Far from Perfect: Synovial Fluid Next-Generation Sequencing (NGS) in Diagnosing Periprosthetic Joint Infection

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INTRODUCTION: Next-generation sequencing (NGS) is being increasingly preferred for the accurate detection of infecting organism in periprosthetic joint infection (PJI). With this molecular technique, results can be obtained in less than 24 hours as compared to ample time needed in culturing organisms. Nevertheless, adult reconstructive surgeons ordering NGS in PJI workup at our institution grew concerned about inadequacies of this test in identifying organisms, which led to this investigation. Thus, our objectives were as follows: 1) to test the accuracy of NGS to diagnose PJI with the 2018 ICM PJI definition as a gold standard and 2) to assess the concordance of this technique with cultures in identifying infecting organisms.

METHODS: A retrospective review was performed on consecutive 100 NGS tests ordered from 01/2020 to 04/2022 by 4 surgeons in a single institution to diagnose PJI. All patients had a synovial fluid aspiration for NGS and other test results incorporated in the 2018 ICM PJI definition. PJI diagnostic workup was performed before the following operations (hips=22 and knees=78): revision joint arthroplasties (n=86), or reimplantations (n=14). To assess accuracy for PJI diagnosis, NGS (+) and NGS (-) test results were compared with the 2018 ICM PJI definition ("gold standard"). To further evaluate the ability to identify organisms, NGS was analyzed against cultures which had an identified infecting organism. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

RESULTS: With the 2018 ICM PJI definition as a gold standard, NGS demonstrated poor sensitivity (59%) and NPV (60.3%), but high specificity (91.4%) and PPV (91%). On comparing NGS with culture results, predictive measures dropped down, specificity (77%) more so than poorer sensitivity (57.8%) (Table 1). Out of 38 synovial fluid/tissue samples in which infecting organism was cultured, NGS failed to identify 16 out of 38 (false negative rate=42.1%) (Table 2). Phenotypically identical organisms were isolated from at least two separate samples from the joint in 50% of these false negatives cases (major criteria in the 2018 ICM PJI definition for diagnosis of PJI). In 14 tests before reimplantation, NGS missed 3 of 6 culture positive cases with known organisms.

DISCUSSION AND CONCLUSION: Synovial fluid NGS has poor sensitivity for PJI diagnosis and fails to identify infecting organisms confirmed on cultures from the prosthetic joint.

Table 1. Next-generation sequencing (NGS) in diagnosing periprosthetic hip or knee infection (2018 ICM PJI definition=gold standard).

	2018 ICM (-)	2018 ICM (+)	Total
NGS (-)	32	21	53
NGS (+)	3	30	33
Total	35	51	86

Accuracy = 100 x 30+32/30+32+21+3 = **72%**
Sensitivity = 100 x 30/51 = **59%**
Specificity = 100 x 32/35 = **91.4%**
Positive predictive value = 100 x 30/33 = **91%**
Negative predictive value = 100 x 32/53 = **60.3%**
Positive Likelihood Ratio = 0.59/1-0.914= **6.86**
Negative Likelihood Ratio = 1-0.59/0.914 = **0.45**

Table 2. Next-generation sequencing (NGS) in identifying infecting organisms in culture positive or negative periprosthetic hip or knee infection.

	Culture (-)	Culture (+)	Total
NGS (-)	37	16	53
NGS (+)	11	22	33
Total	48	38	86

Accuracy = 100 x 22+37/22+37+16+11 = **68.6%**
Sensitivity = 100 x 22/38 = **57.8%**
Specificity = 100 x 37/48 = **77%**
Positive predictive value = 100 x 22/33 = **66.6%**
Negative predictive value = 100 x 37/53 = **70%**
Positive Likelihood Ratio = 0.578/1-0.77 = **2.51**
Negative Likelihood Ratio = 1-0.578/0.77 = **0.548**