CLINICAL MEDICAL POLICY	
Policy Name:	Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders
Policy Number:	MP-013-MD-PA
Responsible Department(s):	Medical Management
Provider Notice/Issue Date:	03/01/2025; 09/01/2023; 02/01/2023: 09/01/2022; 05/01/2022; 02/13/2021; 02/17/2020; 03/18/2019; 04/15/2018; 10/01/2016
Effective Date:	04/01/2025; 10/01/2023; 03/01/2023; 10/01/2022; 06/01/2022; 03/15/2021; 03/16/2020; 03/18/2019; 04/15/2018; 10/01/2016
Next Annual Review:	12/2025
Revision Date:	12/18/2024; 07/19/2023; 12/21/2022; 06/15/2022; 12/15/2021; 11/18/2020; 12/18/2019; 11/14/2018; 12/13/2017; 08/09/2017; 03/15/2017
Products:	Highmark Wholecare℠ Medicaid
Application:	All participating hospitals and providers
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Policy History

Date	Action
04/01/2025	Provider Effective date
01/28/2025	PARP Approval
12/18/2024	QI/UM Committee review
12/18/2024	Annual Review: No changes to clinical criteria. Updated 'Summary of Literature' and 'Reference Sources' sections.
09/01/2023	Provider Effective date
08/07/2023	PARP Approval
07/19/2023	QI/UM Committee review
07/19/2023	Urgent Review: Per PA DHS: the following CPT codes are no longer considered 'noncovered': 81425, 81426, & 81427. The CPT codes will be considered as an Option #3, and will require a Program Exception for approval. CPT code 81546 has been added and will also be considered as an Option #3 and will require a Program Exception for approval.
03/01/2023	Provider Effective date
01/10/2023	PARP Approval

12/21/2022	QI/UM Committee review
12/21/2022	Annual Review: No changes to clinical criteria. Reformatted 'Procedure' section numbering.
10/01/2022	Provider Effective date
07/25/2022	PARP Approval
06/15/2022	QI/UM Committee review
06/15/2022	Urgent Review: Updated PA TAG information, which removes the case-by-case Medical Director review requirement for Whole Exome Sequencing (WES) therapy only. No other changes to clinical criteria.

Disclaimer

Highmark Wholecare℠ 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 Wholecare℠ does not provide coverage under the medical-surgical laboratory benefits of the Company's Medicaid products for whole exome and whole genome sequence 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.

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

Definitions

Prior Authorization Review Panel (PARP) – 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 (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. Whole Exome Sequencing (WES) is considered medically necessary when ALL of the following conditions are met:
    A. The individual and their family history have been evaluated by a Board Certified or Board Eligible Medical Geneticist (see provider descriptions under *'2. Genetic Counseling'* below); AND
    B. A clinical letter from a Geneticist (see provider descriptions under *'2. Genetic Counseling'* below); is provided which includes ALL of the following information:
        1) Differential diagnoses; AND
        2) Testing algorithm; AND
        3) Any previous tests performed, with results; AND
        4) A conclusion that genetic etiology is the most likely explanation; AND
        5) A recommendation that WES is the most appropriate test; AND
        6) Impacts to the patient's plan of care; AND
    C. The individual is 21 years of age or younger; AND
    D. A genetic etiology is considered to be the most likely reason for the phenotype, based on EITHER of the following:
        1) Multiple congenital anomalies defined by ANY ONE of the following:
            a) Two (2) or more major anomalies affecting different organs; OR
            b) One (1) major and two (2) or more minor anomalies affecting different organs; OR
        2) ANY TWO (2) of the following conditions are met:
            a) major abnormality affecting at minimum a single organ system*; AND/OR
            b) formal diagnosis of autism, significant developmental delay, or intellectual disability (e.g., characterized by significant limitations in both intellectual functioning and in adaptive behavior), AND/OR
            c) symptoms of a complex neurodevelopmental disorder (e.g., self-injurious behavior, reverse sleep-wake cycles, dystonia, ataxia, alternating hemiplegia, neuromuscular disorder); AND/OR
            d) severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome); AND/OR
            e) period of unexplained developmental regression; AND/OR
            f) laboratory findings suggestive of an inborn error of metabolism; AND

    E. Alternate etiologies have been previously considered and ruled out (e.g., environmental exposure, injury, infection); AND

F. Clinical presentation does not fit a well-described syndrome that has first-tier testing available (e.g., single gene testing, comparative hybridization [CGH]/chromosomal microarray testing [CMA]); AND
G. Multiple targeted panels are appropriate based on the patient's clinical presentation; AND
H. There is a predicted impact on the individual's health outcomes including ANY of the following:
    1) Application of specific treatments; OR
    2) Withholding of contraindicated treatments; OR
    3) Surveillance for later-onset comorbidities; OR
    4) Initiation of palliative care, OR
    5) Withdrawal of care; AND
I. A diagnosis cannot be made by a standard clinical exam, excluding invasive procedures such as a muscle biopsy.

*__Note__: Major structural abnormalities are generally serious enough as to require medical treatment on their own (such as surgery) and are not minor developmental variations that may or may not suggest an underlying disorder.

2. Genetic Counseling

   Pre- and post-test genetic counseling is required to be performed by an independent (not employed by a genetic testing lab) genetic specialist/counselor prior to genetic testing for mutations. This service is necessary in order to inform persons being tested about the benefits and limitations of a specific genetic test for the specific patient. Genetic testing for mutation requires documentation of medical necessity from one of the following providers who has evaluated the patient and intends to see the patient after testing has been performed for counseling:
   - Board Eligible or Board Certified Genetic Counselor
   - Advanced Genetics Nurse
   - Genetic Clinical Nurse
   - Advanced Practice Nurse in Genetics
   - Board Eligible or Board Certified Clinical Geneticist
   - A physician with experience in cancer genetics
   - A physician specializing in pediatric neurology and/or developmental pediatrics

3. WES is considered not medically necessary for conditions other than those listed above, scientific evidence of medical necessity has not been established. Examples of not medically necessary indications for WES include, but are not limited to:
   - Prenatal diagnosis by exome sequencing is considered experimental/investigational
   - Exome deletion/duplication analysis is considered experimental/investigational
   - WES is considered experimental/investigational for screening for genetic disorders in asymptomatic or pre-symptomatic individuals

4. Whole Genomic Sequencing (WGS) is considered experimental/investigational and is not medically necessary.

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

6. Place of Service
   The proper place service for whole exome sequencing testing is outpatient.

7. Related Policies
   - MP-071-MD-PA Non-Oncologic Genetic Testing Panels

Operational Guidelines *Do not include on external version*

- For both professional and facility providers, the diagnosis and procedure codes are applied as preservice, prepayment basis.
- As of 11/03/2021, WES therapy was granted an Option #1 (*Approved - Will be added to the Fee Schedule*) determination by PA TAG and will no longer require a case-by-case Medical Director review for approval, specifically for CPT codes 81415, 81416, and 81417. A prior authorization will still be required.
- As of 04/11/2023, the following CPT codes were granted an Option #3 (*Approved with [or denied due to] Limited/Minimal Evidence of Effectiveness - Will require Program Exception)* determination by PA TAG: 81425, 81426, 81427, & 81546.

Governing Bodies Approval

Helix, a population genomics company, has received *de novo* authorization from the U.S. Food & Drug Administration (FDA) for the Helix Laboratory Platform, a WES platform with coverage of approximately 20,000 genes. The Helix Laboratory Platform is a qualitative in vitro diagnostic device intended for exome sequencing and detection of single nucleotide variants (SNVs) and small insertions and deletions (indels) in human genomic DNA extracted from saliva samples collected with Oragene® Dx OGD-610. The Helix Laboratory Platform is only intended for use with other devices that are germline assays authorized by FDA for use with this device. The device is performed at the Helix laboratory in San Diego, CA (BioSpace, 2021).

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.

CMS
The Centers for Medicare and Medicaid Services (CMS) has published no specific guidance on WES or WGS. The following address information pertaining to biomarkers:

- Local Coverage Determination (LCD) Biomarkers Overview (L35062) addresses the emergence of personalized laboratory medicine.

- Local Coverage Article (LCA) Billing and Coding: Biomarkers Overview (A56541) provides billing and coding guidance for LCD (L35062) Biomarkers Overview (this LCA does not address WES/WGS coding).

The Pennsylvania Department of Human Services Technology Assessment Group (TAG) workgroup meets quarterly to discuss issues revolving around new technologies and technologies or services that were previously considered to be a program exception. During this meeting, decisions are made as to whether or not certain technologies will be covered and how they will be covered. TAG's decisions are as follow:

- Option #1: Approved - Will be added to the Fee Schedule
- Option #2: Approved as Medically Effective - Will require Program Exception
- Option #3: Approved with (or denied due to) Limited/Minimal Evidence of Effectiveness - Will require Program Exception
- Option #4: Denied - Experimental/Investigational

In May 2021, the TAG workgroup assigned whole exome sequencing an Option # 1, specifically for CPT codes 81415, 81416, and 81417.

In April 2023, the TAG workgroup assigned the following CPT codes an Option #3: 81425, 81426, 81427, and 81546,

Coding Requirements

Procedure 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)
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)
81546	Oncology (thyroid), mRNA, gene expression analysis of 10,196 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious)

Non-Covered Procedure Codes

CPT Code	Description
0094U	Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis

Reimbursement

Participating facilities will be reimbursed per their Highmark Wholecare℠ contract.

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