| 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:** | 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:** | 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:** | 12/2024 |
| **Revision Date:** | 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 |
| **Page Number(s):** | 1 of 13 |

**Policy History**

| Date | Action |
|---|---|
| 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 |

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|---|---|
| 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. |
| 06/01/2022 | Provider Effective date |
| 03/25/2022 | PARP Approval |
| 12/15/2021 | QI/UM Committee review |
| 12/15/2021 | Annual Review: Coverage for WES changed from E/I to medical review status. Added updated coverage criteria changes to 'Procedures' section. WGS will continue to be considered E/I. Updated Summary of Literature and Reference Sources sections. The following CPT codes will be reviewed by a Medical Director for consideration: 81415, 81416, & 81417. |
| 03/15/2021 | Provider Effective Date |
| 02/02/2021 | PARP Approval |
| 11/16/2020 | QI/UM Committee Review |
| 11/16/2020 | Annual Review: No criteria changes. Updated Summary of Literature and References sections. |
| 03/16/2020 | Provider Effective Date |
| 01/16/2020 | PARP Approval |
| 12/18/2019 | QI/UM Committee Review |
| 12/18/2019 | Annual Review: No change in coverage determination; updated Summary of Literature and references; added new procedure code 0094U. |
| 05/11/2016 | PARP Approval |

## 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 patient and the patient's 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 patient 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 or more major anomalies affecting different organs; OR
            b) One major and two or more minor anomalies affecting different organs; OR
        2) ANY TWO 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 patient'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

## 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,

## 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. WES/WGS 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 WES, including:

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

WGS refers to sequencing the entire genome, both the noncoding regions (introns) and coding regions (exons). Currently, the ability to interpret the intronic regions is limited, and WGS is not routinely being performed in the clinical setting. WES, which involves sequencing only the exons or protein-coding regions of the genome, is more frequently used in clinical genetics testing. Exons generally have greater clinical relevance and applicability to patient care, and most of our understanding of Mendelian inherited disorders is derived from research on variants in the exome, which comprises only 1% of the human genome (ACOG, 2018).

The American College of Medical Genetics and Genomics (ACMG) recommends considering WES when specific genetic tests available for a phenotype, including targeted sequencing tests, have failed to arrive at a diagnosis in a fetus with multiple congenital anomalies suggestive of a genetic disorder.

The ACMG has provided seven points to refer to when considering DNA-based screening:

1. The ACMG secondary findings recommendations do not constitute a primary health screening recommendation or strategy.
2. DNA-based screening should not replace a standard-of-care evaluation for individuals with a clinical indication for diagnostic assessment.
3. Disease risks identified through screening should not include DNA variants of uncertain significance (VUS).
4. DNA-based screening should be linked to opportunities for evidence-based risk-reducing clinical care.
5. Risk-reducing clinical follow-up for DNA-based screening should be consistent with best practices outlined by professional societies with appropriate expertise.
6. Organizations involved in DNA-based screening are expected to participate in sharing of outcomes-related data.
7. DNA-based screening applications with proven beneficial clinical outcomes should be made available to entire populations to promote health-care equity and limit health disparities (ACMG, 2021).

The ACMG and pprofessional organizations have consistently endorsed an informed consent process prior to germline genetic testing to review the potential benefits, harms, and limitations of testing, including the implications of results for the patient and their family member. With an ES/GS screening test, the complexities of potential test results that should be understood include:

- The potential positive and negative impact of ES/GS screening test results and their implications for family members.
- Awareness that the laws protecting genetic privacy and nondiscrimination are not comprehensive, and that those that do exist have not been fully tested; some groups may not be protected by existing laws.
- Lifetime disease risks are often not known, including penetrance and variable expressivity of a pathogenic variant.
- A false negative result: A person may be at risk for a health problem not identified by the ES/GS test due to technical (a pathogenic variant is present but not detected) or interpretive error (a pathogenic variant is interpreted as benign) or because not all gene–disease associations are known.
- A false positive result: A person may not be at risk for a health problem suggested by the ES/GS screening test results due to technical (a reported pathogenic variant is not actually present) or interpretive error (a benign variant is interpreted as pathogenic).
- Evolving interpretation: The results of a genetic test may indicate risk for disease; however, the clinical significance of variants, gene–disease associations, penetrance of pathogenic variants, and opportunities for clinical interventions can change with time.
- Evidence to support clinical actions based on ES/GS findings may not be available.
- Results may indicate a need for a medical evaluation, preventive services, or ongoing surveillance; however, access to health care may be limited or restricted due to out-of-pocket costs or lack of insurance.

- Options for the type of genetic test result to be reported such as carrier status for recessive conditions, adult-onset medically actionable or nonactionable findings, pharmacogenomics results (ACMG, 2021).

Despite WES' promise for increasing the ability to diagnose many diseases in children or adults, there are important limitations to this technology in prenatal testing. As of 2016, the use of WES prenatally is hampered by long turnaround times because of the need to sequence and analyze the entire exome. As the ability to analyze the exome improves with state-of-the-art bioinformatics protocols and tools, this turnaround time is expected to decrease. The turnaround time in adults and children ranges from 5 weeks to 18 weeks. There are no consistent data for prenatal whole-exome sequencing, although the potential for long turnaround times limits the use of whole-exome sequencing for prenatal diagnosis, and especially for reproductive decision making. These limitations and the current dearth of peer-reviewed data and validation studies proving the clinical utility of this technology, the College and the Society for Maternal–Fetal Medicine currently do not recommend whole-exome sequencing for routine use in prenatal diagnosis (ACOG, 2016).

Rationale

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).

In 2021, an ACMG evidence-based clinical practice guideline was developed for the use of WES/WGS in the care of pediatric patients with one or more congenital anomalies (CA) with onset prior to age 1 year or developmental delay (DD) or intellectual disability (ID) with onset prior to age 18 years. Congenital anomalies (CA), developmental delay (DD), and intellectual disability (ID) are among the most common indications for genetic referral in the pediatric population and comprise a heterogeneous group of conditions that can impact a child's physical, learning, or behavioral function. In contrast to early childhood mortality, which declined by 50% from 1990 to 2016, the prevalence of developmental disabilities was unchanged over the same period, according to the Global Burden of Diseases, Injuries and Risk Factors Study. The Pediatric Exome/Genome Sequencing Evidence-Based Guideline Work Group (n = 10) used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence to decision (EtD) framework based on the recent American College of Medical Genetics and Genomics (ACMG) systematic review, and an Ontario Health Technology Assessment to develop and present evidence summaries and health-care recommendations. The document underwent extensive internal and external peer review, and public comment, before approval by the ACMG Board of Directors. The ACMG strongly recommend that ES/GS be considered as a first- or second-tier test for patients with CA/DD/ID (ACMG, 2021).

According to the U.S. National Library of Medicine, while many genetic changes can be identified with whole exome and whole genome sequencing than with select gene sequencing, the significance of much of this information is unknown. Because not all genetic changes affect health, it is difficult to know whether identified variants are involved in the condition of interest. Sometimes, an identified variant is associated with a different genetic disorder that has not yet been diagnosed (these are called incidental or secondary findings) (U.S. National Library of Medicine, 2021).

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. There is a lack of data surrounding the long-term effects versus harms of routine genome sequencing in healthy people. WGS shows an absence of significant family history for most of the indicated conditions, which concludes an unclear interpretation and management of the variants. Additionally, UpToDate concludes a lack of available prospective data, which presents unclear indication of achieved gains (Hulick, 2021).

WES is considered to be one of the most comprehensive genetic tests to identify various diseases caused by changes in the exome. The exome constitutes approximately 1% of the whole genome but 85% of all disease causing mutations are located. WES targets all protein coding exons and ± 20 base pairs from the exon-intron boundary. The test also includes >1500 selected non-coding, deep intronic disease causing variants.

Genome sequencing is typically performed by next-generation sequencing of sheared genomic DNA. Genome sequencing techniques have non-standardized, highly variable coverage. The coverage of the genome is less than 100% and varies by laboratory. A study by Telenti et al (2016) sequenced more than 10,000 genomes at a mean read depth of 30-40x (i.e., each DNA fragment was sequenced an average of 30 to 40 times); the authors reported that 91.5% of exons and 95.2% of known pathogenic variant positions could be sequenced with high confidence. The clinical sensitivity of genome sequencing is unknown (Wallace & Bean, 2017).

Although genome sequencing can identify variants outside of the coding regions, most of the confirmed pathogenic variants identified by genome sequencing are within the exome (Taylor et al, 2015). The diagnostic utility of exome sequencing and genome sequencing (~20%-30%) remains similar. As more noncoding pathogenic variants are identified, the clinical sensitivity and value of genome sequencing should increase (Wallace & Bean, 2017).

WES is beginning to be introduced for prenatal genetic diagnosis for pregnancies with fetal anomalies for which standard testing with chromosomal microarray analysis (CMA) and karyotyping has been unrevealing. Research and early clinical experience with fetal WES indicate that the detection rate of clinically significant sequence variants varies by indication and type of fetal anomalies present but is likely higher than that of CMA. This higher molecular diagnostic rate has significant benefits for prenatal

diagnosis but as with CMA, there is an associated risk for detecting variants of uncertain significance and incidental findings unrelated to the fetal phenotype. Although diagnostic fetal WES under guidance by genetics experts can be considered for fetal anomalies, more studies are needed to determine its clinical utility and optimal integration into prenatal diagnosis, and to establish how best to manage variants of uncertain significance and incidental findings (Van de Veyver, 2019).

In prenatal testing, genome sequencing (GS) involves assessing both the coding and noncoding regions of the genome, although a complete genome sequence is challenging to attain due to difficulty of sequencing and analysis in certain regions. Exome sequencing (ES) is limited to the protein coding regions of more than 20,000 genes, comprising about 1–2% of the genome. According to the American College of Medical Genetics and Genomics (ACMG), although GS may be more informative due to its scope, it requires greater data analytics and is not routinely utilized in clinical testing at this time. GS and ES in prenatal testing needs additional research on patient perspectives of the consent process, effective and appropriate communication of uncertainty, return of results and reinterpretation, and health and economic outcomes (Monaghan, Leach, Pekarek, et al, 2020).

Hayes, Inc.
Prenatal Whole Genome Sequencing and Prenatal Whole Exome Sequencing

- An insufficient rating was provided for the use of prenatal whole exome sequencing (WES) and whole genome sequencing (WGS) to improve diagnosis and inform pregnancy and post-pregnancy patient management where fetal abnormalities have been detected by ultrasound or other testing. Evidence from 4 studies, including 66 fetuses in total, suggests that prenatal WES can be used to inform management decisions when standard genetic testing is negative. However, all studies identified were small studies with highly selected populations. These data are limited and of very low quality
- An insufficient rating was provided for the use of prenatal whole genome sequencing (WGS) to improve diagnosis and inform pregnancy and post-pregnancy patient management where fetal abnormalities have been detected by ultrasound or other testing. No peer-reviewed studies outside of the case literature were identified that evaluated the clinical utility of prenatal WGS. Studies are needed that include a sizable cohort and report clinical management decisions and patient outcomes directly resulting from prenatal WGS.

Whole Genome Sequencing (WGS) In Neonatal and Pediatric Patients

- **C Rating** – For use of whole genome sequencing (WGS) to identify or confirm the genetic etiology of a known or unknown disorder in clinically affected neonatal and pediatric patients. This Rating reflects an assessment of articles relevant only to clinical utility and for which a low-quality body of evidence was observed, the limitations of this report, and the emerging use of this technology. The Rating weighs the benefit from identification of the underlying genetic cause(s) of the disease(s), the impact on patient clinical management, and the ability to alter the management of family members resulting from WGS of the proband, and balances this with the current limitations of WGS and the potential harms and ethical concerns resulting from WGS of pediatric patients.
- **D2 Rating** – For use of WGS for newborn screening. This Rating reflects the lack of studies that demonstrate the clinical utility of WGS for this indication.

## 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.

## Reference Sources

American College of Medical Genetics and Genomics (ACMG) Board of Directors. Points to consider in the clinical application of genomic sequencing. Genet Med. 2012. Accessed on October 4, 2021.

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. July 2013. Accessed on October 4, 2021.

Hulick P. Principles and clinical application of next-generation DNA sequencing. Up-To-Date. September 14, 2021. Accessed on October 4, 2021.

Schwarze K, Buchanan J, Taylor JC, 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 (ACMG) February 15, 2018. Accessed on October 4, 2021.

Klee EW. Centers and programs: Center for individualized medicine. Translation Genomics Program. Mayo Clinic. No date provided. Accessed on November 20, 2019.

Monaghan KG, Leach NT, Pekarek D., et al. The use of fetal exome sequencing in prenatal diagnosis: a points to consider document of the American College of Medical Genetics and Genomics (ACMG). Genet Med 22, 675–680. January 8, 2020. Accessed on October 4, 2021.

U.S. National Library of Medicine. Genetics Home Reference: What are whole exome sequencing and whole genome sequencing? Updated on July 28, 2021. Accessed on October 4, 2021.

Wallace SE, Bean LJH. Educational Materials — Genetic Testing: Current Approaches. GeneReviews®. March 14, 2017. Accessed on October 4, 2021.

Hayes, Inc. Clinical Utility Evaluation: Prenatal Whole Genome Sequencing and Prenatal Whole Exome Sequencing. June 15, 2020. Annual Review May 3, 2021. Accessed on October 4, 2021.

Hayes, Inc. Clinical Utility Evaluation: Whole Genome Sequencing (WGS) In Neonatal And Pediatric Patients. September 22, 2016. Annual Review August 12, 2019. Accessed on October 4, 2021.

Van de Veyver IB. Perinatal Genetics. Chapter 13 – Exome and Genome Sequencing. Pages 137-48. 2019. Accessed on October 4, 2021.

Centers for Medicare and Medicaid Services (CMS). Local Coverage Article (LCA) Billing and Coding Biomarkers Overview (A56541). Original Effective date May 30, 2019. Revision Effective date July 1, 2020. Accessed on October 4, 2021.

Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD) Biomarkers Overview (L35062). Original Effective date October 1, 2015. Revision Effective date July 1, 2020. Accessed on October 4, 2021.

Murray MF, Giovanni MA, Doyle DL et al. DNA-based screening and population health: a points to consider statement for programs and sponsoring organizations from the American College of Medical Genetics and Genomics (ACMG). Genet Med 23, 989–995. March 16, 2021. Accessed on October 4, 2021.

Bean L, Scheuner MT, Murray MF, Biesecker LG, et al. DNA-based screening and personal health: a points to consider statement for individuals and health-care providers from the American College of Medical Genetics and Genomics (ACMG) Genetics in Medicine 23:979–988. 2021. Accessed on October 4, 2021.

BioSpace. Helix Laboratory Platform Granted the First and Only FDA Authorization for a Whole Exome Sequencing Platform. January 11, 2021. Accessed on November 30, 2021.

American College of Obstetricians and Gynecologists (ACOG). Technology Assessment: Modern Genetics in Obstetrics and Gynecology. Number 14. September 2018. Accessed on November 30, 2021.

American College of Obstetricians and Gynecologists (ACOG). Committee Opinion: Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology. Number 682. December 2016. Accessed on November 30, 2021.

American College of Medical Genetics and Genomics (ACMG). Practice Guideline: Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability. Genetics in Medicine 23:2029–2037. 2021. Accessed on November 30, 2021.

Pennsylvania Department of Human Services. Technology Assessment Group (TAG) Coverage Decisions. Managed Care Operations Memorandum: November 3, 2021. Option #1 for WES only. Accessed on May 4, 2022.

Pennsylvania Department of Human Services. Technology Assessment Group (TAG) Coverage Decisions. Managed Care Operations Memorandum: April 11, 2023. MCOPS Memo # 05/2023-006. Option #3. Accessed on June 26, 2023.