to 97.7%]) and in 10 aseptic revisions (27.0% [95% CI, 13.8% to 44.1%]) (Fig. 2). A 6-month follow-up was obtained for all patients and is displayed in Table II.

Culture-Positive Infections

The first analysis was to examine the concordance between culture and next-generation sequencing in patients who were infected and had positive cultures (n = 17). There was 1 case of *Escherichia coli*-positive cultures in which next-generation sequencing did not detect the organism. Next-generation sequencing was positive in the remaining 16 cases. Of these, 15 cases showed complete concordance between next-generation sequencing and culture. In 6 cases, next-generation sequencing had detected several other organisms. Yet, in most cases, 1 organism predominated, making up >90% of the sample (Fig. 3). Two patients were identified as being infected with *Staphylococcus aureus* by culture, whereas next-generation sequencing had detected *S. lugdunensis*. These cases were considered to be completely concordant, given the morphological and clinical similarities between the 2 species[27,28]. One case was partially concordant, where cultures were positive for *Klebsiella pneumoniae, S. epidermidis,* and *S. aureus,* but next-generation sequencing detected only *S. epidermidis.* There were 2 cases of discordance related to bacterial resistance. In 1 of them, next-generation sequencing detected the mecA gene and classified the organisms as methicillin-resistant *S. aureus* (MRSA) and culture identified the organism as methicillin-sensitive *S. aureus* (MSSA). In the other case, next-generation sequencing detected MSSA and culture was positive for MRSA.

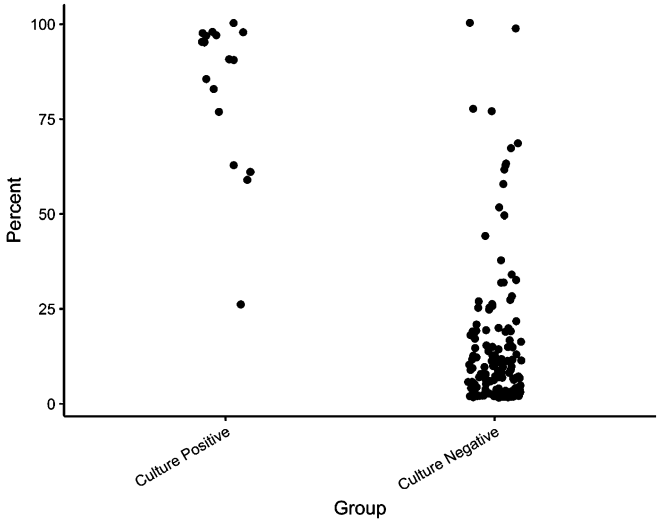

Fig. 3

Plot showing the percentage of bacteria by species in the sample of patients who had positive cultures compared with patients who had negative cultures. In patients who were clearly infected (with >2 positive cultures), 1 or 2 organisms were predominant in the majority of cases and they composed a high percentage of the sample.

Culture-Negative Infections

There were 11 patients (39.3% [95% CI, 21.5% to 59.4%]) classified as MSIS-positive who had negative cultures. Next-generation sequencing was able to identify an organism in 9 cases (81.8% [95% CI, 48.2% to 97.7%]) and these included known pathogens such as *S. epidermidis*, *Streptococcus canis*, *Burkholderia cepacia*, and *Pseudomonas stutzeri*[29]. The remaining 2 patients with negative next-generation sequencing results were classified as infected on the basis of the presence of sinus tracts. Notably, in both cases, both next-generation sequencing and culture failed to isolate an infecting organism.

Aseptic Revisions

One patient who did not meet the MSIS criteria for periprosthetic joint infection had a single positive "very light" growth of Coryneform bacteria on culture, which was assumed to be a contaminant. Next-generation sequencing identified *Propionibacterium acnes* in the same patient.

There were 36 patients undergoing revision arthroplasty who did not meet the criteria for periprosthetic joint infection and had negative cultures. Next-generation sequencing isolated microbial DNA in 9 cases (25.0% [95% CI, 12.1% to 42.2%]). In all cases, >3 different bacteria were present in the sample. *P. acnes* was the most prevalent organism in this group, positive in 6 cases. There was 1 case positive for fungi.

Primary Arthroplasty

Patients undergoing primary knee arthroplasty (n = 8) and primary hip arthroplasty (n = 9) were also examined. Next-generation sequencing identified an organism in 6 cases (35.3% [95% CI, 14.2% to 61.7%]). All positive samples originated from tissue, and swabs and fluid were all negative. Many of the positive results were organisms originating from phyla shown to be part of the microbiome[30]; in 3 cases, the predominant organism originated from the Proteobacteria phylum, representing 98%, 66%, and 50% of the sample. In other samples, organisms from the Fusobacteria and Actinobacteria phyla were detected with high percentages.

Performance of Next-Generation Sequencing and Correlation with Cultures

In patients who were clearly infected (>2 positive cultures), 1 or 2 organisms were predominant in the majority of cases. However, in patients presumed to be not infected, next-generation sequencing detected a large number of organisms, with no predominant species. There was a significant difference ($p < 0.001$) in the mean number of pathogens detected by next-generation sequencing between the infected group (4.7 pathogens) and the noninfected group (8.9 pathogens).

The sensitivity and specificity of next-generation sequencing were compared with those of culture (Table III). Next-generation sequencing was more sensitive at 89.3% compared with culture at 60.7%, with a difference of 28.6% (95% CI, 9.1% to 48.0%; $p = 0.01$), but next-generation sequencing was less specific at 73.0% than culture at 97.3%, with a difference of 24.3% (95% CI, 4.9% to 43.8%; $p = 0.003$), in

TABLE III Sensitivity and Specificity for the Detection of Any Bacteria and ≥59.5% of a Single Organism on Next-Generation Sequencing Compared with Organism Isolation by Culture

	Infected* (N = 28)	Noninfected* (N = 37)	Sensitivity†	Specificity†
Next-generation sequencing				
Detection of any bacteria			89.3% (71.77% to 97.73%)	73.0% (55.88% to 86.21%)
Any bacteria	25	10		
None	3	27		
Detection of a single organism representing ≥59.5% of bacteria present			71.4% (51.33% to 86.78%)	94.6% (81.81% to 99.34%)
Yes	20	2		
No	8	35		
Culture				
Organism isolation			60.7% (40.58% to 78.50%)	97.3% (85.84% to 99.93%)
Culture-positive	17	1		
Culture-negative	11	36		

*The values are given as the number of patients. †The values are given as the estimate, with the 95% CI in parentheses.

detecting any presence of bacteria in the sample. Setting a threshold of 59.5% for the percentage of bacteria belonging to a single species the next-generation sequencing sample showed the highest AUC value (0.85). Although this improved specificity to 94.6% (95% CI, 81.81% to 99.34%), it decreased sensitivity to 71.4% (95% CI, 51.33% to 86.78%).

Discussion

This study investigating the utility of next-generation sequencing in diagnosing periprosthetic joint infection reveals several findings. First, next-generation sequencing was found to be capable of identifying an organism in almost 90% of patients with periprosthetic joint infection (as determined by the MSIS criteria) compared with culture with a sensitivity of 60.7%. Second, and more importantly, next-generation sequencing detected a potential pathogen in approximately 80% of culture-negative periprosthetic joint infections. Third, next-generation sequencing had 88.2% concordance with culture at our institution. However, next-generation sequencing was positive in approximately 35% of primary arthroplasties and 25% of revision of arthroplasties, in which the patients were presumed to be noninfected. Given that the prevalence of culture-negative periprosthetic joint infection is 27% to 55%, our results indicate that next-generation sequencing may be useful as an adjunct in the diagnosis of culture-negative periprosthetic joint infection[7-11]. Given the high rate of positive next-generation sequencing results in both primary and aseptic revision arthroplasties, the pre-test probability determined by the clinical picture and other laboratory investigations should be closely examined when interpreting the results of next-generation sequencing.

Infections associated with implants are known to exist as biofilm, which interferes with the isolation of the infecting organism using culture[31]. In the last several years, there has been a drive to identify a biomarker for periprosthetic joint infection, such as alpha-defensin and leukocyte esterase. Although these biomarkers may provide important diagnostic information, they simply indicate the presence or absence of infection with no identification of the causative organism[32]. Several investigators have evaluated different techniques to remedy this problem. Xu et al.[33] examined specimens from 25 joint aspirations or revision total joint arthroplasties for suspected periprosthetic joint infection. They used broad-range PCR aimed at the 16S rRNA gene and then cloning of the amplicon and sequencing of a limited number of clones. In that study, an organism was detected in only 11 patients, 5 of whom had negative cultures. We previously reported a high detection rate of culture-negative periprosthetic joint infection with the use of PCR-based electron spray ionization time-of-flight mass spectrometry[14]. That technique identified an organism in all infected cases, including 4 of 5 culture-negative periprosthetic joint infections. However, it had also detected an organism in many revisions presumed to be aseptic (50 of 57). In the present study, next-generation sequencing was able to detect a pathogen in almost 90% of cases and in 81.8% of culture-negative cases. It also showed improved specificity. In 9 of 11 culture-negative periprosthetic joint infection cases, next-generation sequencing detected multiple organisms (≥3). Given the quantitative results that the test can provide, better insight can be obtained into these supposedly polymicrobial infections. Treatment of polymicrobial infection has been shown to have lower success rates compared with monomicrobial infection[34], and a better understanding of these infections is needed to determine if they are truly polymicrobial in nature, or rather an infection with a dominant organism with other organisms acting in concert.

Earlier studies have shown bacteria to be present in presumed aseptic revisions in up to 77% of cases[35]. Some of these may be subclinical infections[36,37], and other organisms

may reflect part of the microbiome and are unlikely to cause an infection. Next-generation sequencing permits the generation of thousands of individual sequences from a single broad-range PCR. This provides comprehensive information on the organisms occupying the joint and thus a better understanding of the joint microbiome. In approximately one-third of supposedly noninfected revision cases in this study, next-generation sequencing had detected bacteria. In many of these cases, *P. acnes* was the predominant organism. Propionibacterium is known to cause periprosthetic joint infection, particularly in the shoulder, and typically follows an indolent postoperative course[38], yet its presence in cases of aseptic loosening is not fully understood[39]. However, other organisms isolated in our study were mostly microbiota and the relative contribution of each organism was low. In 1 aseptic case, next-generation sequencing detected an organism that resulted in the subsequent failure of that arthroplasty, with culture identifying the same infecting organism at failure. It is plausible that, with further follow-up, we may witness the failure of additional cases with the same organism that was identified by next-generation sequencing. These results support the current practice of an infectious work-up prior to all revision procedures[40].

Several molecular diagnostics methods have been suggested to address the issue of diagnosing biofilm-associated infections[8,9,13,41,42]. The main issue with these methods relates to the uncertainties of whether identified organisms are actually resident in the joint, contaminants, or true pathogens[43]. In the current study, an organism was identified in 6 of 17 patients undergoing primary arthroplasty, compared with 5 of 7 such patients having a positive result in our previous study using mass spectrometry, and this reduced rate of false-positives is certainly promising[14]. The isolation of an organism in a patient with an arthritic joint and no prior operation should not be dismissed. Several areas of the body have been shown to have distinct microbiomes, and dysbiosis of these intrinsic microbial communities has been postulated to contribute to the pathogenesis of conditions thought to be noninfectious in nature, such as degenerative disc disease and breast cancer[30,44,45].

The main limitation of this current study was the sample size, which precludes us from making any generalizable conclusions. Nevertheless, the numbers are sufficiently high to show the utility of next-generation sequencing in isolating the infecting organism in the majority of the culture-negative infections. No molecular methods were concurrently tested along with next-generation sequencing; thus, we were not able to make direct comparisons with other techniques. However, culture remains the gold standard for isolation of the infecting organism and hence was used as a comparison. Our follow-up data on patients were limited; therefore, we could not reach any conclusion with regard to some important findings such as the clinical relevance of aseptic revisions that were positive in next-generation sequencing. Finally, our interpretation of data could be affected by limited understanding of the microbiome. Thus, we considered aseptic patients with positive next-generation sequencing as false positives and primary arthroplasties as negative controls, which may prove to be an erroneous assumption. A better understanding of the native organism profile in the joint could help to further interpret our findings. Future studies should focus on this group of patients in the long term. It is plausible that the majority of periprosthetic joint infections may be polymicrobial in nature, and this may lead to the design of different treatment strategies for these patients in the future.

Appendix

eA A description of the DNA extraction and real-time PCR is available with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/E508). ■

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