Anthem

Medical Policy

Subject: Metagenomic Sequencing for Infectious Disease in the Outpatient Setting
Document #: LAB.00050
Status: Reviewed

Publish Date: 04/01/2025
Last Review Date: 11/14/2024

Description/Scope

This document addresses metagenomic sequencing of infectious pathogens in the outpatient setting. Metagenomic testing, which employs next generation sequencing (NGS), analyzes microbial DNA from a clinical sample without reliance on traditional culture or targeted molecular tests. Clinical metagenomic testing is used for comprehensive detection of all pathogens in a single test.

This document does not address targeted or multiplex (panel-based) nucleic acid tests (NAAT) or metagenomic sequencing of infectious diseases in the inpatient setting.

Position Statement

Investigational and Not Medically Necessary:

Metagenomic sequencing for infectious diseases in the outpatient setting is considered **investigational and not medically necessary** for all indications.

Rationale

Urinary Tract Infections (UTIs)

McDonald and colleagues (2017) published a study comparing DNA next-generation sequencing (NGS) testing (MicroGenDx test) for UTIs with standard urine culture in 44 individuals who had symptoms of acute cystitis. Participants were randomized to receive either treatment based on culture results (Arm A, n=22) or treatment based on DNA NGS test results (Arm B, n=22). This was an open-label study and did not include blinding of participants or evaluators. Urine samples from all participants were tested using both methods. Treatment consisted of use of a single antibiotic for 7 days. Symptoms were measured with a validated self-administered instrument, the UTI Symptom Assessment questionnaire, which has scores potentially ranging from 0 to 21 (higher scores indicated greater severity of symptoms). Scores were assessed at baseline, each day for the first week and on day 14.

A total of 13 of 44 individuals (30%) had positive urine cultures and all 44 individuals had positive DNA NGS results. Seven culture-positive individuals were in Arm A and 6 were in Arm B. The mean symptom score at baseline was 9.0 in Arm A and 10.2 in Arm B; the difference between groups was not statistically significant. In Arm A, the mean score decreased after treatment to 5.3. In Arm B, results were reported by subsets. Subset 3 consisted of the 6 individuals in Arm A who were culture positive, and subset 4 was the 16 individuals who were culture-negative. In subset 3, the mean symptom score at follow-up decreased from 11.2 to 4.3 and in subset 4, the mean score decreased from 11.6 to 3.7. Mean symptom scores at follow-up were not reported for the randomized groups, Arm A versus Arm B.

Findings of this small study of a common condition are insufficient to conclude that more general use of DNA NGS testing would result in better health outcomes than standard methods of diagnosing and managing UTIs. Lack of blinding may have influenced the subjective primary outcome. Additional prospective, randomized, and blinded studies in larger groups of individuals and with longer follow-up are needed.

Liss and colleagues (2023) published an RCT comparing the rate of post-surgical UTI in individuals who did and did not undergo DNA NGS testing to help guide selection of prophylactic antibiotics. The study included individuals who were at least 18 years old, were planning to undergo kidney or bladder stone removal, and had a negative pre-operative urine culture. DNA NGS testing results from individuals in the intervention group were sent to an infectious disease pharmacist. The pharmacist's antibiotic recommendation and test results were then sent to the treating physicians. The treating

physicians selected an antibiotic and were not required to follow the pharmacist's recommendation. Physicians in the control group selected prophylactic antibiotics using standard care. Research staff were not blinded to treatment group, and surgeons in the intervention group were not blinded to DNA NGS results. The primary study outcome was UTI within 14 days after surgery.

A total of 240 individuals underwent randomization: 119 to the intervention group and 121 to the control group. After randomization, some individuals were non-evaluable due to positive cultures, insufficient urine provided for culture, cancelled surgery or loss to follow-up. The analysis included 157 of 240 (65%) randomized individuals, 74 intervention participants and 83 control participants. In a modified intention-to-treat (ITT) analysis, 1 of 74 (1.3%) in the intervention group and 7 of 83 (8.4%) in the control group had a post-operative infection. This represented a 7.1% (95% confidence interval [CI], 0.73 to 15%) difference between groups, which was statistically significant (p=0.045), but the lower limit of the CI was under 1%. In a per-protocol analysis, 0 of 50 individuals in the intervention group and 7 of 82 (8.5%) in the control group had a postoperative infection, for a difference of 8.5% (95% CI, 0.88 to 16%, p=0.032). This study was affected by significant attrition. Over a third (35%) of the randomized individuals were excluded from the analysis, and 32% of the evaluable individuals in the intervention group were excluded from the per protocol analysis. Moreover, the difference in the primary outcome, 7.1%, was statistically significant, but may not be clinically significant.

Peri-Operative Joint Infection

Rao and colleagues (2019) reported on a prospective observational study in 25 individuals undergoing primary total shoulder arthroplasty who did not have signs of active infection. Tissue samples were evaluated both with standard cultures and with DNA NGS analysis (MicroGenDx). Positive test results (presence of bacterial species) were found in 10 skin samples (40%) and 3 deep tissue samples (12%) evaluated by standard culture. DNA NGS analysis detected at least 1 bacterial species in 17 skin samples (68%) and 7 deep tissue samples (28%).

A study by Tarabichi and colleagues (2018) evaluated synovial fluid samples from 86 individuals who had hip or knee joint surgery and were undergoing routine evaluation to identify prosthetic infection. Samples were analyzed with culture tests and with DNA NGS analysis (MicroGenDx). Routine laboratory tests (e.g., c-reactive protein [CRP] analysis, total neutrophil count, human neutrophil elastase and alpha-defensin) were also measured. Among the 30 culture-positive samples, DNA NGS detected at least 1 organism in 26 of them. In 25 of these 26 samples (96%), there was concordance between the bacteria detected in culture and the predominant organism detected by NGS sequencing. There were 4 culture-positive samples for which DNA NGS did not detect any organisms. Among the 56 culture-negative samples, DNA NGS detected an organism in 10 samples (18%).

Ivy and colleagues (2018) evaluated 168 synovial fluid samples from the site of total knee arthroplasty (TKA). Samples were collected from individuals with culture-positive or culture-negative prosthetic joint infections or aseptic implant failures and were analyzed using metagenomic shotgun sequencing. The study did not appear to use a commercially available metagenomic test but instead used a technique developed by study investigators at the Mayo clinic. Performance of the metagenomic test was compared to results of synovial fluid culture analysis. Metagenomic sequencing had the same finding as synovial fluid culture analysis in 56 of 61 (92%) cases of aseptic failure, 67 of 82 (82%) cases of culture-positive synovial fluid and 21 of 25 (84%) cases of culture-negative synovial fluid. Organisms were missed by metagenomics in 1 case of aseptic failure and 14 cases of culture-positive synovial fluid. New organisms were identified by metagenomics in 4 (6.6%) aseptic failure cases, 3 (3.7%) of culture-positive synovial fluid cases and 4 (16.0%) of culture-negative synovial fluid cases.

The Ivy study demonstrated that metagenomic sequencing can identify pathogens in joint fluid but does not show that prospective use of this testing is a useful guide to therapy compared to standard treatment protocols. Limitations of the study include its small sample size, its non-random design, and a lack of clear selection criteria, all raising concerns about possible selection bias. This study lacked sufficient information about subject characteristics and procedures, including type of implant, and used a proprietary metagenomic sequencing protocol. These factors limit the study's generalizability outside of this research setting. The authors themselves noted that validation of the methods including the reference genome databases used in the study were incomplete.

In 2023, Hantouly and colleagues published a systematic review and meta-analysis of studies comparing metagenomic NGS to culture for diagnosing periprosthetic joint infection. The review included seven studies. One of the studies was Tarabichi (2018), discussed above, and the others were conducted in China and used tests that are not commercially available in the United States. A meta-analysis of the seven studies yielded a pooled sensitivity of 94% (95% CI, 91 to 97%) for NGS and 70% (95% CI, 61 to 79%) for culture. In addition, a meta-analysis of study data found a pooled specificity of 89% (95% CI, 82 to 95%) for NGS and 95% (95% CI, 88 to 98%) for culture.

The published literature to date on DNA NGS for detecting peri-operative joint infections does not include data on how test information was used to manage patients and does not evaluate health outcomes after DNA NGS analysis versus culture

tests.

Fracture Non-Union

In 2022, Goswami and colleagues published a study of 37 individuals who were undergoing surgical interventions for long-bone non-unions and 17 individuals undergoing fixation for acute fracture. Prior to surgery, all individuals underwent testing with the MicroGenDx DNA NGS test. Study participants were followed for a minimum of 6 months. Among the 37 individuals undergoing open surgical interventions, 22 had achieved union by 6 months and 15 had not healed and were considered to have persistent non-unions. The investigators found that a positive DNA NGS test result was significantly associated with persistent non-union (p=0.048). Among individuals who did not achieve union, 10 individuals (67%) had a positive DNA NGS test and 5 (33%) had a negative test. The study did not evaluate whether patient management based on findings of the DNA NGS test improved health outcomes and did not compare outcomes in individuals who were managed with and without use of the DNA NGS test.

Other Applications

In 2020, Hogan and colleagues published a five-center retrospective cohort study reporting on 82 individuals who were evaluated with the Karius test for any indication. Karius assesses the presence of microbial cell-free DNA in a sample. The most common indications for testing were fever of unknown origin (23.2%), suspected respiratory infection (13.4%), sepsis (9.8%), suspected endocarditis (8.5%) and febrile neutropenia (7.3%). A total of 50 of 82 (61%) tests had positive findings. The investigators developed a set of criteria to assess the clinical impact of Karius test results. According to these criteria, there was no clinical impact in 71 (87%) individuals. For 6 (7.3%) individuals, the test had a positive impact such as earlier diagnosis or initiation of appropriate therapy. There was a negative impact, including unnecessary treatment and unnecessary diagnostic tests, for 3 (3.7%) individuals. Overall, the findings of the metagenomic sequencing had either no impact or a negative impact for 92.7% of the sample. Prospective studies are needed to validate the derived criteria and to determine whether or not use of this test leads to improved health outcomes.

A 2023 study by Weiss and colleagues reported on a retrospective analysis of 27 hospitalized individuals who were evaluated with the Karius assay for any indication. Two individuals underwent testing twice on separate admissions for different indications (total of 29 tests). There were 3 categories of reasons for testing; 1) suspected infection with negative microbiologic work-up, 2) known infectious syndrome but continued suspicion of infection, and 3) non-specific signs and symptoms. Testing identified causative agents in 2 of 15 (13%) cases in the first group, 7 of 9 cases (78%) in the second group and none of the cases in the third group. Overall, the authors identified a positive impact of testing in 13 (45%) of cases, a negative impact in 3 (10%) of cases and no impact in 15 (52%) of cases. The highest rate of positive impact was in the second group, those with continued suspicion of infection. In this group, the Karius test did not identify any new causative organism but confirmed the causative pathogen in 7 of the 9 cases.

No published studies were identified that evaluated commercially available metagenomic sequencing tests for other outpatient clinical uses such as prostate infections, wound infection diagnosis or nail fungus diagnosis.

Other Relevant Information

No FDA labeled indications were identified for tests that conduct metagenomic sequencing for infectious disease in the outpatient setting. Moreover, no Centers for Medicare & Medicaid Services (CMS) National Coverage Determinations (NCDs) or Local Coverage Determinations (LCDs), and no nationally recognized clinical practice guidelines were identified that have recommendations on the tests addressed in this document.

Background/Overview

Approximately 10.2 million physician office visits per year have infectious or parasitic diseases as the primary diagnosis (CDC, 2023). In 2018, there were 3.4 million emergency department visits that had infectious and parasitic diseases as the primary diagnosis. The most common principal diagnoses among these infectious disease hospitalizations were pneumonia, urinary tract infections (UTI) and unspecified septicemia (Kennedy, 2019).

Microbial culture is a conventional method for identification of infectious agents. This technique is limited by the relatively long time required to culture organisms, the difficulty growing many microorganisms in culture, and the need for invasive procedures to obtain samples of deep-seated infection. Newer approaches to identification of microbial agents use DNA sequencing technology, including polymerase chase reaction (PCR) techniques. A limitation of ‘first-generation sequencing technology’, including PCR, is that only one sequencing can be analyzed at one time and thus the DNA from a biological sample needs to be divided into fragments to test for multiple agents. Moreover, unlike culture tests, PCR methods are unable to test for drug/antibiotic susceptibility. Molecular diagnostic and targeted nucleic acid detection tests (NATs)

reference methods that detect DNA or RNA specific infectious organisms (for example, bacteria, viruses) as a means of diagnosis. Multiplex (or panel-based) nucleic acid amplification tests (NATs) combine multiple individual NATs into a single test, thereby allowing clinicians to test for an array of potential pathogens that may cause a clinical syndrome at the same time.

Metagenomic sequencing has been proposed as a method to diagnose infection by comparing genetic material found in a patient's sample to a database of thousands of bacteria, viruses, and other pathogens. Metagenomics is a molecular tool used to analyze DNA acquired from environmental samples, in order to study the community of microorganisms present, without the necessity of obtaining pure cultures. Metagenomic sequencing employs next generation sequencing (NGS) testing, also referred to as massively parallel sequencing or high-throughput sequencing. Metagenomic NGS technology allows sequencing for multiple agents in parallel without the physical separation of samples into pieces. Millions or billions of sequencing reactions can occur and be analyzed simultaneously. NGS thus allows for the comprehensive identification of the species of bacteria and fungi in an infectious disease sample without culturing the organisms. Metagenomic NGS has the potential to provide a direct, unbiased analysis of the microbial composition of clinical samples without reliance on traditional culture or targeted molecular tests, and has the capacity to identify a broad range of pathogens in a single test.

Several metagenomic sequencing tests for diagnosing microbial infection are commercially available and are offered in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories. The MicroGenDx test (MicroGen Diagnostics LLC, Lubbock, TX) is marketed for diagnosing microbial infections in a variety of specialties including urology (e.g., urinary tract infections, prostate infections), ENT (e.g., sinus infection diagnosis), wound care (e.g., wound infection diagnosis), orthopedics (e.g., post-operative infection diagnosis) and podiatry (e.g., nail fungus diagnosis). Microbial DNA is extracted from patient samples (e.g., cell swabs, tissue samples, urine samples) using NGS DNA sequencing techniques and analyzed using molecular diagnostic methods. Test result reports, returned within 3-5 days, contain information about all of the microbes and fungi detected in the sample and any antibiotic resistance genes that were identified. In 2022, MicroGen Diagnostics, along with Evvy, launched a metagenomic-based vaginal infection test kit. Tests are processed in the MicroGen laboratory.

The Karius Test (Karius Inc, Redwood City, CA), which involves NGS of cell-free DNA is being marketed for detecting pathogens in culture-negative infections including sepsis and endocarditis, identifying microorganisms involved in invasive fungal infections, targeting antimicrobial therapy and monitoring immunocompromised patients susceptible to infection. The Karius test has been evaluated in the inpatient setting, including testing individuals who met sepsis alert criteria and testing immunocompromised individuals with unknown infections, but no published studies were identified on outpatient applications of the test.

There are other metagenomic sequencing tests for evaluating microbes, including ThermoFisher Scientific's Ion 16S™ Metagenomics Kit and the Illumina whole genome microbial NGS sequencing test. Both of these tests appear to be intended for research purposes at this time; no studies were identified on outpatient applications of the tests. In addition, John Hopkins is developing a metagenomic sequencing test using cerebrospinal fluid samples (Simner, 2018) but no studies on the clinical use of this test were identified.

Definitions

Clinical metagenomics: The comprehensive analysis of all nucleic acid material present within a clinical sample to recover clinically relevant microbial information such as potential pathogens.

Next-generation sequencing: A laboratory test that allows rapid sequencing of large numbers of segments of DNA, up to and including entire genomes.

Pathogen: Bacteria, viruses or other microorganism that can cause disease.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure codes; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

0112U	Infectious agent detection and identification, targeted sequence analysis (16S and 18S rRNA genes) with drug-resistance gene MicroGenDX qPCR & NGS For Infection, MicroGenDX, MicroGenDX
0152U	Infectious disease (bacteria, fungi, parasites, and DNA viruses), microbial cell-free DNA, plasma, untargeted next-generation sequencing, report for significant positive pathogens Karius® Test, Karius Inc, Karius Inc
0323U	Infectious agent detection by nucleic acid (DNA and RNA), central nervous system pathogen, metagenomic next-generation sequencing, cerebrospinal fluid (CSF), identification of pathogenic bacteria, viruses, parasites, or fungi Johns Hopkins Metagenomic Next Generation Sequencing Assay for Infectious Disease Diagnostics, Johns Hopkins Medical Microbiology Laboratory
0480U	Infectious disease (bacteria, viruses, fungi, and parasites), cerebrospinal fluid (CSF), metagenomic next-generation sequencing (DNA and RNA), bioinformatic analysis, with positive pathogen identification Bacteria, Viruses, Fungus, and Parasite Metagenomic Sequencing, Spinal Fluid (MSCSF), Mayo Clinic, Laboratory Developed Test
0531U	Infectious disease (acid-fast bacteria and invasive fungi), DNA (673 organisms), next-generation sequencing, plasma NeXGen™ Fungal/AFB NGS Assay, Eurofins Viracor, LLC, Eurofins Viracor, LLC
87999	Unlisted microbiology procedure [when specified as other NGS analysis of microbes]

ICD-10 Diagnosis

All diagnoses

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Peer Reviewed Publications:

1. Goswami K, Tipton C, Clarkson S et al. Fracture-associated microbiome and persistent nonunion: Next-generation sequencing reveals new findings. J Orthop Trauma. 2022; 36(Suppl 2):S40-S46.
2. Hantouly AT, Alzobi O, Toubasi AA et al. Higher sensitivity and accuracy of synovial next-generation sequencing in comparison to culture in diagnosing periprosthetic joint infection: a systematic review and meta-analysis. Knee Surg Sports Traumatol Arthrosc. 2023;31(9):3672-3683.
3. Hogan CA, Yang S, Garner OB et al. Clinical impact of metagenomic next-generation sequencing of plasma cell-free DNA for the diagnosis of infectious diseases: A multicenter retrospective cohort study. Clin Infect Dis. 2020 January 14: Online ahead of print.
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5. Kennedy JL, Haberling DL, Huang CC, et al. Infectious disease hospitalizations: United States, 2001 to 2014. Chest. 2019; 156(2):255-268.
6. Liss MA, Reveles KR, Tipton CD et al. Comparative effectiveness randomized clinical trial using next-generation microbial sequencing to direct prophylactic antibiotic choice before urologic stone lithotripsy using an interprofessional model. Eur Urol Open Sci. 2023; 57:74-83.
7. McDonald M, Kameh D, Johnson ME, et al. A head-to-head comparative phase II study of standard urine culture and sensitivity versus DNA next-generation sequencing testing for urinary tract infections. Rev Urol. 2017;19(4):213-220.
8. Rao AJ, MacLean IS, Naylor AJ, et al. Next-generation sequencing for diagnosis of infection: is more sensitive really better? J Shoulder Elbow Surg. 2020; 29(1):20-26.
9. Simner PJ, Miller HB, Breitwieser FP et al. Development and optimization of metagenomic next-generation sequencing methods for cerebrospinal fluid diagnostics. J Clin Microbiol. 2018 Aug 27;56(9):e00472-18.
10. Tarabichi M, Shohat N, Goswami K, et al. Can next generation sequencing play a role in detecting pathogens in synovial fluid? Bone Joint J. 2018; 100-B(2):127-133.
11. Weiss ZF, Pyden AD, Jhaveri TA et al. The diagnostic and clinical utility of microbial cell-free DNA sequencing in a real-world setting. Diagn Microbiol Infect Dis. 2023;107(2):116004.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics: Infectious Disease. Last updated January 25, 2023. Available at: https://www.cdc.gov/nchs/fastats/infectious-disease.htm. Accessed on

September 19, 2024.

Websites for Additional Information

1. Urology Care Foundation of the American Urological Assocation (AUA). Urinary Tract Infections in Adults. Last updated 2023. Available at: https://www.urologyhealth.org/urologic-conditions/urinary-tract-infections-in-adults. Accessed on September 19, 2024.

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The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
	04/01/2025	Updated Coding section with 04/01/2025 CPT changes, added 0531U.
Reviewed	11/14/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised Rationale and References sections.
	10/01/2024	Updated Coding section with 10/01/2024 CPT changes, added 0480U.
New	11/09/2023	MPTAC review. Initial document development. Moved contents of GENE.00053 to new medical policy document with the same title.

Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.