

Clinical Appropriateness Guidelines

Whole Exome and Whole Genome Sequencing

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Scope

This document addresses the diagnostic use of whole exome sequencing (WES) in the evaluation of rare disease. It does not address the use of WES as a technology for tumor profiling (see Clinical Appropriateness Guidelines for Molecular Testing of Solid and Hematologic Tumors and Malignancies). All tests listed in these guidelines may not require prior authorization or may have separate coverage criteria; please refer to the health plan.

Genetic Counseling Requirement

Genetic testing included in these guidelines is covered when:

1. The patient meets coverage criteria outlined in the guidelines
2. A recommendation for genetic testing has been made by one of the following:
 - An independent board-certified or board-eligible medical geneticist not employed by a commercial genetic testing laboratory*
 - An American Board of Medical Genetics or American Board of Genetic Counseling-certified genetic counselor not employed by a commercial genetic testing laboratory*
 - 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*

Who:

- Has evaluated the case and performed pre-test genetic counseling with the patient or the patient's legal guardian
- Has completed a three-generation pedigree
- Intends to engage in post-test follow-up counseling with the patient or the patient's legal guardian

**A physician, genetic counselor or genetic nurse employed by a laboratory that operates within an integrated, comprehensive healthcare delivery system is not considered to be an employee of a commercial genetic testing laboratory for the purpose of these guidelines.*

Appropriate Use Criteria

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Whole Exome Sequencing

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 (below) are also met.

Phenotype Suspicious for a Genetic Diagnosis

- Testing is ordered after an individual has been evaluated by a board-certified medical geneticist or other board-certified specialist physician with specific expertise in the conditions being tested for and relevant genes AND any of the following:
 - Individual with multiple major structural or functional congenital anomalies affecting unrelated organ systems (including major metabolic disorders), OR
 - Individual with one major structural congenital anomaly and two or more minor structural anomalies, OR
 - Individual with at least two of the following criteria:
 - Major structural congenital anomaly affecting a single organ system
 - Neurological features (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)
 - Family history strongly implicating a genetic etiology
 - Personal and family history of neurological features is excluded from coverage unless additional criteria are met
 - 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

- Standard diagnostic genetic testing (chromosomal microarray analysis (CMA) and/or karyotype) of the fetus has been performed and is uninformative **AND**
- Testing is ordered in conjunction with a board-certified medical geneticist or genetic counselor **AND**

- Testing is performed on direct amniotic fluid/chorionic villi, cultured cells from amniotic fluid/chorionic villi or DNA extracted from fetal blood or tissue **AND**
- 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 (please note exclusions below) **AND** family history strongly suggests a genetic etiology
 - Isolated anomalies excluded from coverage:
 - Isolated increased nuchal translucency
 - Isolated talipes (clubfeet)
 - Isolated neural tube defect
 - Isolated congenital heart defects
 - Isolated cleft lip and/or palate
 - Isolated congenital diaphragmatic hernia

Fetal WES is not medically necessary for any of the following indications:

- Healthy pregnancies
- Indications other than fetal structural anomalies
- Ultrasound soft markers of aneuploidy (e.g. choroid plexus cysts, echogenic bowel, intracardiac echogenic focus)

General Criteria for WES Testing

(All of the following criteria are necessary to pursue WES testing in the clinical scenarios above):

- WES results will directly impact clinical decision-making and/or clinical outcome
- 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 is available
- The differential diagnosis list and/or phenotype warrant testing of multiple genes, and at least 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 (“diagnostic odyssey”) that would be recommended in the absence of testing

WES is not medically necessary in the following scenarios:

- Testing using cell-free DNA
- Preimplantation testing of an embryo
- Genetic carrier screening
- Oncology indications

Whole Exome Reanalysis

Reanalysis of previously obtained uninformative whole exome sequence (81417) is medically necessary when any of the following criteria is met:

- There has been onset of additional symptoms that broadens the phenotype assessed during the original exome evaluation
- There has been the 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 patient’s findings and specific genes/pathogenic or likely pathogenic variants AND at least 18 months have passed since the last analysis

Whole Genome Sequencing

Whole genome sequencing (WGS) is not medically necessary*.

Whole genome sequencing of the transcriptome (RNA sequencing) is not medically necessary.

*Please refer to the health plan for exceptions.

CPT Codes

The following codes are associated with the guidelines outlined in this document. This list is not all inclusive. Medical plans may have additional coverage policies that supersede these guidelines.

Covered when medical necessity criteria are met:

- | | |
|-------|---|
| 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)

Codes that do not meet medical necessity criteria:

- 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)
- 0094U Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis
- 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 (Do not report 0212U in conjunction with 81425)
- 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) (Do not report 0213U in conjunction with 81426)
- 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 (Do not report 0214U in conjunction with 81415)
- 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) (Do not report 0215U in conjunction with 81416)

Background

Whole exome sequencing (WES) is a method of analyzing the protein coding regions, also called the exome, which comprise 1-2% of the entire genome. With the ability to screen all genes, WES theoretically captures at least 85% of the genetic variants associated with human Mendelian disorders (Rabbani et al. 2014). Limitations of WES do exist and currently include reduced ability to detect copy number variants, reduced coverage depth for select genes and the potential for variants of uncertain significance and secondary findings (Zou et al. 2020; Srivastava et al. 2019). These mitigating factors have not precluded the technology from increasingly becoming a common molecular diagnostic test for individuals with suspected rare genetic disorders. WES is most appropriate when used for patients whose phenotype is strongly suggestive of a genetic disorder, but targeted testing has either been negative or is impractical due to a wide or uncertain differential diagnosis (ACMG 2012).

Several large studies have demonstrated the diagnostic utility of WES, in which diagnosis rates have ranged between 22-57% (Clark et al. 2018; Yang et al. 2014; Lee et al. 2014). Though diagnostic utility does not always directly correlate with clinical utility, providing a molecularly confirmed diagnosis can often shorten the diagnostic odyssey, improve disease management, allow for targeted treatments and surveillance for later-onset comorbidities for a subset of patients, and inform genetic counseling with respect to recurrence risks and prenatal diagnosis options for families (Sawyer et al. 2016; Malinowski et al. 2020). Even in cases for which treatments are not available, using WES to confirm a lethal diagnosis in acutely ill pediatric patients allows for the avoidance of invasive biopsies, additional workup, and appropriate implementation of palliative care (Stark et al. 2018).

Rationale for Genetic Counseling for WES

Pre-test genetic counseling provides individuals seeking genetic testing the opportunity to make informed decisions about their genetic testing and subsequent medical management options. Genetic counseling combines expertise in obtaining and interpreting family history information, the ability to identify the most beneficial individual in a family to initiate testing, identification of the most appropriate testing options, experience in obtaining informed consent for testing and proficiency in genetic variant interpretation, in order to maximize the genetic testing experience for patients and their healthcare providers. The genetic counseling informed consent process also educates and empowers patients to consider the psychological, financial, employment, disability, and insurance implications of genetic testing and results (Al-Khatib et al. 2018). Patients who receive genetic counseling report increased knowledge, understanding, and satisfaction regarding their genetic testing experience (Armstrong et al. 2015; Harvey et al. 2007).

The advent of multi-gene panels and genome-scale sequencing have increased the complexity of the genetic testing landscape. Misuse of genetic testing increases the risk for adverse events and patient harm, including missed opportunities for diagnosis and disease prevention (Bellcross et al. 2011; Plon et al. 2011). Genetic information requires expert interpretation and ongoing re-evaluation to ensure the most accurate interpretation is utilized to inform medical management decision making. The multitude of genetic testing options as well as the complex information revealed by genetic testing can make choosing the most appropriate test and interpretation of results difficult for non-genetics healthcare providers (Ray 2011). Involvement of a clinical genetics provider has been shown to ensure the correct test is ordered, limit result misinterpretation and allow patients to make informed, evidence-based medical decisions with their healthcare providers (Cragun et al. 2015).

Genetic counseling not only improves patient outcomes but also reduces unnecessary healthcare spending. Pre-test genetic counseling has been shown to reduce inappropriate test ordering and prevent unnecessary medical procedures and interventions that follow from inaccurate result interpretation (DHHS 2011). While genetic testing is now available for almost all clinical specialties, correct use and interpretation is necessary to prevent adverse outcomes. While genetic counseling may benefit any patient considering or undergoing genetic testing, tests that offer predictive information or have a higher chance of identifying variants of uncertain significance often carry stronger recommendations in the form of consensus guidelines and professional statements recommending genetic counseling by trained genetics professionals.

There is consensus that genetic counseling by trained genetics professionals represents best practice prior to and after ordering such tests and can identify the most appropriate tests (e.g. multi-gene panels or WES) and the most appropriate testing candidates (Yang et al. 2013).

Obtaining informed consent and providing pre-test genetic counseling by a trained genetics professional is an essential component of WES. The American College of Medical Genetics (ACMG) published specific recommendations (ACMG Board of Directors 2013):

1. Pre-test counseling should be done by a medical geneticist or an affiliated genetic counselor and should include a formal consent process
2. 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
3. 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

Variants of uncertain significance and incidental or secondary findings not only complicate genetic counseling but also interpretation of WES results, and they carry a risk of harm to the patient if misinterpreted by an inexperienced clinician. Incidental or secondary findings, where variants unrelated to the clinical phenotype are identified, pose issues of informed consent but often have clear medical management recommendations (ACMG 2013; Green 2013). However, even among the list of 59 genes recommended for the reporting of secondary findings by the American College of Medical Genetics and Genomics, there are challenges in determining the phenotypic consequences of variants identified (Jurgens 2015). A study assessing clinical and psychosocial actions following receipt of secondary incidental findings revealed an overall adjusted prevalence of incidental findings in the ACMG recommended genes of 1.7% with little to no adverse impact on participants as well as only modest to near term healthcare costs (Hart et al. 2019).

Phenotype Suspicious of a Genetic Diagnosis

While WES is useful in diagnosing complex phenotypes, targeted testing (when possible) is typically a more cost-effective approach with a lower risk of variants and incidental findings. 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. Shashi et al. (2014) retrospectively evaluated a cohort of 500 patients who received traditional medical genetics

evaluations and concluded that the clinical utility of genomic testing is greater when testing is applied after an initial clinical genetics evaluation. To further this point, Baldridge, et al (2017) performed a retrospective analysis of 155 patients who underwent WES as part of their Exome Clinic. They report that after medical genetics evaluation, prior test results/clinical exam, and use of additional diagnostic modalities, their clinic's diagnostic yield was 43%. They further note that clinical management was altered in 12% of diagnosed cases.

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. WES has been shown to reduce healthcare costs by limiting downstream medical interventions, regardless of whether a molecular diagnosis is confirmed (Vrijenhoek et al. 2018). However, WES is only cost effective if it replaces the need for multiple individual tests, and it is not as cost-effective when it is used 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 chromosomal microarray or targeted panels. Recommendations from the Clinical Genetics Think Tank, an association of American and Canadian geneticists, suggest that a targeted gene panel should be utilized if available as first-tier testing when the patient's clinical presentation is specific to a known genetic condition, and WES should only be considered as a next step if the previous panel is outdated, the patient's phenotype is atypical or has evolved, or there is clinical urgency.

These recommendations were echoed by the American College of Medical Genetics and Genomics in a 2012 statement advocating the use of genomic testing in phenotypically affected individuals when: 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; or a patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.

Whole Exome Reanalysis

There may be scenarios in which reanalysis of previously uninformative whole exome sequence data is medically necessary. This includes the onset of additional symptoms that broaden the phenotype assessed during the original exome evaluation, or the birth or diagnosis of a similarly affected first-degree relative that has expanded the clinical picture. In addition, due to the rapid increase in knowledge surrounding disease genes and phenotypes, WES reanalysis can be helpful at future time intervals. Reanalysis of exome 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 re-classify previously detected variants of uncertain significance.

Whole Exome Sequencing in Early Onset Epileptic Encephalopathy

There is evidence of utility for the use of WES in patients with early onset epilepsies. Sheidley et al. (2018) discussed possible utility of genetic testing for epilepsy includes avoidance of treatment (i.e. epilepsy surgery) and invasive diagnostic tests (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. Diagnostic criteria for early infantile epileptic encephalopathy (EIEE) 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 ILAE and many have overlapping or

heterogeneous genetic causes (Palmer et al. 2018). In this population a rapid diagnosis can significantly impact treatment options (i.e. GLUT1 deficiency of B6 dependent early onset epilepsy) or referral to other specialties or palliative care (Myers et al. 2018). Additionally, 40-50% of EE remain undiagnosed after first tier assessment (neurological, neuroimaging, evaluation, screening for metabolic disorders, CMA and targeted genetic testing) (Palmer et al. 2018).

Vissers et al. (2017) examined 150 patients with neurological disorders (including 5 with epilepsy and 39 patients with Intellectual Disability (ID)+epilepsy or ID+movement disorder) and found that WES identified significantly more conclusive diagnoses (29.3%) than the standard care pathway (7.3%) without incurring higher costs. Nolan et al. (2016) found a diagnostic rate for WES, through a retrospective chart review, increased from 25% - 48%. Howell et al. (2018) reported an increased diagnostic yield of 67% with WES in 114 patients with severe epilepsies of infancy (SEI). Myers et al. (2018) compiled studies that utilized WGS and WES studies in epilepsy and encephalopathy and found that the diagnostic rate ranged from 12.5-77% for patients with various forms of early life epilepsies.

Whole Exome Sequencing for 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 et al. (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 et al. (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 et al. (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 et al. (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.

Whole Exome Sequencing in the Prenatal Setting

Data has demonstrated 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 (Abou Tayoun and Mason-Suares 2019; Lord et al. 2019; Petrovski 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 (Yates et al. 2017; Drury et al. 2015) providing an alternative to current commercially available panels which may not contain newly discovered pathogenic variants.

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; Abou Tayoun and Mason-Suares 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. Identification of fetal structural anomalies using ultrasonography limits the ability for clinicians to ascertain the full phenotypic spectrum which may impact the interpretation of WES (Aarabi et al. 2018). 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 (Felice et al. 2019). Prenatal WES may also be considered in the context of research in cases that do not meet clinical criteria for testing.

Professional Society Guidelines

American College of Medical Genetics and Genomics (ACMG)

ACMG Statement. The Use of Fetal Exome Sequencing in Prenatal Diagnosis: A Points to Consider Document.

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Revision History

Medical Advisory Board Review:

- v1.2021 11/13/2020: Approved
- v2.2020 05/08/2020: Reviewed
- v1.2020 11/04/2019: Reviewed
- v2.2019 05/23/2019: No Criteria Changes
- v1.2019 11/07/2018: Reviewed
- v1.2018 03/31/2018: Reviewed

Clinical Steering Committee Review:

- v1.2021 10/13/2020: Approved
- v2.2020 04/06/2020: Approved
- v1/2020 10/11/2019: Approved
- v2.2019 04/03/2019: Approved

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v1.2019 10/03/2018: Approved

v1.2018 02/28/2018: Approved

v1.2017 01/25/2017: Approved

Revisions:

Version	Date	Editor	Description
v1.2021	9/11/2020	Heather Dorsey, MS, CGC	Semi-annual update. Genetic counseling requirements were updated as well as criteria across WES testing for phenotype suspicious of a genetic disorder, epilepsy, hearing loss and reanalysis. CPT codes, professional society guidelines and the background were updated.
v2.2020	03/13/2020	Carrie Langbo, MS, CGC	Whole exome sequencing criteria was updated to include coverage criteria for fetal testing, and individuals with hearing loss. CPT codes, professional society guidelines, background and references were updated.
v1.2020	9/11/2019	Samantha Freeze, MS, CGC	Semi-annual review. No criteria changes.
v2.2019	04/03/2019	Laura Rebek, MS, CGC	Semi-annual review. No criteria changes. Updated references.
v1.2019	10/03/2018	Heather Dorsey, MS, CGC	Semi-annual review. Additional criteria for early-onset epilepsy added. Background, professional society guidelines and references updated. Administrative change to genetic counseling requirement - moved from client policy to guidelines. CPT code list reformatted. PMID added.
v1.2018	03/31/2018	Heather Dorsey, MS, CGC	Semi-annual review. No criteria changes. Disclaimer sentence added to scope. Background,

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			professional society guidelines and references updated.
v1.2017	10/27/2017	Heather Dorsey, MS, CGC	Quarterly review. No criteria changes. Updated references.
v1.2017	09/11/2017	Megan Czarniecki, MS, CGC	Formatted references to NLM style. Moved methodological considerations to appropriate use criteria and background. Updated associated CPT codes. Removed genetic counseling recommendation. Approved by Policy Lead.
v1.2017	07/03/2017	Heather Dorsey, MS, CGC	Quarterly review. No criteria changes. Added statement to clarify that WES for carrier screening is not included in coverage criteria. Updated references. Approved by Policy Lead.
v1.2017	04/25/2017	Gwen Fraley, MS, CGC	Quarterly review. No criteria changes. Updated references.
v1.2017	12/20/2016	Heather Dorsey, MS, CGC	Quarterly review. No criteria changes. Updated references and renumbered to 2017.
v1.2016	10/03/2016	Gwen Fraley, MS, CGC	Added criteria for exome reanalysis. Updated references.
v1.2015	08/27/2015	Gwen Fraley, MS, CGC	Original version

Original Effective Date: 08/27/2015

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