Medical Coverage Policy

Effective Date 1/15/2024
Next Review Date 1/15/2025
Coverage Policy Number.....0519

Whole Exome and Whole Genome Sequencing for Non-Cancer Indications

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Genetic Testing for Hereditary Cancer Susceptibility Syndromes
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Overview

This Coverage Policy addresses whole exome and whole genome sequencing for the evaluation of germline genetic disease, whole genome optical mapping, and transcriptome sequencing.

For genetic testing for germline hereditary cancer syndromes, see Medical Coverage policy 0518 Genetic Testing for Hereditary Cancer Susceptibility Syndromes.

For genetic testing for somatic (oncology/hematology) indications, see Medical Coverage policy 0520 Molecular and Proteomic Diagnostic Testing for Hematology and Oncology Indications.

Coverage Policy

Many benefit plans limit coverage of genetic testing and genetic counseling services. Please refer to the applicable benefit plan language to determine benefit availability and terms, conditions and limitations of coverage for the services discussed in this Coverage Policy.

Pre- and post-test genetic counseling is required for any individual undergoing whole exome or whole genome sequencing. Please see disease specific criteria below for additional information regarding genetic testing.

Whole exome or whole genome sequencing is considered medically necessary when criteria listed below are met and when a recommendation for testing is confirmed by ONE of the following:

- an independent Board-Certified or Board-Eligible Medical Geneticist
- an American Board of Medical Genetics and Genomics or American Board of Genetic Counseling-certified Genetic Counselor not employed by a commercial genetic testing laboratory (Genetic counselors are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).
- a genetic nurse credentialed as either a Clinical Genomics Nurse (CGN) or an Advanced Clinical Genomics Nurse (ACGN) by the Nurse Portfolio Credentialing Commission, Inc. OR a genetic nurse with an Advanced Genetics Nursing Certification (AGN-BC) renewed by the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory (genetic nurses are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself)

  who:
  - has evaluated the individual
  - completed a three generation pedigree
  - intends to engage in post-test follow-up counseling

General Criteria

Whole exome or whole genome sequencing is considered medically necessary when ALL of the following criteria are met:

- individual has been evaluated by a board-certified medical geneticist or other board certified specialist physician specialist with specific expertise in the conditions and relevant genes for which testing is being considered
- testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested
- no other causative circumstances (e.g., environmental exposures, injury, prematurity, infection) can explain symptoms
- clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing (e.g., comparative genomic hybridization [CGH]/chromosomal microarray analysis [CMA]), is available
- the differential diagnosis list and/or phenotype warrant testing of multiple genes and ONE of the following:
    - Whole exome or whole genome sequencing is more practical than the separate single gene tests or panels that would be recommended based on the differential diagnosis.
    - Whole exome or whole genome sequencing results may preclude the need for multiple and/or invasive procedures, follow-up, or screening that would be recommended in the absence of testing.

Disease Specific Criteria

Whole exome or whole genome sequencing is considered medically necessary for ANY of the following clinical scenarios when ALL of the general criteria listed above are also met:

- Phenotype suspicious for a genetic diagnosis:
    - ANY of the following:
        - individual with multiple major structural or functional congenital anomalies affecting unrelated organ systems, including metabolic disorders
        - individual with one major structural congenital anomaly and two or more minor structural anomalies
        - individual with at least two of the following:
            - major structural congenital anomaly affecting a single organ system
            - neurological features including at least two of the following:
                - autism
                - severe psychological/psychiatric disturbance (e.g., self-injurious behavior, reversed sleep-wake cycles) or severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome)
                - symptoms of a complex neurodevelopmental disorder (e.g., dystonia, ataxia, alternating hemiplegia, neuromuscular disorder)
            - family history strongly implicating a genetic etiology
            - period of unexplained developmental regression (unrelated to autism or epilepsy)
- Epilepsy:
    - individual with known or suspected developmental and epileptic encephalopathy (onset before three years of age) for which likely non-genetic causes of epilepsy

(e.g. environmental exposures; brain injury secondary to complications of extreme prematurity, infection, trauma) have been excluded

- Hearing Loss:
  - individual with confirmed bilateral sensorineural hearing loss of unknown etiology
- Global developmental delay:
  - individual diagnosed with global developmental delay* following formal assessment by a developmental pediatrician or neurologist
- Intellectual disability:
  - individual diagnosed with moderate/severe/profound intellectual disability** following formal assessment by a developmental pediatrician or neurologist
- Fetal testing, when ALL of the following criteria are met:
  - standard diagnostic genetic testing (chromosomal microarray analysis (CMA) and/or karyotype) of the fetus has been performed and is uninformative
  - testing is performed on direct amniotic fluid/chorionic villi, cultured cells from amniotic fluid/chorionic villi or DNA extracted from fetal blood or tissue
  - at least one of the following is present:
    - multiple fetal structural anomalies affecting unrelated organ systems
    - fetal hydrops of unknown etiology
    - a fetal structural anomaly affecting a single organ system and family history strongly suggests a genetic etiology

*Global developmental delay is defined as significant delay in younger children, under age five years, in at least two of the major developmental domains: gross or fine motor; speech and language; cognition; social and personal development; and activities of daily living.

**Moderate/severe/profound intellectual disability as defined by Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, diagnosed by 18 years of age.

Whole Exome/Genome Reanalysis and Retesting

Whole exome or whole genome sequencing retesting OR reanalysis of previously obtained uninformative whole exome or whole genome sequence data is considered medically necessary when the above criteria for whole exome/genome sequencing and ANY of the following conditions are met:

- onset of additional symptoms that broadens the phenotype assessed during the original exome/genome evaluation
- birth or diagnosis of a similarly affected first-degree relative*** that has expanded the clinical picture
- New scientific knowledge suggests a previously unknown link between the individual's findings and specific genes/pathogenic or likely pathogenic variants AND at least 18 months have passed since the last analysis.

***A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children.

Each of the following is considered experimental, investigational, or unproven for any indication:

- whole genome sequencing of the transcriptome (RNA sequencing)
- whole genome optical mapping

Testing using whole exome or whole genome sequencing is considered not medically necessary for ANY of the following indications:

- testing using cell-free DNA
- preimplantation testing of an embryo
- genetic carrier screening
- non-syndromic autism spectrum disorder (isolated autism)
- isolated speech delay
- mild intellectual disability

Testing of a fetus using whole exome or whole genome sequencing is considered not medically necessary for ANY of the following indications:

- healthy pregnancy
- indications other than fetal structural anomalies
- ANY of the following fetal anomalies:
  - isolated increased nuchal translucency
  - isolated talipes (i.e., clubfoot)
  - isolated neural tube defect
  - isolated congenital heart defects
  - isolated cleft lip and/or palate
  - isolated congenital diaphragmatic hernia
  - isolated ultrasound soft markers of aneuploidy (e.g., echogenic bowel, intracardiac echogenic focus, choroid plexus cysts)

Concurrent whole exome and whole genome sequencing is considered not medically necessary.

Whole exome or whole genome sequencing in the general population is considered not medically necessary.

General Background

Genetic Counseling
Genetic counseling is defined as the process of helping an individual understand and adapt to the medical, psychological and familial indications of genetic contributions to disease. Genetic counseling services span the life cycle from preconception counseling to infertility evaluation, prenatal genetic screening and diagnosis, and include predisposition evaluation and genetic diagnosis. Genetic counseling is recommended both pre-and post-genetic test to interpret family and medical histories to assess the chance of disease occurrence and recurrence, educate regarding inheritance, testing, management prevention and resources, and counsel to promote informed choices and adaptation to risk or condition (National Society of Genetic Counselors [NSGC], 2023). Due to the likelihood of discovery of a variant of uncertain significance (VUS) or other incidental findings, pre- and post-test genetic counseling for any individual undergoing whole exome sequencing (WES) is consistently recommended by multiple professional societies and experts (Shashi, et al., 2014). Genetic counseling by an independent provider can reduce unnecessary use of this test.

A variety of genetics professionals provide genetic counseling services: Board-Certified or Board-Eligible Medical Geneticists; an American Board of Medical Genetics and Genomics or American Board of Genetic Counseling-certified Genetic Counselor; and genetic nurses credentialed as either a Clinical Genomics Nurse (CGN) or an Advanced Clinical Genomics Nurse (ACGN) by the Nurse

Portfolio Credentialing Commission, or with an Advanced Genetics Nursing Certification (AGN-BC) renewed by the American Nurses Credentialing Center (ANCC). Individuals should not be employed by a commercial genetic testing laboratory, although counseling services by these individuals are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself.

Whole Exome Sequencing (WES)
Sequencing is a laboratory method that can determine the precise order of the four chemical building blocks (bases) that make up the deoxyribonucleic acid (DNA) molecule. A genome is the genetic code of all the hereditary information contained in an individual's DNA. Exons are the areas of the genome that contain the genes. Genes contain information for making proteins, which perform important functions within a cell. Whole exome sequencing (WES), also called exome sequencing, is a testing strategy to selectively look at only the protein-coding gene regions (i.e., exons) of a genome. Because most known disease-causing variations occur in exons, exome sequencing can be used to efficiently identify such variations. The exome comprises about 1-2% of the genome.

Determining genetic causality for disease and establishing a molecular diagnosis in clinical practice can: confirm a suspected or established clinical diagnosis; inform prognosis; aid in selecting treatment, surveillance or preventive options; reveal mode of inheritance; identify carrier/risk status of family members; and/or guide research regarding new therapies or patient management (Blue Cross Blue Shield Technology Evaluation Center [BCBS Tec], 2013).

The evolution of next generation sequencing has spurred the development of tests that sequence multiple genes simultaneously, and such testing is expected to enable widespread evaluation of patients' genomes in the clinical setting (Johansen Taber, et al., 2014). This technology also allows rapid DNA sequencing at a much lower cost than prior sequencing methods. Large-scale genomic sequencing, including WES, has been proposed for use in undiagnosed disorders that involve multiple congenital anomalies suggesting a single genetic etiology, but lacking a clear diagnostic testing path and in which stepwise testing can result in costly and a prolonged diagnostic odyssey (Biesecker 2014; American College of Medical Genetics and Genomics [ACMG], 2013; ACMG, 2012).

One of the most complex issues surrounding genomic testing is the risk of finding incidental or secondary findings, where mutations unrelated to the clinical phenotype or variants of uncertain significance (VUS) are identified. While incidental identification of clinically significant variants pose issues of informed consent, these findings often have clear medical management recommendations (ACMG, 2013; Green, et al., 2013). However, even among the genes recommended for the reporting of incidental findings by ACMG, there are challenges in determining the phenotypic consequences of variants identified (Jurgens, et al., 2015). Persons of European/Caucasian heritage have been consistently overrepresented in genetic sequencing. It has been reported that approximately 78% of participants in genome-wide association studies are of European ancestry (Sirugo, et al., 2019). Patients of a non-European/Caucasian background have an increased likelihood of VUS results, and disease-causing variants found in non-European Caucasian individuals may not be identified due to a lack of data, may be labeled as a VUS, or may not be reported (East, et al., 2017).

The identification of variants of uncertain significance may put the health care provider at risk of under- or over-managing the patient depending on the true underlying clinical implications of the variant. Obtaining informed consent by a specially-trained genetics professional is critical to the utility of WES. The expertise of clinical genetics specialists allows them to accurately evaluate patients and determine whether targeted testing would produce a more resource-effective and

higher yield than WES. Experts agree that the involvement of trained genetics professionals in consulting with patients is essential prior to and after ordering such tests to identify the appropriate patients for large multi-gene panels or WES (Yang, et al., 2013).

Although targeted gene testing typically caries a lower risk of incidental findings, WES may be appropriate for certain individuals when: a relevant differential diagnosis list is documented; the results will directly impact clinical decision-making and clinical outcomes; clinical presentation is consistent with a genetic etiology; and the phenotype warrants testing of multiple genes. Documentation should support the effectiveness of WES compared to separate testing for each gene in question and that test results may preclude the need for more resource-intense and/or invasive procedures, follow-up, or screening.

In spite of its limitations, the potential resource-effectiveness of such testing is a compelling reason to consider its use in clinical practice. However, WES is only resource- and time- effective if it replaces the need for multiple individual gene tests, and it is not as resource-effective when it is utilized after performing and receiving uninformative results from multiple other genetic tests. For this reason, genetics providers may consider when WES should be performed prior to more traditional testing, such as comparative genomic hybridization (CGH)/chromosome microarray analysis (CMA) or targeted panels. Since microarray is most powerful for detecting deletions/duplications involving multiple genes, which typically results in a broad phenotype, medical geneticists may weigh whether a targeted panel or WES may be a more appropriate first-tier test when the patient meets WES testing criteria and the phenotype is more suggestive of a single gene disorder rather than multi-gene deletion or duplication (e.g., skeletal dysplasia). Concurrent testing of WES with any other genetic test is not appropriate.

U.S. Food and Drug Administration (FDA): While many genetic and genomic tests are regulated by the FDA, laboratory developed tests (i.e., in vitro diagnostic tests that are designed, manufactured and used within a single laboratory) go to market without independent analysis.

There are several high throughput DNA sequencing platforms in use. Most platforms do not have FDA approval and are for research purposes only, however some devices have received FDA approval. The Illumina MiSeqDx Platform (Illumina, Inc., San Diego, CA) was granted approval as a Class II device for clinical use, however the platform "is not intended for whole genome or de novo sequencing". The Helix Laboratory Platform for whole exome sequencing (Helix OpCo, LLC, Toronto, Canada) received FDA approval as a Class II device in 2020.

Literature Review: Shashi et al. (2014) retrospectively evaluated a cohort of 500 patients who received traditional medical genetics evaluations. Thirty-nine patients were determined to not have a genetic disorder; 212 of the remaining 461 (46%) received a genetic diagnosis, and 72% of these were diagnosed on the first visit. WES would not have contributed to the care of these diagnosed individuals, but it may have been clinically and economically useful in the remaining pool of undiagnosed individuals. Data suggested that the clinical utility of genomic testing is greater when testing is applied after an initial clinical genetics evaluation.

A review by Blue Cross Blue Shield Technology Evaluation Center (2013) noted the diagnostic yield of exome sequencing in the six larger patient series evaluated (n>10; each study sequenced 12 to 118 exomes) varied from 10% to 54%. The studies were largely positive or negative on the basis of the index case, and few negative results were found in this group of studies; selective reporting of positive results could have occurred. Beyond diagnostic yield, occasional anecdotal reports were identified of clinical benefit following molecular diagnosis by exome sequencing; however, no systematic study of clinical outcomes was identified. The authors note that for some patients, exome sequencing obtained after initial diagnostic evaluation (that may include other genetic testing) has failed may avoid the diagnostic odyssey and return a likely causal variant. The

diagnostic yield appears to be no greater than 50% and possibly less for patients with a suspected genetic disorder accompanied by multiple anomalies. Medical management decisions, including initiation of new treatment or discontinuing inappropriate treatment, may result for only a subset of those diagnosed. Reproductive decisions for parents considering an additional pregnancy may be informed by determining the mode of inheritance. Appropriate use of exome sequencing requires considerable genetic, clinical, and genetic counseling expertise.

Whole Genome Sequencing (WGS)
Whole genome sequencing (WGS) is a next generation sequencing (NGS) technique which analyzes over 90% of the genome to determine the order of the nucleotides in an individual's DNA, and to identify variations. WGS can detect complex variations such as translocations and rearrangements, copy number variations (CNVs), small insertions and deletions, and single nucleotide variations (SNVs). A typical whole genome has 4.1-5 million single-nucleotide and insertion-deletion variants per sample (Auton, et al., 2015). WGS has been proposed as a tool to establish a diagnosis in individuals with exceptionally complex and severe phenotypes and has also been used in the oncology setting to characterize tumor genomes. WGS is most commonly performed at tertiary medical centers in a research capacity.

It has been suggested that WGS may have increased diagnostic yield over WES due to potential technological advantages, including improved exon coverage and the ability to detect additional variants (e.g., mitochondrial variants, certain structural variants) (Lionel, et al., 2018). In the research setting however, this increase in diagnostic yield has been found to be limited, with several studies reporting additional yields ranging from 10%-17%; the yield of WES reanalysis was higher in several of these same studies (Palmer, et al., 2021; Shashi, et al., 2019; Alfares, et al., 2018; Lionel, et al., 2018; Splinter, et al., 2018).

A prospective randomized study of patients who received clinical genome sequencing as the first-line test in the diagnostic workup process versus standard of care testing (e.g., microarray; panel testing) showed no significant differences in diagnostic yield between the two groups (Brockman, et al., 2021). A meta-analysis of 37 other studies determined that the diagnostic utility of WGS was not significantly different from WES (Clark, et al., 2018). For patients who have previously had uninformative WES, subsequent reanalysis of the data has been suggested as a first step, rather than pursuing additional sequencing of the entire genome (Shashi, et al., 2019; Alfares, et al., 2018).

The use of whole genome sequencing as a first tier test is a growing area of study, and there is increasing support for the use of WGS for select indications. The use of WGS in the general population and/or for routine clinical testing is not supported at this time. Pretest genetic counseling, including expectations of results, discussion of optional choices (e.g., secondary findings and carrier status), and follow up plan remains standard of care (Bowling, et al., 2022; Lazier, et al., 2021; Manickam, et al., 2021).

WES/WGS in Developmental and Epileptic Encephalopathy
Developmental and epileptic encephalopathy (DEE) refers to a group of epilepsies which are characterized by seizures and developmental delay, or even loss of developmental skills. DEE is a severe presentation in which there is an underlying cause contributing to the developmental delay, in addition to frequent seizures which may substantially worsen developmental problems. Improvement in seizure control may in turn have the potential to improve the developmental consequences of the disorder, however the developmental encephalopathy component will not change (Scheffer, et al., 2017).

Diagnostic criteria for DEE has traditionally been made based on observations on electroencephalography (EEG), imaging, and seizure semiology. However there is significant

clinical and genetic heterogeneity in this group of conditions. Varying electroclinical syndromes are defined by the International League Against Epilepsy (ILAE) and many have overlapping or heterogeneous genetic causes. Up to half of individuals with DEE remain undiagnosed after first tier assessment (e.g., neurological and physical assessment, neuroimaging, screening for metabolic disorders, CMA and targeted genetic testing) (Palmer, et al., 2018). A rapid diagnosis can significantly impact treatment options, referral to other specialties, or palliative care (Myers, et al., 2018). Genetic testing can confirm a diagnosis in an affected individual, predict onset of seizures in at-risk individuals, and/or drive management decisions (Smith, et al., 2017). There is evidence suggesting utility for patients with early onset epilepsies. Sheidley et al. (2018) noted the possible utility of genetic testing for epilepsy includes avoidance of treatment, such as epilepsy surgery and additional invasive diagnostic tests. Additionally there are a number of specific genetic epilepsy diagnoses that lead to immediate and specific treatment recommendations. Weber et al. (2017) noted that for these patients, a positive result may avoid further testing, and help to make medical management decisions.

Literature Review: Currently, there is limited guidance from professional societies regarding genetic testing for epilepsy; however, several clinical trials suggest clinical usefulness of WES for this indication. A prospective study examining children with newly diagnosed epilepsy with an onset at less than three years of age found an increased diagnostic yield with WES compared to next-generation sequencing (NGS) gene panels (33% vs. 27%) (Berg, et al., 2017). These diagnostic yield findings for this patient population have been echoed in other studies evaluating patients with intractable early-onset epilepsy (onset ≤3 years) (37.8%) (Rim, et al., 2018) or early onset epilepsy <3 months (52%) (Kothur, et al., 2018).

Oates et al. (2018) performed targeted NGS of 45–102 epilepsy genes and found the diagnostic yield was highest in the neonatal onset epilepsies (63%), intermediate in the remaining first two years of life (21%), and lowest when onset was later (4%). The authors noted there were limitations to specific epilepsy panel choices and emphasized the need for testing of appropriate patients using a well-designed panel (Oates, et al., 2018).

Peng et al. (2018) examined pediatric drug resistant epilepsy patients and found that 17.3% of these patients had a genetic diagnosis identified through WES. Overall, genetic testing, through both WES and NGS panel, achieved a diagnosis in 86 patients, and 34 patients accepted corrective therapy according to their finding, after which 52.9% became seizure-free and 38.2% achieved seizure reduction. Overall, regardless of results those patients with genetic testing completed had significantly fewer hospitalization incidents (times/half year) than before (positive genetic results group 0.58 vs 0.10; negative genetic results group 0.72 vs 0.12).

Through a retrospective chart review Nolan and Fink (2018) found the diagnostic rate for WES compared to panel testing increased from 25%- 48% for individuals with severe epilepsies of infancy (SEI; defined as onset before 18 months, frequent seizure, epileptiform EEG, and failure of ≥2 antiepileptic drugs).

Vissers et al. (2017) examined 150 patients with neurological disorders and found that WES identified significantly more conclusive diagnoses than the standard care pathway (29.3% versus 7.3%), without higher costs.

WES/WGS in Sensorineural Hearing Loss
Congenital hearing loss (hearing loss that is present at birth) is one of the most common chronic conditions in children. In the majority of cases, congenital hearing loss is due to genetic variants, with roughly 20% of genetic diagnoses involving one of over 400 syndromes. The remaining 80% of cases are classified as nonsyndromic (Korver, et al., 2017). Due to this varied etiology, next-generation sequencing (NGS) panels are commonly used to evaluate a large number of genes to

diagnose sensorineural hearing loss (SNHL). This approach may be limited, however, because a majority of hereditary deafness cases are due to rare genes, and there is a great deal of heterogeneity between families and across ethnicities. Hearing loss panels may differ in region analyzed, methodology, and algorithms, and the sequencing results are generally not compatible for reanalysis and/or comparison across platforms (Zou, et al., 2020).

WES has advanced the discovery of new genes and variants associated with hearing loss, and has increased the rate of genetic diagnosis for infants with congenital hearing impairment (Zou et al., 2020; Downie, et al., 2019; Bademci, et al., 2016). Using whole exome with clarification by microarray, Downie et al. (2019) reported a genetic diagnosis rate of 56% for infants with congenital bilateral hearing impairment. There is also substantial opportunity for an early diagnosis in individuals who may not yet have developed syndromic features, and/or are too young to know if their hearing loss is stable or progressive. Confirmation of syndromic SNHL provides an opportunity for earlier screening and access to treatment or clinical trials. Downie et al. (2019) found that 92% of the subjects in their study who received a genetic diagnosis had some change in their medical management. The study also noted that 36% of infants with bilateral SNHL were discharged from further surveillance after nonsyndromic variants were identified, thereby alleviating the need for additional screening and the unnecessary utilization of healthcare resources.

WES/WGS in Autism Spectrum Disorder, Global Developmental Delay, and Intellectual Disability

Approximately one in 36 children in the United States has been identified with autism spectrum disorder (ASD) (Centers for Disease Control and Prevention [CDC], 2023). ASD is four times more common in males than in females, and more prevalent in white children compared to Black or Hispanic children (1.1 and 1.2 times more prevalent, respectively). Black and Hispanic children are less likely to be identified with ASD than white children, suggesting that Black and Hispanic children may face socioeconomic or other barriers (e.g. stigma, non-English primary language, non-citizenship) that lead to a lack of or delayed access to evaluation, diagnosis, and services. However, the CDC has reported that the differences in ASD identification among white, Black, and Hispanic children have been getting smaller over time. These reduced differences may be due to more effective outreach directed toward minority communities and efforts to have all children screened for ASD (CDC, 2019).

The broad phenotypic spectrum of ASD presents a challenge to reach a genetic diagnosis. There is a wide array of clinical manifestations in ASD that varies in the type and severity of symptoms. Studies suggest a higher diagnostic yield for WES/WGS in ASD patients presenting with additional clinical features, compared to those who present with non-syndromic (isolated) ASD. Tammimies et al. (2015) reported a diagnostic yield of 16.7% in the most complex ASD cases (e.g., co-occurring congenital anomalies), 28.6% in less complex presentations, and only 3% in ASD children without syndromic features. These findings have been supported by other studies in which exome sequencing diagnostic yields were highest in patients with ASD complicated by additional phenotypes (Arteche-Lopez, et al, 2021; Rossi, et al., 2017).

Global developmental delay (GDD) is significant delay affecting children under five years of age, in at least two or more of the major developmental domains: gross or fine motor; speech/language; cognition; social/personal development; and activities of daily living. Children with GDD present with delays in achieving developmental milestones at the anticipated age. This implies deficits in learning and adaptation, which in turn suggests that the delays are significant and may predict future intellectual disability (Moeschler, et al., 2014).

Intellectual disability (ID) is a neurodevelopmental disorder that begins in childhood and is characterized by intellectual difficulties as well as difficulties in conceptual, social, and practical

areas of living. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published by the American Psychiatric Association, requires three criteria for a diagnosis of ID:

- deficits in intellectual functioning (reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and learning from experience), confirmed by clinical evaluation and individualized standard intelligence testing
- deficits in adaptive functioning that significantly hamper conforming to developmental and sociocultural standards for the individual's independence and ability to meet their social responsibility
- onset of these deficits during childhood

ID may be further classified as mild, moderate, severe, or profound. The designation depends upon the degree of impairment in an individual's daily living skills, conceptual developmental, and social development; and level of support needed (National Academies of Sciences, Engineering, and Medicine, 2015). Characteristics of each classification may include (Badesch, 2021):

- Mild: Able to live independently with minimum levels of support; difficulties in learning academic skills; impaired abstract thinking, executive functioning, and short-term memory; concrete approach to problems and solutions; immature in social interactions; possible difficulty in regulating emotion; limited understanding of risk in social situations
- Moderate: Independent living may be achieved with moderate levels of support, such as those available in group homes; conceptual skills markedly delayed; needs daily assistance to complete conceptual tasks of day-to-day life; needs support for all use of academic skills; decision-making abilities are limited, needs caregivers to assist with personal life decisions; may misinterpret social cues; marked differences from peers in social and communicative behavior
- Severe: Requires daily assistance with self-care activities and safety supervision; caregivers provide extensive support for problem-solving; attainment of conceptual skills is limited; poor understanding of written language and/or certain concepts involving numbers, time, quantity; limited spoken vocabulary and grammar; simple speech; possible speech augmentative device; understands simple speech and gestural communication
- Profound: Requires 24-hour care and close supervision with self-care activities; often will have congenital syndromes; sensory and physical impairments may limit social activities; very limited communication, largely nonverbal; may understand some simple instructions or gestures; conceptual skills involve the physical world; very limited understanding of symbolic communication; may use objects purposefully; may obtain some visuospatial skills

In 2021, the American College of Medical Genetics and Genomics (ACMG) published a practice guideline for exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability. The guideline strongly recommended WES/WGS as a first- or second-tier test (guided by clinical judgment and often physician–patient/family shared decision making after CMA or focused testing) for children with one or more congenital anomalies prior to one year of age, or for patients with GDD/ID with onset prior to 18 years of age. Supporting meta-analyses showed that WES/WGS impacted the rates of short-term medical management, long-term medical management, and reproductive-focused outcomes (8%, 10-17%, and 9%, respectively), demonstrating clinical utility. The use of WES/WGS after CMA or targeted testing yielded more diagnoses at a lower cost, versus using WES/WGS only after extensive testing (e.g., large sequencing panels and/or multiple testing approaches), or using standard testing alone. Potential harms of testing included misattributed paternity and financial strain, but otherwise no clinically significant undesirable effects were reported. ACMG concluded that "compared with standard genetic testing, ES/GS has a higher diagnostic yield and may be more cost-effective when ordered

early in the diagnostic evaluation" (Manickam, et al., 2021). Isolated autism (i.e., autism without intellectual disability or congenital malformation) was out of scope for the ACMG recommendation.

WES/WGS in the Fetal (Prenatal) Setting
Standard diagnostic testing in the prenatal setting includes karyotype and/or microarray. If the results of such testing is uninformative, emerging data supports the clinical utility of WES in some cases. Diagnostic yields may range from 10-57%, and are dependent on any related findings on ultrasound (Lord, et al., 2019). Fu et al. (2018) reported that WES achieved molecular diagnostic rates of 22.3% in fetuses with a single malformation, and 30.8% in those with multiple malformations, following a normal karyotype and microarray. A high diagnostic yield ranging from 9-47% has also been reported for WES in fetal hydrops, including the identification of pathogenic variants which may not be present in commercial panels (Yates, et al., 2017; Drury, et al., 2015).

Some studies have found a low diagnostic yield for monogenic disorders using WES in fetuses with isolated ultrasound "soft markers", (findings that are generally not abnormalities themselves, but which may indicate an increased risk for another underlying abnormality). Such soft markers may include: increased nuchal translucency, choroid plexus cysts, echogenic foci in the heart or bowel, thickened nuchal fold, absent nasal bone, single umbilical artery, or persistent right umbilical vein (Lord, et al., 2019; Fu, et al., 2017). Generally, diagnostic yield is proportional to the severity of the ultrasound findings, (i.e., higher for fetuses with more than two anomalies) (Monaghan, et al., 2020; Lord, et al., 2019). Interpreting WES results for isolated findings such as complex cardiac defects remains challenging (Pasipoularides, 2018). It is recommended that testing for isolated congenital anomalies be considered only with established informative results and high diagnostic yield.

The American College of Medical Genetics and Genomics (ACMG) has published guidance for the use of WES in prenatal diagnosis, suggesting that WES may be considered for a fetus with ultrasound anomalies when standard testing has failed to provide a definitive diagnosis (Monaghan, et al., 2020). However, a limitation of WES in the prenatal setting is the relatively long turnaround time for results, especially if ultrasound anomalies are not detected until later in the pregnancy (Daum, et al., 2019).

Whole Exome/Genome Reanalysis and Retesting
Certain scenarios may warrant reanalysis of previously uninformative WES/WGS sequencing data; that is, re-examining an individual's existing genomic data, typically using the same method. These include the onset of additional symptoms that broaden the phenotype assessed during the initial exome analysis, or the birth or diagnosis of a similarly affected first-degree relative which has expanded the clinical picture (a first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children). Due to the rapid expansion in knowledge of disease genes and phenotypes, reanalysis can also be helpful at future time intervals. Reanalysis of sequencing data has shown to increase the diagnostic yield by 11-16% when performed one to three years after initial testing (Alfares, et al., 2018; Ewans, et al., 2018; Hiatt, et al., 2018). Reanalysis can also help to reclassify previously detected variants of uncertain significance. Retesting may be warranted in some cases, in order to gather additional data beyond the scope of the initial testing method (e.g., WGS performed for an individual with nondiagnostic results by exome sequencing) (Robertson, et al., 2022; Deignan, et al., 2019). Concurrent testing with WGS and WES is not supported; the most appropriate test should be performed based on the specific circumstances in each clinical scenario.

Whole Transcriptome Sequencing
A ribonucleic acid (RNA) sequence mirrors the DNA sequence from which it was transcribed. By analyzing the entire collection of RNA sequences in a cell (the transcriptome), researchers can

determine when and where each gene is turned on or off in the cells of an organism. Whole transcriptome sequencing is the analysis of all of the RNA sequences present in a particular tissue type. This may include both coding and non-coding RNA (Koks, et al., 2021). Due to cellular regulatory differences, the transcriptome varies between tissues, making sample choice a key consideration for testing. RNA sequencing allows analysis of what DNA is actively being expressed in that tissue type, and provides a different viewpoint than DNA-based sequencing.

Whole transcriptome sequencing has been proposed for use in many areas of medicine, including inherited genetic disorders and cancer indications. Lee et al. (2020) utilized whole transcriptome sequencing in 48 families/cases with various congenital conditions highly suspicious for a genetic cause, who were referred to the Undiagnosed Diseases Network. The participants had remained undiagnosed despite prior genetic testing including whole genome sequencing. The authors reported that RNA analysis helped to establish a diagnosis in 15% of the subjects. Limitations of the study included a small, highly selected patient population, evaluated at an expert referral center. Further studies are needed to evaluate the application of whole transcriptome analysis in a broader population of patients who may or may not have access to this level of care. Additional data on the clinical usefulness of whole transcriptome sequencing, stratified by population and tissue type, is needed prior to broad clinical application.

Whole Genome Optical Mapping
Optical genome mapping (OM) is a technique that consists of imaging very long linear single DNA molecules that have been labeled at specific sites, to create a genome-wide high resolution "map" (Mantere, et al., 2021). The resulting optical map represents the physical location of selected enzymes, rather than the base-by-base nucleotide information obtained in next-generation sequencing. OM has been proposed for a variety of applications, including hereditary genetic disorders, prenatal testing, and hematological malignancies. It is purported to provide more detailed information than standard cytogenetic testing (i.e., karyotype, fluorescent in-situ hybridization [FISH], and/or chromosomal microarray [CMA]), including large-scale structural variations. Currently the technology cannot detect hyperdiploidy or loss of regions of heterozygosity (Sahajpal, et al., 2021). Further, OM platforms vary and often use different methods, bioinformatics pipelines, and interpretation strategies (Yuan, et al., 2020). OM is currently primarily used in a research capacity, as technical limitations and inconsistency across different platforms are barriers to widespread clinical application.

Professional Societies/Organizations
American College of Medical Genetics and Genomics (ACMG): In 2021, the ACMG published a practice guideline in support of exome and genome sequencing as first- or second-tier testing (guided by clinical judgment and often after microarray or focused testing) for pediatric patients with one or more congenital anomalies prior to one year of age, or developmental delay and/or intellectual disability with onset prior to 18 years of age. The recommendation asserts that exome/genome sequencing can assist in confirming or establishing a clinical diagnosis that may lead to changes in management and preclude the need for further testing (Manickam, et al., 2021). Of note, the guideline refers to exome sequencing and genome sequencing interchangeably, and makes no recommendation of one over the other.

Also in 2021, the ACMG published its recommendations for reporting of secondary findings (SFs) in exome and genome sequencing. The purpose of the companion SF list is to guide clinical laboratories as to which medically actionable genes (unrelated to the primary indication for testing) should be evaluated and reported as part of exome/genome sequencing (Miller, et al., 2021a). The policy recommendations included the following:

- Unless otherwise noted in the list, variants that are classified as "pathogenic" or "likely pathogenic" should be reported as a SF.

- Variants classified as "variant of uncertain significance", "likely benign", or "benign" should not be returned as a SF.
- The recommendations apply to clinical settings, and do not pertain to research trials.
- Findings from mitochondrial DNA sequencing are outside the scope of the SF list.

The updated secondary findings list groups genes/variants by phenotype: cancer, cardiovascular, inborn errors of metabolism, and miscellaneous. When evaluating which genes to add to the list, consideration is given to a variant's morbidity/mortality, ability to be detected on standard clinical exome/genome sequencing, penetrance, rarity, and available interventions (Miller, et al., 2021b). The 2022 update included five genes related to cardiovascular phenotypes. Of particular note, one of the genes newly added to the list was TTR (hereditary TTR [transthyretin] amyloidosis). Its inclusion was due to the nonspecific symptoms of the disease which may progress to heart failure; the availability of treatment that may be more effective earlier on in disease progression; and its high prevalence in individuals with West African ancestry. The authors noted that the most common pathogenic variant in TTR globally has a particularly high frequency in individuals of West African ancestry (1%-2.5%), and is a common cause of heart failure in persons of African descent. The ACMG workgroup "determined that genes associated with conditions that disproportionately affect 1 or more minoritized group will not be penalized if they are rare or have lower penetrance in the US population as a whole. In other words, we assess rarity and penetrance in the context of specific populations so as not to perpetuate or exacerbate existing disparities in genomic medicine. From an ethical perspective, then, the working group takes an equity approach (considering what each population needs to maximize health) rather than an equality approach (treating each population identically)" (Miller, et al., 2022).

The ACMG practice resource for the clinical evaluation and etiologic diagnosis of hearing loss included the following recommendations specific to genetic testing for nonsyndromic hearing loss (HL):

- For individuals lacking physical findings suggestive of a known syndrome a tiered diagnostic approach should be implemented:
  - Unless clinical and/or family history suggests a specific genetic etiology, comprehensive HL gene panel testing should be initiated. If panel testing is negative, genome-wide testing, such as exome sequencing or genome sequencing, may be considered. However, issues related to genomic testing, such as the likelihood of incidental or secondary findings, will have to be addressed.
  - The HL panel should include the genes recommended by the HL Gene Curation Expert Panel. Because of the existing variations in gene number and content among currently available HL gene panels, clinicians must be aware of the genes included in the test (panel) chosen and the performance characteristics of the platform chosen, including coverage, analytic sensitivity, and what types of variants will be detected. Additional testing strategies may need to be adopted to address the technical challenges caused by highly homologous regions, including pseudogenes. It should be noted that the cost of these new genetic sequencing technologies is decreasing so rapidly that the use of large sequencing panels targeted toward HL-related genes as the initial test, may, in many cases, already be more cost-effective in the evaluation of HL.
  - If genetic testing reveals variant(s) in an HL–related gene, gene-specific genetic counseling should be provided, followed by appropriate medical evaluations and referrals.
  - If genetic testing fails to identify an etiology for a patient's hearing loss, the possibility of a genetic etiology remains. This point must be emphasized because it can be misunderstood by clinicians and by patients and their families. For interested patients and families, further genetic testing may be pursued on a research basis.

- Regardless of whether genetic test results are positive, negative, or inconclusive, results should be communicated through the process of genetic counseling and potential risks to other family members should be conveyed (Li, et al., 2022).

On behalf of the ACMG, Monaghan et al. (2020) noted Points of Consideration regarding use of WES for prenatal diagnosis:

- Exome sequencing may be considered for a fetus with ultrasound anomalies when standard CMA and karyotype analysis have failed to yield a definitive diagnosis.
- At the present time, there are no data supporting the clinical use for exome sequencing (ES) for other reproductive indications, such as the identification of sonographic markers suggestive of aneuploidy or a history of recurrent unexplained pregnancy loss.
- Trio analysis consisting of the proband and both biological parents is preferred to singleton (fetus only) or duo (fetus and one parent) analyses.
- As a new diagnostic test in fetal medicine, ES may be considered when a diagnosis cannot be obtained using routine prenatal methods in a fetus with one or more significant anomalies.

The ACMG published a statement regarding use of genomic testing that recommends testing be considered in phenotypically affected individuals when (ACMG, 2012):

- The phenotype or family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available on a clinical basis.
- A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making whole exome sequencing (WES) or whole genome sequencing (WGS) analysis of multiple genes simultaneously a more practical approach.
- A patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.
- A fetus with a likely genetic disorder in which specific genetic tests, including targeted sequencing tests available for that phenotype, have failed to arrive at a diagnosis.
- Prenatal diagnosis by genomic (i.e., next-generation whole exome- or whole genome-) sequencing has significant limitations. The current technology does not support short turnaround times which are often expected in the prenatal setting. There are high false positive, false negative, and variants of unknown clinical significance rates.

The ACMG published specific recommendations about how this process should occur (ACMG, 2012):

- Pre-test counseling should be done by a medical geneticist or an affiliated genetic counselor and should include a formal consent process.
- Prior to initiating WGS/WES, participants should be counseled regarding the expected outcomes of testing, the likelihood and type of incidental results that could be generated, and what results will or will not be disclosed.
- As part of the pre-test counseling, a clear distinction should be made between clinical and research based testing. In many cases, findings will include variants of unknown significance that might be the subject for research; in such instances a protocol approved by an institutional review board must be in place and appropriate prior informed consent obtained from the participant.

American Academy of Pediatrics (AAP): In 2020, the AAP published a clinical report on the identification, evaluation, and management of children with autism spectrum disorder (ASD). As part of the etiologic workup for ASD, the AAP advocated that a genetic evaluation be offered and

recommended to the family. Identifying a genetic etiology may provide information regarding prognosis, co-occurring conditions, and familial recurrence risk, as well as identify resources and avoid unnecessary testing. The AAP advocated that chromosomal microarray (CMA) was the most appropriate initial laboratory test, followed by more targeted testing if a specific syndrome or metabolic disorder was suspected (e.g. fragile X syndrome). If history and physical exam, CMA, and fragile X (or other syndrome) testing did not identify an etiology, whole exome sequencing may be considered (Hyman, et al., 2020).

International Society for Prenatal Diagnosis (ISPD), the Society for Maternal Fetal Medicine (SMFM), and the Perinatal Quality Foundation (PQF): A joint position paper published in 2018 regarding the use of genome-wide sequencing for fetal diagnosis notes the following:

- The routine use of prenatal sequencing as a diagnostic test cannot currently be supported due to insufficient validation data and knowledge about its benefits and pitfalls.
- Diagnostic sequencing for fetal indications is best done as a trio analysis
- There is currently limited genotype–phenotype correlation for the genetic disorders identified in the fetal period
- Extensive pre-test education, counseling and informed consent, and post-test counseling are essential.
- Although experience is still limited, the current existing data suggest that the following indications are scenarios where fetal sequencing may be beneficial:
    - A current pregnancy with a fetus with a single major anomaly or with multiple organ system anomalies that are suggestive of a possible genetic etiology, but no genetic diagnosis was found after chromosomal microarray analysis (CMA); or in select situations with no CMA result, following a multidisciplinary review and consensus, in which there is a fetus with a multiple anomaly 'pattern' that strongly suggests a single gene disorder.
    - A personal (maternal or paternal) history of a prior undiagnosed fetus (or child) affected with a major single anomaly or multiple anomalies suggestive of a genetic etiology, and a recurrence of similar anomalies in the current pregnancy without a genetic diagnosis after karyotype or CMA.
    - In families with a history of recurrent still births of unknown etiology after karyotype and/or CMA, where the fetus in the current pregnancy has a recurrent pattern of anomalies.
    - There is currently no evidence that supports routine testing on fetal tissue obtained from an invasive prenatal procedure.

In 2021, the Canadian College of Medical Geneticists (CCMG) published a position statement on the clinical application of fetal genome-wide sequencing (GWS) during pregnancy. The term "genome-wide sequencing" encompassed large gene panels, exome sequencing and genome sequencing.

Among the recommendations were the following (Lazier, et al., 2021):

- "Currently, evidence supports the use of clinical GWS in the diagnostic investigation of congenital anomalies affecting more than one system. Consensus opinion among the Working Group was that the following findings should be considered an anomaly: unexplained intrauterine growth retardation (growth < 3rd percentile), unexplained overgrowth (> 97th percentile), increased nuchal translucency (≥ 3.5 millimeters [mm]), and unexplained polyhydramnios and oligohydramnios.
- Clinical GWS may be considered in cases of apparently isolated structural fetal anomalies, although at present evidence is generally limited as to diagnostic yield and is dependent on the specific anomaly.

- The following fetal findings should not be considered eligible anomalies for GWS: isolated neural tube defect (other than encephalocele), gastroschisis, amniotic bands or soft markers.
- Clinical GWS should not be used when maternal diseases or exposures to teratogens are suspected to be the cause of the fetal abnormalities.
- Clinical GWS should only be used to interrogate the genome for sequence variants in genes known to cause disease.
- Clinical GWS should only be ordered in pregnancy by, or in collaboration with, a medical geneticist with expertise in prenatal diagnosis and care, the use of the technology, and clinical interpretation of the results.
- Rapid aneuploidy diagnosis must be completed prior to GWS. Chromosomal microarray should be completed in parallel, or prior to, GWS, depending on the urgency of test results.
- Clinicians should consider whether single-gene testing or comprehensive multigene panels are a better approach given that they cost less (although this may change over time), may take less time and usually guarantee better coverage.
- Laboratories should not purposefully analyze prenatal GWS data for diseases unrelated to the primary reason for referral (eg, secondary findings), even if the results might be medically actionable for the fetus or the parents.
- Incidental findings unintentionally identified that show a pathogenic or likely pathogenic variant that reveals a fetal risk for a significant Mendelian pediatric-onset condition, whether or not medically actionable, should be reported.
- Incidental findings unintentionally identified that show a pathogenic or likely pathogenic variant revealing a fetal susceptibility for medically actionable adult-onset diseases should not by default be reported. Should a laboratory have a policy for reporting incidental findings in medically actionable adult-onset conditions, they should only be reported with explicit opt-in consent signed by the tested individuals.
- It is recommended that laboratories do not report fetal carrier status unless directly related to the primary indication for testing.
- Reporting of parental incidental findings should be limited to only those present in the fetus.
- Patients should be counselled that clinical GWS is not a rule-out test
- Postnatal reanalysis could be requested if there is additional phenotype information to contribute to analysis or if knowledge of postnatally reportable VUS would be helpful.
- Future analysis may lead to a diagnosis at a later date when more genetic knowledge becomes available."

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD		No Determination found	
LCD		No Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare and Medicaid Services (CMS) code updates may occur more frequently than policy updates.

2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
81415	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure)
81417	Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)
81425	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81426	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (eg, parents, siblings) (List separately in addition to code for primary procedure)
81427	Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family
0094U	Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis
0425U	Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis, each comparator genome (eg, parents, siblings)
0426U	Genome (eg, unexplained constitutional or heritable disorder or syndrome), ultra-rapid sequence analysis

HCPCS Codes	Description
S0265	Genetic counseling, under physician supervision, each 15 minutes

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
81479†	Unlisted molecular pathology procedure
0454U	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping

†Note: Considered Experimental/Investigational/Unproven when used to report whole transcriptome sequencing.

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Revision Details

Type of Revision	Summary of Changes	Date
Annual review	• Updated policy statement for genetic counseling.	1/15/2024