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Nationwide Results of Microorganism Antigen Testing as a Component of Preoperative Synovial Fluid Analysis

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Investigation performed at the Rothman Orthopaedic Institute, Philadelphia, Pennsylvania, and Zimmer Biomet, Warsaw, Indiana

Background: Antigen immunoassays to detect synovial fluid (SF) microorganisms have recently been made available for clinical use. The purpose of this study was to determine the sensitivity and specificity of an SF microorganism antigen immunoassay detection (MID) panel, evaluate the panel's capability to detect microorganisms in the setting of culture-negative periprosthetic joint infection (PJI), and determine diagnostic predictive values of the MID panel for PJI.

Methods: This study included 67,441 SF samples obtained from a hip or knee arthroplasty, from 2,365 institutions across the United States, submitted to 1 laboratory for diagnostic testing. All data were prospectively compiled and then were analyzed retrospectively. Preoperative SF data were used to classify each specimen by the International Consensus Meeting (2018 ICM) definition of PJI: 49,991 were not infected, 5,071 were inconclusive, and 12,379 were infected. The MID panel, including immunoassay tests to detect Staphylococcus, Candida, and Enterococcus, was evaluated to determine its diagnostic performance.

Results: The MID panel demonstrated a sensitivity of 94.2% for infected samples that yielded positive cultures for target microorganisms (Staphylococcus, Candida, or Enterococcus). Among infected samples yielding positive cultures for their respective microorganism, individual immunoassay test sensitivity was 93.0% for Staphylococcus, 92.3% for Candida, and 97.2% for Enterococcus. The specificity of the MID panel for samples that were not infected was 98.4%, yielding a false-positive rate of 1.6%. The MID panel detected microorganisms among 49.3% of SF culture-negative infected samples. For PJI as a diagnosis, the positive predictive value of the MID panel was 91.7% and the negative predictive value was 93.8%. Among MID-positive PJIs, 16.2% yielded a discordant cultured organism instead of that detected by the antigen test.

Conclusions: SF microorganism antigen testing provides a timely adjunct method to detect microorganisms in the preoperative SF aspirate, yielding a low false-positive rate and enabling the detection of a microorganism in nearly one-half of SF culture-negative PJIs.

Level of Evidence: Prognostic Level II. See Instructions for Authors for a complete description of levels of evidence.

The diagnosis of periprosthetic joint infection (PJI) is dependent on 2 main conceptual principles: (1) the identification of a substantial host immune response (laboratory inflammatory tests) and (2) the detection of a microorganism. Ideally, clinical PJIs can be confirmed when a microorganism is detected in the setting of an anti-pathogen host response, confirming both key tenets of clinical infection. Throughout the history of arthroplasty, microbiological culture has been considered the gold standard to identify the infecting microorganism with a specificity of >95%; however, preoperative synovial fluid (SF) culture has only 60% to 70% sensitivity[1-3]. Although culture of tissue obtained intraoperatively

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJS/H398).

TABLE I Study Inclusion and Exclusion Criteria*

Inclusion criteria	Hip or knee arthroplasty source
	SF culture completed
	MID panel completed
	SF-CRP, SF-WBC, SF-PMN% completed
	Alpha-defensin test completed
Exclusion criteria	Poor-quality SF sample
	Sample received >5 days after aspiration

*SF-WBC = SF white blood-cell count, and SF-PMN% = SF polymorphonuclear cell percentage.

can increase the detection of a microorganism[3,4], results are not available for up to 14 days postoperatively, rendering them irrelevant to preoperative surgical decision-making. Although the field of arthroplasty has made great gains in developing standards to identify the typical host response consistent with PJI[5,6], the development of new pathogen identification techniques has been challenging. Immunoassays have the advantage of being rapid, cost-efficient, and standardized in the field of diagnostics[7].

Recently, an SF microorganism antigen immunoassay detection (MID) panel was introduced to detect antigen from the genera of Staphylococcus, Candida, and Enterococcus. These tests use technology similar to a rapid strep test for identifying *Streptococcus pyogenes* in cases of pharyngitis. Each MID test contains antibodies to microorganisms from their respective genus and therefore is not species-specific. MID panel testing of SF from cases of possible PJI has 2 potentially high-value roles: (1) timely pathogen detection to complement traditional SF culture, and (2) pathogen detection among culture-negative PJIs.

The purpose of this study was to determine the sensitivity and specificity of an SF MID panel, evaluate the panel's capability to detect microorganisms in the setting of culture-negative PJI, and determine diagnostic predictive values of the MID panel for PJI.

Materials and Methods

SF Samples, Laboratory Testing, and Diagnosis

All data were collected prospectively on a daily basis, using rigorous data entry methodology and error checking in the course of testing clinical SF specimens submitted to 1 clinical laboratory specializing in SF diagnostic testing (CD Laboratories, Zimmer Biomet), which is certified by the Clinical Laboratory Improvement Amendments (CLIA) to perform testing in bacteriology, general immunology, routine chemistry, and hematology. Data were deidentified under an institutional review board (IRB)-approved protocol (Western IRB-Copernicus Group [WCG] IRB). Analysis was performed retrospectively to address the specific predetermined study purpose. In all, 2,365 institutions across all states in the United States submitted 76,406 SF samples for comprehensive diagnostic testing from December 2016 to May 2022. Of 76,406 samples submitted, 73,401 met inclusion criteria (Table I) and 5,960 of these samples were excluded for poor quality[8], leaving 67,441 MID results for analysis.

All SF cultures were processed as a set of BACT/ALERT (bioMérieux) facultative aerobic and anaerobic bottles and were monitored for growth with the BACT/ALERT system at the same central laboratory performing all tests in this study. The MID panel (Table II) evaluated in this study was developed to directly detect microorganism antigens in SF (Synovasure Microbial Identification test, CD Laboratories, Zimmer Biomet). The results of the MID panel are generally reported within 12 hours of the sample arrival at the laboratory. The combined MID panel reported in this article consists of 3 immunoassays targeting different genera: Staphylococcus, Candida, and Enterococcus.

A modified 2018 International Consensus Meeting (2018 ICM) definition of PJI[6] was used as the gold standard. The ICM 2018 definition was modified by replacing the serum C-reactive protein (CRP) with SF-CRP (threshold of 6.6 mg/L), which has been previously shown to be diagnostically equivalent[9] or superior[10] to serum CRP for diagnosing PJI. This definition was used to categorize all samples as not infected, inconclusive, or infected. The ICM scores in this study were calculated exclusively from the SF test data from each sample, as other clinical data components of the score were not available. Every sample in this study had every SF laboratory test completed, providing sufficient data to attain a potential score of 9 using the 2018 ICM scoring system.

Diagnostic Evaluation of the MID Panel

The sensitivity of the MID panel was measured by calculating the positive testing rate among infected samples (2018 ICM[6] score, ≥6) that yielded microbiologic cultures that were positive for Staphylococcus, Candida, or Enterococcus. The specificity of the MID panel was calculated as the rate of a negative result among SF samples that were classified as not infected (2018 ICM[6] score, ≤2). The SF culture-negative microorganism detection rate was

TABLE II Components of the MID Test Panel Immunoassay*

Component	Immunogen	Host Animal	Antibody Type	Target Genus
Staphylococcal panel	*Staphylococcus aureus* and *Staphylococcus epidermidis*	Rabbit	Polyclonal	Staphylococcus
Candidal panel	*Candida albicans*	Rabbit	Polyclonal	Candida
Enterococcal panel	*Enterococcus faecalis*	Rabbit	Polyclonal	Enterococcus

*Each component of the MID panel detects a different genus of microorganism. The test for each component genus was developed by injecting the immunogens into host animals to develop polyclonal antibodies that detect the specific genera.

TABLE III Diagnostic Classification of Study Samples

ICM Result	No. of Patients
Not infected	49,991 (74.1% of 67,441)
SF culture-negative	49,772 (99.6%)
SF culture-positive	219 (0.4%)
Inconclusive	5,071 (7.5% of 67,441)
SF culture-negative	4,902 (96.7%)
SF culture-positive	169 (3.3%)
Infected	12,379 (18.4% of 67,441)
SF culture-negative	3,413 (27.6%)
SF culture-positive	8,966 (72.4%)

determined by calculating the positive MID panel testing rate among samples classified as infected but SF culture-negative. All samples classified as not infected or infected were included to calculate the positive predictive value (PPV) and negative predictive value (NPV) of the MID panel.

Data Management and Statistical Analysis

Clinical laboratory test results were digitally transferred daily from the instruments to a laboratory information system (CGM LABDAQ; CompuGroup Medical), which has a high-data-integrity architecture built on an industry standard atomicity, consistency, isolation, durability (ACID)-compliant relational database management system (RDBMS), Microsoft SQL Server. All data analysis in this study was performed in duplicate by 2 independent authors from different institutions, starting from the raw data, to confirm the accuracy and integrity of the analysis.

Standard diagnostic parameters including sensitivity, specificity, PPV, and NPV were calculated with 95% confidence intervals (CIs) around the point estimate (diagnostic test evaluation calculator, version 20.2; MedCalc Software). The p values for 2 × 2 categorical comparisons were calculated using a 2-tailed chi-square test with a Yates correction (Prism software, version 9.1.1; GraphPad Software).

Source of Funding

There was no external funding received for this study.

Results

The 67,441 study samples were categorized as not infected (n = 49,991), inconclusive (n = 5,071), or infected (n = 12,379). The rate of a diagnosis of infection in this data set was 18.4% (95% CI, 18.1% to 18.7%), and 27.6% (95% CI, 26.8% to 28.4%) of infected samples were culture-negative (Table III). The associated mean laboratory results for all diagnostic categories were calculated (Table IV).

Evaluation of MID Panel Sensitivity and Specificity

The MID panel had a sensitivity of 94.2% (95% CI, 93.6% to 94.7%) for detecting the microorganisms that it was designed to detect, yielding a positive result in 5,978 of 6,349 infected samples with a microbiologic culture positive for Staphylococcus, Candida, or Enterococcus. The sensitivities of the staphylococcal, candidal, and enterococcal immunoassays individually were 93.0% (95% CI, 92.3% to 93.7%), 92.3% (95% CI, 88.9% to 94.9%), and 97.2% (95% CI, 95.3% to 98.5%) for infected samples that were microbiologically culture-positive for their respective target genus (Table V and VI).

The MID panel demonstrated a specificity of 98.4% (95% CI, 98.2% to 98.5%) and a false-positive rate of 1.6%, as it correctly yielded a negative result in 49,168 of 49,991 samples that were not infected. The specificities of the individual immunoassays were 98.9% (95% CI, 98.8% to 99.0%) for Staphylococcus, 99.7% (95% CI, 99.7% to 99.8%) for Candida, and 99.6% (95% CI, 99.6% to 99.7%) for Enterococcus; in samples that were not infected, these yielded individual false-positive rates of 1.1% for Staphylococcus, 0.3% for Candida, and 0.4% for Enterococcus.

There were 1,068 samples with multiple-antigen positivity: 1,002 were double-antigen positive and 66 were triple-antigen positive. Multiple-antigen positive samples were observed among 0.08% (42) of 49,991 samples that were not infected, 2.3% (119) of 5,071 inconclusive samples, and 7.3% (907) of 12,379 infected samples. Multiple-antigen positivity was 87 times more likely ($p < 0.0001$) to be observed among infected samples (7.3%) than samples that were not infected (0.084%). Of the 907 multiple-antigen positive PJI samples, 52.0% yielded SF cultures with at least 1 matching genus, 21.8% yielded negative SF cultures, and 26.1% yielded growth of microorganisms that did not match the antigen results.

TABLE IV Mean Laboratory Values for Diagnostic Classifications*

ICM Result	ICM Sum	Alpha-Defensin *(S/CO)*	SF-CRP *(mg/L)*	SF-WBC *(cells/μL)*	SF-PMN%	SF Culture Positivity	SF MID Positivity
Not infected	0.2	0.1	2.3	706	36.2%	0.4%	1.6%
Inconclusive	4.2	1.2	6.1	11,105	68.2%	3.3%	28.4%
Infected	8.1	2.8	32.2	38,640	91.5%	72.4%	73.8%
Culture-negative	7.0	2.2	29.0	23,204	89.2%	0.0%	49.3%
Culture-positive	8.6	3.1	33.5	44,516	92.3%	100.0%	83.2%

*S/CO = signal/cutoff, SF-WBC = SF white blood-cell count, and SF-PMN% = SF polymorphonuclear cell percentage.

TABLE V Diagnostic Characteristics of the MID Panel and Its Individual Components*

	Sensitivity		Specificity		Percentage of False-Positives	
	Mean†	No. of Patients/ Total	Mean†	No. of Patients (N = 49,991)	Mean†	No. of Patients (N = 49,991)
MID panel	94.2% (93.6% to 94.7%)	5,978/6,349	98.4% (98.2% to 98.5%)	49,168	1.6% (1.5% to 1.8%)	823
Staphylococcus	93.0% (92.3% to 93.7%)	5,190/5,581	98.9% (98.8% to 99.0%)	49,454	1.1% (1.0% to 1.2%)	537
Candida	92.3% (88.9% to 94.9%)	312/338	99.7% (99.7% to 99.8%)	49,849	0.3% (0.2% to 0.3%)	142
Enterococcus	97.2% (95.3% to 98.5%)	452/465	99.6% (99.6% to 99.7%)	49,803	0.4% (0.3% to 0.4%)	188

*Individual genus sensitivities were calculated in infected samples that were culture-positive for the respective microorganism. †The values are given as the mean and the 95% CI.

MID Panel Detection of Microorganism in Culture-Negative PJI

The MID panel yielded a positive result in 49.3% (95% CI, 47.7% to 51.0%) of SF culture-negative infected samples (Table IV). This 49.3% microorganism detection rate among culture-negative infected samples was 31-fold higher than the 1.6% detection rate among samples that were not infected ($p < 0.0001$). The rate of MID panel positivity increased progressively with increasing ICM score ($y = 0.014\ x^2$, $r^2 = 0.99$), peaking at 83% (Fig. 1).

The combination of SF culture and MID panel results detected a microorganism in 86.0% (10,650) of 12,379 infected samples, which was greater than the SF microbiologic culture detection rate alone (72.4%) ($p < 0.0001$).

Diagnostic Predictive Value

The MID panel had a PPV of 91.7% (95% CI, 91.1% to 92.3%) for infected samples. Among MID-panel-positive samples that were classified as infected (n = 9,140), 65.4% had a positive culture that matched the MID result, 18.4% were culture-negative, and 16.2% had a positive culture that did not match the MID result (Table VII). Among 12,379 infected samples, there were 2,617 culture-positive samples that did not grow Staphylococcus, Candida, or Enterococcus, but instead yielded another microorganism. Of these samples, 56.5% (1,478 of 2,617) had an MID result that was positive for Staphylococcus, Candida, or Enterococcus.

The MID panel yielded an NPV of 93.8% (95% CI, 93.6% to 94.0%) for the diagnosis of samples that were not infected.

Discussion

An increasing clinical understanding of culture-negative PJI has led to the development of alternative techniques to detect SF microorganisms. The results of this study describe an SF microorganism immunoassay antigen panel that demonstrated high sensitivity (94.2%) and specificity (98.4%) for PJI, providing adjunct results to conventional SF microbiological culture. The MID panel has 2 major clinical utilities in the diagnosis of PJI. First, the MID panel provides results meaningfully faster than traditional SF cultures. Second, the MID panel was positive among 49.3% of SF culture-negative infected samples, supporting the presence of a microorganism in roughly one-half of PJIs with a negative culture.

This study reveals that the MID panel had a sensitivity of 94.2% and a specificity of 98.4% for the detection of the microorganisms that it was designed to detect (Staphylococcus, Candida, and Enterococcus) in the setting of PJI. As reference comparisons, meta-analysis studies have demonstrated a pooled sensitivity of 85.6% and specificity of 95.4% for the antigen tests used to diagnose pediatric strep throat[11] and a pooled sensitivity of 81% and specificity of 96% for the antigen tests used to diagnose pediatric respiratory syncytial virus[12]. Therefore, the diagnostic

TABLE VI Antigen Positivity Among Infected Samples for Species within the Target Genera*

Species	No. of Patients	Positive for Antigen†
Staphylococcus		
All Staphylococcus	5,581	93.0% (5,190)
Staphylococcus epidermidis	2,399	91.8% (2,203)
Staphylococcus aureus	1,890	96.4% (1,822)
Staphylococcus lugdunensis	669	87.1% (583)
Other	634	93.4% (592)
Candida		
All Candida	338	92.3% (312)
Candida albicans	157	96.8% (152)
Candida parapsilosis	120	85.0% (102)
Other	62	95.2% (59)
Enterococcus		
All Enterococcus	465	97.2% (452)
Enterococcus faecalis	383	97.4% (373)
Enterococcus faecium	74	95.9% (71)
Other	8	100.0% (8)

*Antigen positivity is presented for multiple species within each genus category. The sum of the species within a genus may not equal the total number for the genus, due to rare cases in which cultures grew >1 species within that genus. †The values are given as the percentage, with the number of patients in parentheses.

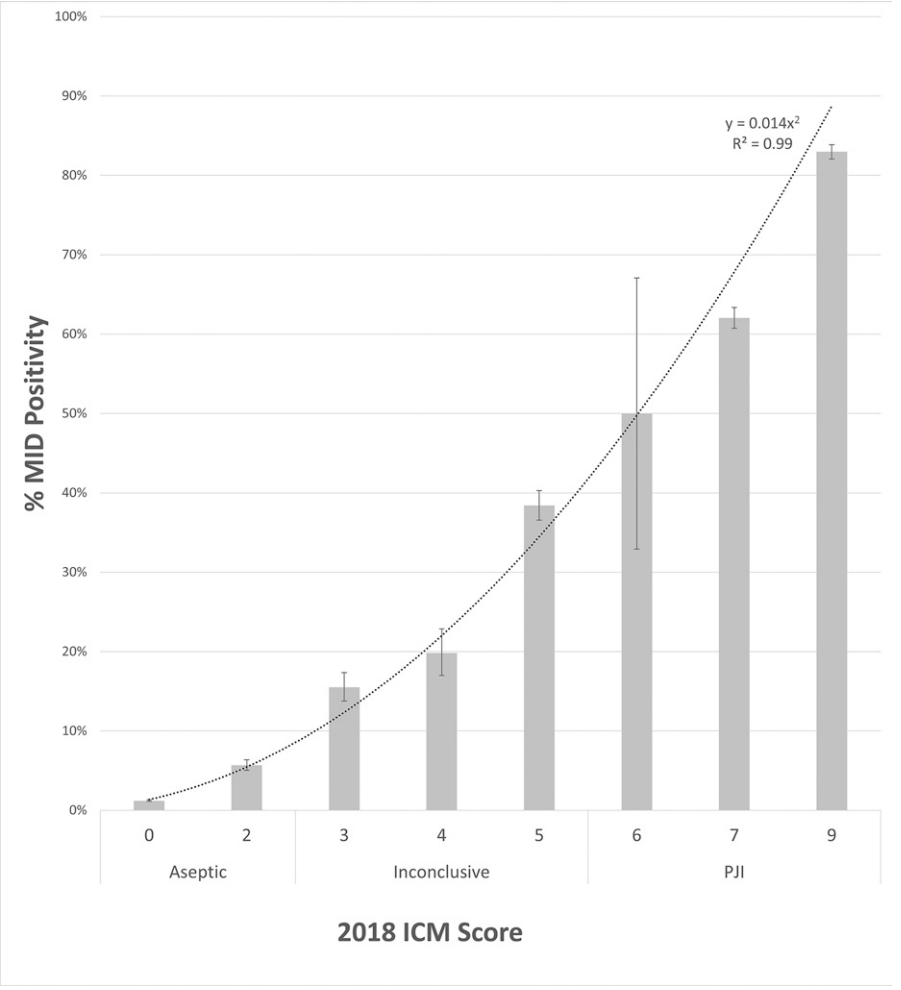

Fig. 1

MID panel positivity rate versus the calculated 2018 ICM score. Test positivity increased exponentially with increasing ICM score. Due to ICM scoring rules, all samples with an ICM score of 0 and 3 had negative culture results and all samples with a score of 6 or 9 had positive culture results. The mean culture positivity for sample scores was 4.5% for a score of 2, 12.3% for a score of 4, 2.9% for a score of 5, and 36.2% for a score of 7. The error bars are the 95% CIs.

performance of the MID panel to detect Staphylococcus, Candida, and Enterococcus in SF is excellent, as it matches or outperforms other infectious disease immunoassays that are currently in widespread clinical use. The performance of the MID panel in this study also compares favorably to a previous report on the use of a serum microorganism immunoassay to detect PJI, which revealed a sensitivity of 72.3% and a specificity of 80.7% for targeted Staphylococcus PJI[13]. The higher sensitivity and specificity in the current study may be attributable to the likely increased microorganism antigen concentration in SF compared with blood.

MID positivity increased exponentially (Fig. 1) as the ICM score increased from 0 to 9, demonstrating a strong correlation with the diagnosis of PJI. This observation is not surprising for a test that detects microorganisms, as the likelihood of true infection should increase progressively with each additional positive test for PJI in the ICM score. Maximal MID panel positivity of 83.0% was observed among samples with an ICM score of 9, which is the ICM group most likely to have a true infection, considering that all tests, including culture, are required to be positive to achieve a score of 9 in this study. Given the overall MID panel sensitivity of 94.2% in detecting target microorganisms, it is not surprising that the vast majority of ICM = 9 samples with a negative MID panel result yield a microorganism other than Staphylococcus, Candida, or Enterococcus.

The study also reveals that the MID panel detected microorganisms in 49.3% of SF culture-negative infected samples. We consider this the most clinically important finding of this study, as the confirmation of a microorganism is important to the preoperative diagnosis of PJI. It is critical to recognize that, in this study, the detection of a microorganism in culture-negative infected samples was 31-fold higher (49.3%) than the detection of a microorganism among samples that were not infected (1.6%) ($p < 0.0001$), suggesting that the positivity among SF culture-negative PJI is unlikely due to spurious MID panel false-positivity. The MID panel increased the preoperative detection of SF microorganisms among infected samples from 72.4%, observed with culture alone, to 86.0% when the MID panel

TABLE VII Sample Classifications by MID Result

Classification	No. of Patients
Negative MID result	52,407
Not infected	49,168 (93.8%)
Negative culture	48,989 (99.6%)
Positive culture	179 (0.4%)
Infected	3,239 (6.2%)
Negative culture	1,729 (53.4%)
Positive culture	1,510 (46.6%)
Positive MID result	9,963
Not infected	823 (8.3%)
Negative culture	783 (95.1%)
Positive culture	40 (4.9%)
Infected	9,140 (91.7%)
Negative culture	1,684 (18.4%)
Positive matching culture	5,978 (65.4%)
Positive non-concordant culture	1,478 (16.2%)

results were utilized as an adjunct test combined with SF cultures. This augmented potential to detect microorganisms in SF preoperatively is clinically advantageous for surgical decision-making, as the next opportunity to detect microorganisms is through the culture of intraoperative tissue biopsies, for which results are not available until after definitive surgical decision-making has been completed.

This study also evaluated the clinical predictive characteristics of the MID panel, revealing a PPV of 91.7% and an NPV of 93.8% for a diagnosis of infection. A positive MID panel result should therefore invoke serious clinical concern for PJI, as 91.7% of samples with a positive MID panel were eventually classified as infected when all preoperative laboratory results were completed and the ICM 2018 score was determined. Interestingly, although the majority of positive MID test results were associated with infected samples that yielded SF cultures of a matching genus or negative cultures, 16.2% of positive MID panel results were associated with infected samples with cultures yielding non-target microorganisms instead of Staphylococcus, Candida, or Enterococcus. This observation could be interpreted as demonstrating either off-target immunoassay microorganism cross-reactivity or the existence of a multi-microorganism PJI in which the MID panel's target microorganism was culture-negative. It is difficult to discriminate between these 2 hypothetical possibilities with the current data. Nevertheless, the observed PPV and NPV of the MID panel for the diagnosis of PJI are comparable with or superior to the predictive values of traditional preoperative tests for PJI as determined in a recent systematic review and meta-analysis[14].

Other recent technologies have been described as an alternative to culture for microorganism detection in the setting of PJI. The polymerase chain reaction (PCR) initially appeared to have great promise for the diagnosis of PJI[15] but has not become widely adopted because of difficulties in striking the balance between sensitivity and specificity[16,17]. The newest form of nucleic acid microorganism detection, next-generation sequencing (NGS), attempts to build on PCR in hopes of providing a method to reliably identify all microorganisms and their antimicrobial susceptibility in cases of PJI. The strengths and weaknesses of antigen testing are opposite to the strengths and weaknesses of NGS, suggesting that they may serve complementary diagnostic roles. Although antigen testing demonstrated false-positivity of only 1.6% among the samples that were not infected in this study, NGS previously detected organisms in 35% of non-infected osteoarthritis samples[18], 16% of aseptic control arthroplasty samples[19], and 11% of sterile swabs exposed to operating-room air[20]. Additionally, although antigen testing is performed on preoperative SF, aiding in the diagnosis of PJI, NGS studies utilize intraoperative tissue sampling[17,18,21], rendering results irrelevant to a preoperative diagnosis. The main weakness of antigen testing is that it does not detect all microorganisms and does not provide antimicrobial susceptibilities, which could be potentially provided by NGS. The advantages and disadvantages of the various methods must be further delineated in an effort to identify the optimal clinical approach toward diagnosing PJI.

There were several limitations to this study that deserve specific discussion. First, although the nationwide inclusion of samples from 2,365 centers in this study minimized the risk of institutional fluid aspiration bias, it also prevented the creation of a well-defined population with clinical inclusion and exclusion criteria. Second, the study was methodologically restricted to the application of only preoperative SF data for determining whether samples met the 2018 ICM definition of PJI because it was not possible to collect clinical data or tissue culture data from 2,365 clinical centers. Although the authors of the 2018 ICM[6] stated that "Not all tests are needed to use this proposed definition and a preoperative diagnosis can be made without the need for intraoperative findings," the use of preoperative SF data for diagnosis could be interpreted as a weakness or a strength of this study. The true diagnostic sensitivity of the MID panel may be overestimated, as there may be cases of PJI that are tissue culture-positive despite being SF culture-negative in this study. However, the focus on the preoperative workup in this study demonstrates that the MID panel can improve the detection of microorganism preoperatively, which is exactly when a surgeon chooses a definitive surgical treatment without the benefit of tissue culture results.

Third, it is important to note that, although the MID panel can augment microorganism detection from preoperative SF, the identification occurs at the genus level and does not include many microorganisms that cause PJI. Therefore, the sensitivity calculations in this study were limited to PJIs caused by the 3 detected genera. In contrast, the specificity, PPV, and NPV calculated in this study could be applied to all PJIs, as all relevant samples were included in these calculations. Considering these limitations, the MID panel could be used in combination with other laboratory tests to aid in the diagnosis of PJI and inform decision-making with regard to surgical treatment but cannot be utilized to make antimicrobial choices. Antimicrobial choices should be made on the basis of susceptibility testing of SF or tissue culture isolates.

In conclusion, SF microorganism antigen testing provides an adjunct method to detect microorganisms in the

preoperative SF aspirate, yielding a low false-positive rate and enabling the early detection of microorganisms in nearly one-half of SF culture-negative PJIs. ■

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