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Medical Policy

Subject:	Metagenomic Sequencing for Infectious Disease in the Outpatient Setting		
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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. The technique has the potential to identify a broad range of 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.

Note: Please see the following related document for information on testing for microbial agents in respiratory infections:

- CG-LAB-14 Respiratory Viral Panel Testing in the Outpatient 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 (NGS) testing (MicroGenDx test) for UTIs with standard urine culture in 44 individuals who had symptoms of acute cystitis. Participants were

randomized to receive treatment based on culture results (Arm A, n=22) or treatment based on DNA NGS test results (Arm B, n=22). 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, with 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 of the 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 study are insufficient to conclude that DNA NGS testing resulted in better health outcomes than standard methods of diagnosing and managing UTIs. Additional studies in larger groups of individuals and with longer follow-up are needed.

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 neurophil 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%).

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.

Other Conditions

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

Background/Overview

Approximately 15.5 million physician office visits per year have infectious or parasitic diseases as the primary diagnosis (CDC, 2017). Between 2001 and 2014, infectious agents led to an annual age-adjusted rate of approximately 1500 hospitalizations per 100,000 individuals in the United States. 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.

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 used in research settings and no studies were identified on outpatient applications of the tests.

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Definitions

Clinical metagenomics: The field related to the sequencing 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), DNA, PCR and next-generation sequencing, plasma, detection of >1,000 potential microbial organisms for significant positive pathogens Karius® Test, Karius Inc, Karius Inc
87999	Unlisted microbiology procedure [when specified as other NGS analysis of microbes]

ICD-10 Diagnosis	
	All diagnoses

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References

Peer Reviewed Publications:

1. Kennedy JL, Haberling DL, Huang CC, et al. Infectious disease hospitalizations: United States, 2001 to 2014. Chest. 2019; 156(2):255-268.
2. 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.
3. 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.
4. 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.

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, 2017. Available at: https://www.cdc.gov/nchs/fastats/infectious-disease.htm. Accessed on December 2, 2019.

Websites for Additional Information

1. Urology Care Foundation of the American Urological Assocation (AUA). Urinary Tract Infections in Adults. Last updated April, 2019. Available at: https://www.urologyhealth.org/urologic-conditions/urinary-tract-infections-in-adults. Accessed on December 2, 2019.

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Karius Test
MicroGenDx

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.

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Document History

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New	02/20/2020	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.

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