CLINICAL MEDICAL POLICY

Policy Name:	Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders
Policy Number:	MP-013-MD-PA
Approved By:	Medical Management
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Products:	Pennsylvania Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 6

Disclaimer

Gateway Health℠ (Gateway) medical payment and prior-authorization policy is intended to serve only as a general reference resource regarding payment and coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

POLICY STATEMENT:

Gateway Health Plan® does not provide coverage under the medical surgical laboratory benefits of the Company's Medicaid products for whole exome and whole genome testing.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrants individual consideration, based upon review of applicable medical records.

(Current applicable PA HealthChoices Agreement Section V. Program Requirements, B. Prior Authorization of Services, 1. General Prior Authorization Requirements.)

DEFINITIONS:

Prior Authorization Review Panel – A panel of representatives from within the PA Department of Human Services who have been assigned organizational responsibility for the review, approval and denial of all PH-MCO Prior Authorization policies and procedures.

Whole Exome Sequencing (WES) – A laboratory testing process used to determine the arrangement (sequence) of the subset of an individual's entire genome that contains functionally important sequences of protein-coding DNA, at a

single time. WES involves obtaining blood samples from the individual and/or family members for the identification of mutations in the genome without having to target a gene or chromosome region based upon an individual's personal or family history.

Whole Genome Sequencing (WGS) – A laboratory testing process used to determine an individual's entire DNA sequence, specifying the order of every base pair within the genome at a single time. This testing requires a DNA sample from an individual's hair, saliva, epithelial cells or bone marrow. WGS is also known as full genome sequencing, complete genome sequencing or entire genome sequencing.

Next-Generation Sequencing – Described as a variety of technologies that allow rapid sequencing of large numbers of segments of DNA, up to and including entire genomes. Massively parallel sequencing (also known as next-generation sequencing), therefore, is not a test in itself or a specific sequencing technology. This term emphasizes a distinction from initial approaches that involve sequencing of one DNA strand at a time.

PROCEDURES

1. When services are not covered
   All whole exome and whole genome sequence testing are considered investigational for all conditions and therefore not medically necessary.

2. Post-payment Audit Statement
   The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Gateway Health Plan® at any time pursuant to the terms of your provider agreement.

3. The place of service for laboratory testing is outpatient.

4. Governing Bodies Approval
   a. FDA
   No U.S. Food and Drug Administration-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test.

   b. CLIA
   WES and WEG laboratory tests are offered as laboratory-developed tests under Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet general regulatory standards of CLIA and must be licensed by CLIA for high complexity testing.

   Additional information available at:
   http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm.

Summary of Literature

Whole exome sequencing (WES) and whole genome sequencing (WGS) using next-generation sequencing have been introduced as a laboratory-developed diagnostic clinical laboratory test. One of the potential major indications for their use is molecular diagnosis of patients with a phenotype that is suspicious for a genetic disorder or for patients with known genetic disorders that have a large degree of genetic heterogeneity involving substantial gene complexity. Such patients may be left without a clinical diagnosis of their disorder, despite a lengthy diagnostic workup involving a variety

of traditional molecular and other types of conventional diagnostic tests. For some of these patients, WES or WGS, after initial conventional testing has failed to make the diagnosis, may return a likely pathogenic variant.

At this time, there are many technical limitations to WES and WGS that prohibit their use in routine clinical care. The limited experience with WES on a population level leads to gaps in understanding and interpreting ancillary information and variants of uncertain significance. As a result, the risk/benefit ratio of WES testing is poorly defined.

WGS has also been used on a limited basis on a population level; additionally, one study demonstrated poor concordance between WGS testing platforms and with other forms of sequencing.

Currently there are no published studies that systematically examine potential outcomes of interest such as changes in medical management. Due to lack of clinical evidence demonstrating an impact on improved health outcomes and the many technical limitations to WES and WGS that prohibit their use in routine clinical care, the use of WES and WGS for the diagnosis of genetic disorders is considered investigational for all indications.

With WES and/or WEG sequence testing there are ethical questions about reporting incidental findings, such as identifying medically relevant mutations in genes unrelated to the diagnostic question, sex chromosome abnormalities, and non-paternity when family studies are performed. Standards for the required components of informed consent before WES/WGS is performed has been proposed and include a description of confidentiality and a description of how incidental findings will be managed.

Therefore, there is insufficient evidence to determine whether WES or WGS sequencing can be utilized to improve patient outcomes. Test results related to variants of uncertain significance may cause harm due to additional unnecessary interventions. This leads to questionable benefits of WES and WEG testing.

Examples of laboratories offering exome sequencing

Laboratory	Laboratory Indication for Testing
Ambry Genetics, Aliso Viejo, CA	"The patient's clinical presentation is unclear/atypical disease and there are multiple genetic conditions in the differential diagnosis"
GeneDx, Gaithersburg, MD	"A patient with a diagnosis that suggests the involvement of one or more of many different genes, which would, even if available and sequencing individually, be prohibitively expensive"
Baylor College of Medicine, Houston, TX	"Used when a patient's medical history and physical exam findings strongly suggest that there is an underling genetic etiology. In some cases, the patient may have had an extensive evaluation consisting of multiple genetic tests, without identifying an etiology"

University of California Los Angeles Health System	"This test is intended for the use in conjunction with the clinical presentation and other markers of disease progression for the management of patients with rare genetic disorders"
EdgeBio, Gaithersburg, MD	Recommended "In situations where there has been a diagnostic failure with no discernible path…In situations where there are currently no available tests to determine the status of a potential genetic disease…In situations with atypical findings indicative of multiple disease(s)"
Children's Mercy Hospitals and Clinics, Kansas City	Provided as a service to families with children who have had an extensive negative work up for a genetic disease; also used to identify novel disease genes.
Emory Genetics Laboratory, Atlanta, GA	"Indicated when there is a suspicion of a genetic etiology contributing to the probands manifestations"

CODING REQUIREMENTS

Noncovered procedure codes would include:

CPT Codes	Description
81415	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (e.g., parents, siblings); (list separately in addition to code for primary procedure)
81417	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (e.g., updated knowledge or unrelated condition/syndrome)
81425	Genome (e.g., unexplained constitutional or heritable disorder or syndrome) sequence analysis
81426	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (e.g., parents, siblings) (list separately in addition to code for primary procedure)
81427	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (e.g., updated knowledge or unrelated condition/syndrome)
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis

Policy Source(s)

Managed Care Operations Memorandum: Technology Assessment Group Decisions:

Available at: https://dpwintra.dpw.state.pa.us/HealthChoices/custom/post/mcopsmemo/mcopsmemo.asp

ACMG Board of Directors. Points to consider in the clinical application of genomic sequencing. Genet Med. 2012;14(8):759-761. Abstract available at: http://www.nature.com/gim/journal/v14/n8/full/gim201274a.html. Accessed on April 27, 2016.

Classen CF, Riehmer V, Landwehr C, et al. Dissecting the genotype in syndromic intellectual disability using whole exome sequencing in addition to genome-wide copy number analysis. Human Genetics. 2013 Jul;132(7):825-41. PMID: 23552953. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23552953. Accessed on April 27, 2016.

Yang Y, Muzny DM, Xia F, et al. Molecular findings among patients referred for clinical whole-exome sequencing. United States, 2014. P. 1870-9. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4326249/. Accessed on April 27, 2016.