Whole Exome and Whole Genome Sequencing

INSTRUCTIONS FOR USE

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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 disease specific 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

*Disease Specific Criteria

Whole exome sequencing (WES) (CPT® code 81415) is considered medically necessary for a phenotypically-affected individual 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 clinical outcome for the individual being tested
• a genetic etiology is the most likely explanation for the phenotype as demonstrated by ANY of the following:
  ➢ multiple abnormalities affecting unrelated organ systems
  ➢ known or suspected early infantile epileptic encephalopathy (onset before three years of age)
  ➢ TWO of the following criteria are met:
    o abnormality affecting a single organ system
    o significant intellectual disability, symptoms of a complex neurodevelopmental disorder (e.g. self-injurious behavior, reverse sleep-wake cycles), or severe neuropsychiatric condition (e.g. schizophrenia, bipolar disorder, Tourette syndrome)
    o family history strongly implicating a genetic etiology
    o period of unexplained developmental regression (unrelated to autism or epilepsy)
• no other causative circumstances (e.g. environmental exposures, injury, 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

Comparator exome sequence analysis (CPT code 81416) is considered medically necessary when the above criteria for WES (CPT code 81415) have been met and WES is being performed concurrently or has been previously performed.
Experimental/Investigational/Unproven

Prenatal diagnosis or preimplantation testing of an embryo using WES is considered experimental, investigational, and unproven.

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**

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 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 mutations 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).

Targeted genetic testing typically carries a lower risk of incidental findings; however, WES may be appropriate for certain individuals if the results will directly impact clinical decision-making and clinical outcomes, clinical presentation is consistent with a genetic etiology, the phenotype warrants testing of multiple genes and a relevant differential diagnosis list is documented. Concurrent testing of WES and any other genetic test is not appropriate. 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.

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). Overall analytical sensitivity is still being defined for WES.

The American College of Medical Genetics and Genomics 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.

One of the most complex issues surrounding genomic testing is the risk of 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).

WES is useful in diagnosing complex phenotypes; however, targeted testing, when possible, is typically a more cost-effective approach with a lower risk of incidental findings. 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 addition to the diagnostic power of WES, the 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.

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. These rates can be expected to be significantly higher than seen when array comparative genomic hybridization is used in prenatal diagnosis (ACMG, 2012).

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 emphasis 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.

**Centers for Medicare & Medicaid Services (CMS):**
- **National Coverage Determinations (NCDs):** No NCD found.
- **Local Coverage Determinations (LCDs):** No LCD found

**Use Outside of the US**
No relevant 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. These rates can be expected to be significantly higher than seen when array CGH is used in

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.

**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).
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:

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<th>CPT®* Codes</th>
<th>Description</th>
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<tr>
<td>81415</td>
<td>Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis</td>
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<tr>
<td>81416</td>
<td>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)</td>
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<td>81417</td>
<td>Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)</td>
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<tr>
<td>96040</td>
<td>Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family</td>
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<tr>
<td>S0265</td>
<td>Genetic counseling, under physician supervision, each 15 minutes</td>
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Considered Not Medically Necessary:

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<tr>
<td>0036U</td>
<td>Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses</td>
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Whole Genome Sequencing

Considered Experimental/Investigational/Unproven:

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<tr>
<td>81426</td>
<td>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)</td>
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<td>81427</td>
<td>Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)</td>
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