HIGHMARK Delaware
HEALTH OPTIONS

CLINICAL MEDICAL POLICY	
Policy Name:	Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders
Policy Number:	MP-013-MD-DE
Responsible Department(s):	Medical Management
Provider Notice Date:	04/01/2019; 04/15/2018; 11/01/2016
Issue Date:	05/06/2019; 05/15/2018
Effective Date:	05/06/2019; 05/15/2018; 12/01/2016
Annual Approval Date:	03/12/2020
Revision Date:	03/12/2019; 12/13/2017; 08/09/2017; 03/14/2017
Products:	Highmark Health Options Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 7

DISCLAIMER

Highmark Health Options medical policy is intended to serve only as a general reference resource regarding 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

Highmark Health Options 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 warrant individual consideration, based upon review of applicable medical records.

The qualifications of the policy will meet the standards of the National Committee for Quality Assurance (NCQA) and the Delaware Department of Health and Social Services (DHSS) and all applicable state and federal regulations.

DEFINITIONS

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 (NGS) –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 is 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 Highmark Health Options at any time pursuant to the terms of your provider agreement.

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

GOVERNING BODIES APPROVAL

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

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

CODING REQUIREMENTS

Requests for the following procedures requires review by a Medical Director

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

REIMBURSEMENT

Participating facilities will be reimbursed per their Highmark Health Options contract.

SUMMARY OF LITERATURE

Whole exome sequencing (WES) and whole genome sequencing (WGS) using next-generation sequencing (NGS) have been introduced as a laboratory-developed diagnostic clinical test. Whole genome or whole exome sequencing results include three distinct categories: a variant known to cause human diseases, a variant suspected to cause human disease, and a variant of uncertain significance. One of the overarching, potential indications is the 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. Patients with the recognized conditions 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 and may return a likely pathogenic variant.

There are two major groups of disorders for diagnostic whole exome sequencing (WES), including:

- Mendelian disorders (caused by variants in a single gene);
- Multifactorial disorders (affected by variants in many genes as well as environmental factors)

A majority of WES studies were conducted for rare conditions with Mendelian inheritance patterns, whereby a single gene affects the condition and a variant is usually rare with a large effect. There has also been some analysis conducted on multifactorial disorders in some neurological disorders, whereby variants in many genes generally each have small effects. Multifactorial is limited for other conditions.

WES has primarily been used for two purposes—discovery and diagnosis. Discovery refers to identification of novel or previously identified variants that may have a protein-altering function on the disease being studied. WES has generally been used as a diagnostic tool in individual cases. Identification of protein-altering variants using WES may provide information on potential new avenues for diagnosis and treatment. The primary indication for whole genome sequencing (WGS) includes the determination of an individual's entire DNA sequence. There is some data that suggest genome sequencing as a preferred test to exome sequencing because of cost decreases and expanded information about the role of non-coding DNA in human disease (Hulick, 2018).

Large investment has been made to develop new approaches, such as NGS (Hulick, 2018). WES and WGS using NGS methods have been used to diagnose children with severe developmental delay or intellectual disability (Hulick, 2018). The Undiagnosed Diseases Network (UDN) has recently expanded NGS to older individuals with established medical conditions that have eluded diagnosis (Hulick, 2018).

Rationale

At this time, there are many technical limitations to WES and WGS that prohibit 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 at the population level; additionally, one study demonstrated poor concordance between WGS testing platforms and with other forms of sequencing.

The American College of Medical Genetics and Genomics (2018) conducted an updated systematic review on whole-exome and whole genome sequencing that investigates the benefits of the tests. There is evidence that indicates improved patient outcomes WES and WGS, but demand has increased for evidence in incremental costs and health outcomes compared to the technologies used in current practice (Schwarze, et al. 2018). The review focused on studies that evaluated conditions that were difficult to diagnose or focused on patients who had previously undergone multiple unsuccessful diagnostic procedures (Schwarze, et al. 2018). The American College of Medical Genetics and Genomics (2018) investigated the use of WES and WGS in many different disorders and conditions with a genetic background. Neurological or neurodevelopmental disorders in children and newborns comprised 36% of the review (Schwarze, et al. 2018). The outcome interpretation found few individual patients had an accurate molecular diagnosis from WES/WGS with concomitant changes in treatment (Schwarze, et al. 2018). Overall, the results of the systematic review indicated limited current health-economic evidence and resources to support the more widespread use of WES and WGS in clinical practice.

There is also NIH literature (2018) indicating that the significance of WES/WGS data is unknown. The literature also discusses difficulty to know whether there are identified variants involved in the condition of interest because not all genetic changes affect an individual's health (NIH, 2018).

There is limited clinical evidence demonstrating an impact on improved health outcomes, and the many technical limitations prohibit the use in routine clinical care. Therefore, WES and WGS testing is considered investigational in the diagnosis of genetic disorders.

WES and/or WGS sequencing raises 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 required components of informed consent before the sequencing is performed have been proposed and include a description

of confidentiality, as well as a description of how incidental findings will be managed. This data provides additional 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, leading to questionable benefits of WES and WEG testing.

UpToDate updated the literature on genome sequencing in healthy people, which suggests that the sequencing of all DNA genes has no known clinical value (Hulick, 2017). There is a lack of data surrounding the long-term effects versus harms of routine genome sequencing in healthy people (Hulick, 2017). WGS shows an absence of significant family history for most of the indicated conditions, which concludes an unclear interpretation and management of the variants (Hulick, 2018). Additionally, UpToDate concludes a lack of available prospective data, which presents unclear indication of achieved gains (Hulick, 2018).

Example 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.
My Genetics Laboratory Atlanta, GA	"Indicated when there is a suspicion of a genetic etiology contributing to the probands manifestations"
Emory Genetics Laboratory	"Indicated when there is a suspicion of a genetic etiology contributing to the proband's manifestations."
Knight Diagnostic Laboratory	"Diagnosing rare hereditary diseases, inconclusive results from targeted panel tests, presentation of multiple phenotypes or when a patient presents an unknown or novel phenotype."

POLICY SOURCE(S)

ACMG Board of Directors. Points to consider in the clinical application of genomic sequencing. Genet Med. 2012; 14(8):759-761. Accessed on April 27, 2016.

Classen C.F., 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. Accessed on April 27, 2016.

Hulick, P. Principles and clinical application of next-generation DNA sequencing. Up-To-Date, October 23rd, 2018. Accessed on December 13, 2017.

Managed Care Operations Memorandum: Technology Assessment Group Decisions:
Accessed on April 27, 2016.

Schwarze, K., Buchanan, J., Taylor, J.C., Wordsworth, S. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. American College of Medical Genetics and Genomics: Systematic Review. Accessed on November 5, 2018.

NIH: U.S. National Library of Medicine. Genetics Home Reference: Your Guide to Understanding Genetic Conditions. Published October 30th, 2018. Accessed on November 5, 2018.

Yang Y., Muzny D.M., Xia F., et al. Molecular findings among patients referred for clinical whole-exome sequencing. United States, 2014. P. 1870-9. Accessed on April 27, 2016.

Policy History

Date	Action
09/06/2016	Initial policy developed & approved by QI/UM
12/01/2016	Provider Effective Date
02/10/2017	Revisions: General formatting of the outline and face sheet (PAGE 1-4), added definitions (PAGE 2), criteria revisions (PAGE 2-4), non-covered criteria revisions and additional Precautions were added (PAGE 5-6), summary of literature update (9,10,11), ICD-10/CPT/HCPCS update and revisions (13-26), and reference revisions and additions (26-29); operational guidelines from post payment to prepayment and added "Policy History"
03/14/2017	QI/UM Committee Review Approval
08/09/2017	Added Disclaimer Statement in opening of medical policy. EHS Revisions: Issue Date added to opening policy box; Operation Guidelines updated to indicate 'services are to deny as not medically necessary', "Informational' added to Attachment C
12/13/2017	Clinical Review: no changes to criteria Revisions: Updated literature and references added
03/13/2018	QI/UM Committee Review Approval
05/15/2018	Provider effective date

03/12/2019	Annual Review Revisions: Formatting updates to definitions, procedures section and attachments; Health Options position remains; Added additional current literature and rationale; removed the hyperlinks in Attachment D- references
03/12/2019	QI/UM Committee Review Approval
05/06/2019	New Provider effective date