

Medical Coverage Policy



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Whole Exome and Whole Genome Sequencing

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Related Coverage Resources

[Genetics](#)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

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 sequencing (WES). Please see disease specific criteria* for additional information regarding genetic testing.

[Whole Exome Sequencing](#)

Medically Necessary

Whole exome 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 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 Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or 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 sequencing (WES) (CPT® code 81415 with or without 81416) 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
- WES 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:
 - WES is more practical than the separate single gene tests or panels that would be recommended based on the differential diagnosis
 - WES 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 sequencing (WES) (81415 with or without 81416) is medically necessary for ANY of the following clinical scenarios when ALL of the general criteria for WES testing 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 EITHER of the following (any combination of the following counts as one criteria):
 - significant intellectual disability, global developmental delay, and/or 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 infantile or early-onset 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
- 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

Not Medically Necessary

Testing using WES is considered not medically necessary for ANY of the following indications:

- testing using cell-free DNA
- preimplantation testing of an embryo
- genetic carrier screening
- oncology or hematology indications
- ANY of the following 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

Testing of a fetus using WES is considered not medically necessary for ANY of the following indications:

- healthy pregnancy
- indications other than fetal structural anomalies
- ultrasound soft markers of aneuploidy (e.g., echogenic bowel, intracardiac echogenic focus, choroid plexus cysts)

WES in the general population is considered not medically necessary.

Whole Genome Sequencing

Experimental/Investigational/Unproven

Whole genome sequencing (WGS) (CPT codes 81425-81427) is considered experimental, investigational, and unproven for any indication.

Overview

This Coverage Policy addresses whole exome and whole genome sequencing. Sequencing is a laboratory method that can determine the precise order of the four chemical building blocks (bases) that make up the DNA molecule.

A genome is the genetic code of all the hereditary information contained in an individual's DNA. Whole genome sequencing, also called genomic sequencing, is a testing strategy to analyze both the coding and non-coding portions of the genome.

Exomes 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, also called exome sequencing, is a testing strategy to selectively look at only the protein-coding gene regions (i.e., exons) of a genome. Exome sequencing can be used to identify disease-causing DNA variations or mutations within or near the regions of the genome that code for proteins.

General Background

Genetic Counseling

Because of the likelihood of discovery of a variant of uncertain significance or other incidental findings (Shashi 2015), pre- and post-test genetic counseling for any individual undergoing WES is required. This recommendation is consistently and widely published by multiple professional societies and experts. Genetic counseling by an independent provider can reduce unnecessary use of this test.

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]; Edwards, 2010).

A variety of genetics professionals provide these services: Board-Certified or Board-Eligible Medical Geneticists, an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor, and genetic nurses credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or 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

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, 2014). This technology also allows rapid deoxyribonucleic acid (DNA) sequencing at a much lower cost than prior sequencing methods. Whole exome sequencing (WES) consists of analysis of the protein-coding regions of the human genome. This comprises <2% of the genome and involves the areas currently believed to be the most likely to include variations that result in clinical phenotypes and disease. Such large-scale genomic sequencing has been proposed for use in scenarios of 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 prolonged diagnostic odyssey (American College of Medical Genetics and Genomics [ACMG], 2013; ACMG, 2012; Biesecker 2014). Overall analytical sensitivity is still being defined for WES.

Although targeted gene genetic testing typically carries a lower risk of incidental findings WES may be appropriate for certain individuals when a relevant differential diagnosis list is documented and if 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 costly and/or invasive procedures, follow-up, or screening. Concurrent testing of WES and any other genetic test is not appropriate.

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 are identified. While incidental identification of clinically significant mutations pose issues of informed consent, these findings often have clear medical management recommendations (ACMG 2013; Green 2013). However, even among the 56 genes recommended for the reporting of incidental findings by ACMG, there are challenges in determining the phenotypic consequences of variants identified (Jurgens 2015).

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 essential 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 cost-effective and higher yield than WES. Experts agree that 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 (Kurian 2014; Yang 2013).

In spite of its limitations, the potential cost-effectiveness of such testing is a compelling reason to consider its use in clinical practice. However, WES is only cost effective if it replaces the need for multiple individual gene tests, and it is not as cost-effective when it is utilized after performing and receiving uninformative results from multiple other genetic tests. For this reason, genetics providers should 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 should 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.

Whole Exome Sequencing in the Fetal (Prenatal) Setting

Emerging data demonstrate clinical utility for WES in the prenatal population after uninformative standard diagnostic testing, (i.e. karyotype and/or microarray). Diagnostic yields are generally quoted as ranging from 10-57% and are dependent on associated ultrasound findings (Lord et al., 2019). Fu and colleagues (2018) reported a definitive diagnosis using WES following a normal karyotype and microarray in 22.3% of fetuses with a single malformation and 30.8% in those with multiple malformations. In addition, a high diagnostic yield (9-47%) has

been reported using WES in fetuses with hydrops, including the identification of pathogenic variants not present on current commercially available panels (Yates et al. 2017; Drury et al. 2015).

Conversely, several studies have revealed a low diagnostic yield for monogenic disorders using WES in fetuses with isolated sonographic soft markers, i.e. 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 (Fu et al., 2017; Lord et al., 2019). Diagnostic yield has also been determined to be 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). There is also concern about difficulties in interpreting WES results for isolated findings such as complex cardiac defects (Pasipoularides 2018). Therefore, when pursuing testing for isolated congenital anomalies it should only be considered in those with demonstrated informative results and high diagnostic yield.

The American College of Medical Genetics (ACMG) has recently published considerations for the use of WES in the prenatal setting (Monaghan et al., 2020). While ACMG has suggested consideration of WES for fetuses likely to have a genetic disorder when other investigations have not yielded a diagnosis, it is important to remain cognizant of the limitations in the prenatal setting. The relatively long turnaround time of WES has historically been a limitation for its use in a prenatal setting, especially when ultrasound findings are not detected until later gestational ages (Daum et al., 2019). However, emerging technologies allow for more rapid completion of test results.

Whole Exome Sequencing in Sensorineural Hearing Loss

Approximately 80% of congenital hearing loss is due to genetic variants with roughly 20% of genetic diagnoses involving one of over 400 genetic syndromes and 80% being classified as nonsyndromic (Korver et al, 2017). Due to this heterogeneous etiology, next-generation sequencing panels are commonly used to assess large numbers of genes for diagnosis of sensorineural hearing loss (SNHL), however this approach is limited given that a majority of cases of hereditary deafness are due to rare genes and there is broad heterogeneity between families and across ethnicities.

Panels differ in covered region, sequence-capturing methodology and data-analyzing pipe-line, making the sequencing results generally not compatible for cross-platform re-analysis and comparison (Zou et al., 2020). In recent years, WES has been used to expedite identification of new genes and variants associated with hearing loss and has increased the rate of genetic diagnosis for infants with congenital hearing impairment (Downie et al., 2019; Bademci et al., 2016; Zou et al., 2020). Downie (2019) reported a 56% rate of genetic diagnosis for infants with congenital bilateral hearing impairment using whole exome with clarification by microarray. In addition, the opportunity for early diagnosis of individuals who may not yet have developed syndromic features, and are too young to know if their hearing loss is stable or progressive, is significant. Confirmation of syndromic SNHL provides an opportunity for earlier screening and access to treatment and/or clinical trials. For example, individuals with Usher syndrome may have an opportunity to participate in clinical trials to prevent vision loss. Downie (2019) found that (54/59) 92% of participants in their study who received a diagnosis had some change in their medical management.

Early confirmation of nonsyndromic hearing loss can also alleviate the need for additional screening. Downie (2019) reports that 37/106 (36%) of infants with bilateral SNHL in their cohort were discharged from further screening and surveillance after nonsyndromic mutations were identified, reducing the burden on the family and alleviating the unnecessary utilization of healthcare resources. Stark (2019) found that for the infants' families in their cohort, the major impact of early genomic diagnosis was the restoration of parental reproductive confidence. Studies are also underway to address the question of secondary findings from WES.

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 be clinically and economically useful in the remaining pool of undiagnosed individuals. Data suggest that the clinical utility of genomic testing is greater when testing is applied after an initial clinical genetics evaluation.

A review by BCBS TEC (2013) noted the diagnostic yield of exome sequencing in the six larger patient series ($n > 10$; 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. Currently, the diagnostic yield appears to be no greater than 50% and possibly less for patients with 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.

Early Infantile Epileptic Encephalopathy

Diagnostic criteria for early infantile epileptic encephalopathy (EIEE) (characterized as onset before three years of age) has traditionally been made based on observations on 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. Forty-fifty percent of individuals with EE 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 (e.g., GLUT1 deficiency of B6 dependent early onset epilepsy), 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 possible utility of genetic testing for epilepsy includes avoidance of treatment, such as epilepsy surgery and additional invasive diagnostic tests (e.g., lumbar puncture, muscle biopsy, frequency of brain imaging). Additionally there are a number of specific genetic epilepsy diagnoses that lead to immediate and specific treatment recommendations. Weber et al. (2017) notes that for these patients, a positive result avoids further diagnostics and aids in making therapeutic/prognostic 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 recent 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 such as with intractable early-onset epilepsy with large next generation sequencing (NGS) panels (onset ≤ 3 years) (37.8%) (Rim et al., 2018) or early onset epilepsy < 3 months (52%) (Kothur et al., 2018).

Oates et al. (2018) offered targeted NGS of 45–102 epilepsy genes and found 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 discuss there are limitations to specific epilepsy panel choices and emphasize the need for testing of appropriate patients using a well-designed panel (Oates et al., 2018). Additionally, 40-50% of children with EIEE remain undiagnosed after first tier assessment (e.g., neurological and physical evaluation, neuroimaging, screening for metabolic disorders, CMA and targeted genetic testing) (Palmer et al., 2018).

Peng et al. (2018) examined pediatric drug resistant epilepsy patients and found that 17.3% (13/74), 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% (18/34) became seizure-free and 38.2% (13/34) 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). 0.33).

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

Whole Genome Sequencing

Whole genome sequencing (WGS) consists of analysis of most of the DNA content in an individual's genome. WGS has been used 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 under the care of large multidisciplinary teams, with a large research component significantly contributing to the diagnostic and evaluation process. The role of whole genome sequencing has not yet been established for any indication. High-quality clinical trial data are lacking in the published peer-reviewed scientific literature to inform on the use and effectiveness of whole genome sequencing in routine clinical practice. At this time there is insufficient evidence in the published, peer-reviewed scientific literature to establish to inform the impact on health outcomes or to establish clinical utility of whole genome sequencing.

Professional Society/Organization

For a summary of professional society recommendations/guidelines regarding whole exome and whole genome sequencing please click [here](#).

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative

No relevant statements.

Use Outside of the US

No relevant information

Medicare Coverage Determinations

	Contractor	Policy Name/Number	Revision Effective Date
NCD	National	N/A	
LCD	N/A	N/A	

Note: Please review the current Medicare Policy for the most up-to-date information.

Appendix A

PROFESSIONAL SOCIETY/ORGANIZATION RECOMMENDATIONS/GUIDELINES

WHOLE EXOME AND WHOLE GENOME SEQUENCING

American College of Medical Genetics and Genomics (ACMG, 2012): The American College of Medical Genetics 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 WES or 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.

On behalf of the AMCG, 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 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.

International League Against Epilepsy (ILAE): ILAE guidelines suggest that genetic evaluation for Dravet syndrome and other infantile-onset epileptic encephalopathies should be available at a tertiary and quaternary level of care (level C), and that the genetic testing strategy can vary according to suspected underlying condition affecting the infant (Wilmhurst et al., 2015).

International Society for Prenatal Diagnosis (ISPD), the Society for Maternal Fetal Medicine (SMFM), and the Perinatal Quality Foundation (PQF):

A joint position published 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 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

North American Consensus Panel: Genetic testing is recommended for all patients with a clinical picture suggestive of Dravet syndrome, but there was no consensus that SCN1A testing versus a larger epilepsy panel should be performed. However for those with atypical manifestations of Dravet, an epilepsy gene panel is preferred (Wirrell et al., 2017).

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Whole Exome Sequencing

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)
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family

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

Considered Not Medically Necessary:

CPT®* Codes	Description
0036U	Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses
0212U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband
0213U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent, sibling)

0214U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband
0215U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator exome (eg, parent, sibling)

Whole Genome Sequencing

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
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)

***Current Procedural Terminology (CPT®) ©2020 American Medical Association: Chicago, IL.**

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