Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

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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 may provide coverage under the medical-surgical benefits of the Company's Medicaid products for medically necessary whole exome testing.

Highmark Health Options does not provide coverage under the medical surgical laboratory benefits of the Company's Medicaid products for 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

Highmark Health Options (HHO) – Managed care organization serving vulnerable populations that have complex needs and qualify for Medicaid. Highmark Health Options members include individuals and families with low income, expecting mothers, children, and people with disabilities. Members pay nothing to very little for their health coverage. Highmark Health Options currently serves Delaware Medicaid: Delaware Healthy Children Program (DHCP) and Diamond State Health Plan and Health Plan Plus members.

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

- Whole genome sequencing is investigational and therefore, not medically necessary.
- Whole exome sequencing is medically necessary once per lifetime to determine a diagnosis for an unexplained disorder when all of the following clinical and testing criteria are met:

One of the following clinical criteria:

- A suspected genetic disorder where a specific single-gene or targeted panel test is not available (American College of Medical Genetics and Genomics, 2012).
- A suspected genetic disorder where corresponding genetic tests have been nondiagnostic (American College of Medical Genetics and Genomics, 2012).
- A complex, unspecific genetic disorder with multiple differential diagnoses when whole exome sequencing would be a more efficient and practical diagnostic approach (American College of Medical Genetics and Genomics, 2012).
- A genetically heterogeneous disorder that requires multiple panel testing or clinical testing when whole exome sequencing may preclude the need for multiple and/or invasive procedures, follow-up, or screening that would be recommended in the absence of testing (American College of Medical Genetics and Genomics, 2012).
- The fetus presents with one or more significant sonographic anomalies suggestive of genetic etiology, and routine prenatal diagnostic methods are nondiagnostic (Monaghan, 2020).

All of the following testing criteria (American College of Medical Genetics and Genomics, 2013, 2015; American College of Obstetricians and Gynecologists, 2016; Kalia, 2017):

- The test is ordered by a genetic specialist.
- The test is analytically and clinically valid (i.e., supported by peer-reviewed published research).
- The test results will directly impact diagnosis, treatment, management, or prevention of disease of the member.
- Genetic counseling is provided before and after testing by a primary care provider and a geneticist (who is a physician or a licensed genetic counselor). If access to a genetic counselor or medical geneticist is not possible, genetic counseling may be initiated by a physician with relevant genetic expertise.
- Informed consent is obtained prior to testing and includes disclosure of the limitations of the testing method, incidental or secondary findings (and the option of not receiving these findings), the risks and benefits of the test information on the member's care and/or family, and current professional guidelines.
- The test results will be discussed with the member or guardian and documented in the clinical record.

- Member or guardian's desire for engagement with the integrated multidisciplinary team is documented in the clinical record.
- 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.

- 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

Covered Codes

Requests for the following procedures requires review by a Medical Director

CPT Codes	Description
81479	Unlisted molecular pathology procedure.

Noncovered Codes

CPT code	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).

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."

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POLICY UPDATE HISTORY

08/19/2021	Approved in Medical Policy Committee
08/31/2021	Approved in QI/UM
04/13/2022	Added noncovered CPT code list