

Clinical Appropriateness Guidelines

Whole Exome and Whole Genome Sequencing

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EFFECTIVE SEPTEMBER 9, 2019



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2067-0919

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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) or prenatal testing (see Clinical Appropriateness Guidelines for Reproductive Carrier Screening and Prenatal Diagnosis). All tests listed in these guidelines may not require prior authorization; 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 individual and performed pre-test genetic counseling
- Has completed a three-generation pedigree
- Intends to engage in post-test follow-up counseling

**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

Whole Exome Sequencing

Whole exome sequencing (WES) (81415 and 81416) is 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 with specific expertise in the conditions being tested for and relevant genes
- WES results will directly impact clinical decision-making and/or clinical outcome
- A genetic etiology is the most likely explanation for the phenotype as demonstrated by one of the following:
 - Multiple abnormalities affecting unrelated organ systems
 - 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

Or two of the following four criteria:

- Abnormality affecting a single organ system
 - Significant intellectual disability or severe psychological/psychiatric disturbance (e.g. self-injurious behavior, reversed sleep-wake cycles)
 - Family history strongly implicating a genetic etiology
 - 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 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 that would be recommended in the absence of testing

Prenatal diagnosis or preimplantation testing of an embryo using WES is not medically necessary.

WES for the purpose of genetic carrier screening is not medically necessary.

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Whole Exome Reanalysis

Reanalysis of previously obtained uninformative whole exome sequence (81417) is medically necessary when one 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

Whole Genome Sequencing

Whole genome sequencing (WGS) is not medically necessary.

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

CPT Codes

The following codes are associated with the guidelines outlined in this document. This list is not all inclusive.

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

Background

Next generation sequencing technology allows high throughput rapid DNA sequencing at a much lower price than previous sequencing methodologies. The evolution of this technology has spurred the development of tests that sequence multiple genes simultaneously, and such testing is expected to increasingly enable widespread evaluation of patients' genomes in the clinical setting (Johansen Taber et al. 2014).

Whole exome sequencing (WES) consists of analysis of the protein-coding regions of the human genome, either DNA or RNA. 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 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 (ACMG 2012; ACMG 2013; Biesecker 2014).

Determining genetic causality for disease and establishing a molecular diagnosis in clinical practice can aid in confirming or establishing a clinical diagnosis, inform prognosis, help select or discontinue treatment, reveal mode of inheritance and risk to family members, and/or guide research regarding new therapies or patient management. Overall analytical sensitivity is still being defined for WES.

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

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):

1. 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
2. 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
3. A patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to arrive at a diagnosis
4. 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 prenatal diagnosis

Recent literature suggests utility for genetic testing, including WES in some cases, in early onset epileptic encephalopathy. Appropriate testing is dependent upon the particular epilepsy phenotype and comorbidity. In some instances, genetic testing can confirm a diagnosis in an affected individual, predict onset of seizures in at-risk individuals, and/or drive management decisions. Among the situations with high clinical utility is genetic testing for the GLUT1 (SLC2A1) gene in children with early-onset absence seizures before age 4 years. Though GLUT1 deficiency is associated with a broad clinical spectrum, 10% of children with this clinical presentation have an SLC2A1 mutation which carries significant clinical implications. A ketogenic diet is recommended for all affected children and can significantly improve prognosis (Michelucci et al. 2012). More recently, testing in all forms of epileptic encephalopathies (characterized by comorbidity of developmental/cognitive delay or regression) has been suggested, as many genes that have been associated with the condition have been determined to be actionable (e.g. SCN1A, ARX, CDKL5, SCN2A) (Weber et al. 2017).

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%. For patients with severe epilepsies of infancy (SEI) (defined as onset before 18 months, frequent seizure, epileptiform EEG, and failure of ≥ 2 antiepileptic drugs), Howell et al. (2018) found that in 114 infants with SEI (incidence = 54/100,000 live births/year), the etiology was determined in 76 (67%). Through modeling the authors found that WES increased diagnostic yield and early targeted WES has a lower associated cost. In addition, the testing pathway that included WES and limited metabolic testing found 7 additional diagnoses versus the pathway that did not include WES (Howell et al. 2018). Myers et al. (2018) compiled recent 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.

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. The American College of Medical Genetics and Genomics recommends laboratories who perform WES report on known pathogenic or expected pathogenic variants in 59 medically actionable genes even when unrelated to the primary indication for testing, with the patient's consent (Kalia et al. 2016). While incidental identification of clinically significant mutations poses issues of informed consent, these findings often have clear medical management recommendations (ACMG 2013; Green et al. 2013). However, even amongst the list of 59 genes recommended for the reporting of incidental

findings by the American College of Medical Genetics and Genomics, there are challenges in determining the phenotypic consequences of variants identified (Jurgens et al. 2015). The identification of variants of uncertain significance also creates a medical management dilemma, putting the health care provider at risk of under- or over-managing the patient depending on the true underlying clinical implications of the variant. In one study by Shashi et al. (2015), variants of uncertain significance were reported in 86% of patients who underwent WES, with 53.7% recommended for follow-up studies, such as additional laboratory tests or genotyping of family members. Due to their uncertain nature, such variants often lead to increased utilization of evaluation, diagnostic, or screening procedures that may be unnecessary, resulting in increased risk of adverse events and costs.

While WES is useful in diagnosing complex phenotypes, targeted testing, when possible, is typically a more cost-effective approach with a lower risk of incidental findings. The Clinical Sequencing Exploratory Research (CSER) program provided an overview of recent advances in genomic medicine, including WES and WGS. They conclude that while there have been many advances, further work is still needed regarding comparative effectiveness and cost-effectiveness. Employing the expertise of clinical genetics specialists facilitates accurate evaluation of patients and assessment of whether targeted testing is likely to 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. Thirty-nine patients were determined to not have a genetic disorder; 212 of the remaining 461 (46%) received a genetic diagnosis, and 72% of those 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 some members of the remaining pool of undiagnosed individuals. The authors propose that the clinical utility of genomic testing is greater when testing is applied after an initial clinical genetics evaluation. Experts agree that involvement of trained genetics professionals in consulting with patients is essential prior to and after ordering such tests and can identify the appropriate patients for large multi-gene panels or WES (Kurian 2014; Yang et al. 2013).

In fact, obtaining informed consent and providing pre-test genetic counseling by a trained genetics professional is an essential piece of WES. The ACMG published specific recommendations (ACMG 2012):

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

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 chromosome microarray or multigene 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).

Vassy et al. (2017) reported on a pilot trial looking at the use of WGS in a healthy adult population and conclude that its use reveals findings of uncertain clinical utility. In addition, committee opinion from the American College of Obstetrics and Gynecology does not recommend the routine use of WES in pregnancy outside the context of clinical trials.

Professional Society Guidelines

American College of Medical Genetics, Board of Directors. Points to consider in the clinical application of genomic sequencing. *Genet Med*. 2012 Aug;14(8):759-61. PubMed PMID: 22863877.

American College of Medical Genetics, Board of Directors. Points to consider for informed consent for genome/exome sequencing. *Genet Med*. 2013 Sep;15(9):748-9. Epub 2013 Aug 22. PubMed PMID: 23970068.

American College of Obstetricians and Gynecologists (ACOG). ACOG Committee Opinion No. 682: microarrays and next-generation sequencing technology: the use of advanced genetic diagnostic tools in obstetrics and gynecology. *Obstet Gynecol*. 2016 Dec;128(6):e262-8. PubMed PMID: 27875474.

Joseph L, Cankovic M, Caughron S, et al. The spectrum of clinical utilities in molecular pathology testing procedures for inherited conditions and cancer: a report of the Association for Molecular Pathology. *J Mol Diagn*. 2016 Sep;18(5):605-619. Epub 2016 Aug 16. PubMed PMID: 27542512.

Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet Med*. 2017 Feb;19(2):249-55. Epub 2016 Nov 17. PubMed PMID: 27854360.

Selected References

- 1 Amendola LM, Jarvik GP, Leo MC, et al. Performance of ACMG-AMP Variant-Interpretation Guidelines among nine laboratories in the Clinical Sequencing Exploratory Research Consortium. *Am J Hum Genet*. 2016 Jun 2;98(6):1067-76. Epub 2016 May 12. PubMed PMID: 27181684.
- 2 Auer PL, Reiner AP, Wang G, et al. Guidelines for large-scale sequence-based complex trait association studies: lessons learned from the NHLBI Exome Sequencing Project. *Am J Hum Genet*. 2016 Oct 6;99(4):791-801. Epub 2016 Ep 22. PubMed PMID: 27666372.
- 3 Biesecker LG, Green RC. Diagnostic clinical genome and exome sequencing. *N Engl J Med*. 2014 Jun 19;370(25):2418-25. Review. PubMed PMID: 24941179.
- 4 Berg AT, Coryell J, Saneto RP, et al. Early-life epilepsies and the emerging role of genetic testing. *JAMA Pediatr*. 2017 Sep 1;171(9):863-71. PubMed PMID: 28759667.
- 5 Best S, Wou K, Vora N, et al. Promises, pitfalls and practicalities of prenatal whole exome sequencing. *Prenat Diagn*. 2018 Jan;38(1):10-19. Epub 2017 Jul 25. PubMed PMID: 28654730.

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- 6 Chang YS, Huang HD, Yeh KT, et al. Evaluation of whole exome sequencing by targeted gene sequencing and Sanger sequencing. *Clin Chim Acta*. 2017 Jun 15;471:222-32. Epub 2017 Jun 15. PubMed PMID: 28624499.
- 7 Costain G, Jobling R, Walker S, et al. Periodic reanalysis of whole-genome sequencing data enhances the diagnostic advantage over standard clinical genetic testing. *Eur J Hum Genet*. 2018 Feb 16;26(5):740-744. Epub 2018 Feb 16. PubMed PMID: 29453418.
- 8 Donley G, Hull SC, Berkman BE. Prenatal whole genome sequencing: just because we can, should we? *Hastings Cent Rep*. 2012 Jul-Aug;42(4):28-40. Epub 2012 Jun 20. PubMed PMID: 22777977.
- 9 Du C, Pusey BN, Adams CJ, et al. Explorations to improve the completeness of exome sequencing. *BMC Med Genomics*. 2016 Aug 27;9(1):56. PubMed PMID: 27568008.
- 10 Green RC, Goddard KA, Jarvik GP, et al. Clinical Sequencing Exploratory Research Consortium: accelerating evidence-based practice of genomic medicine. *Am J Hum Genet*. 2016 Jun 2;98(6):1051-66. Epub 2016 May 12. PubMed PMID: 27181682.
- 11 Goldfeder RL, Priest JR, Zook JM, et al. Medical implications of technical accuracy in genome sequencing. *Genome Med*. 2016 Mar 2;8(1):24. PubMed PMID: 26932475.
- 12 Howell KB, Eggers S, Dalziel K, et al. A population-based cost-effectiveness study of early genetic testing in severe epilepsies of infancy. *Epilepsia*. 2018 Jun;59(6):1177-87. Epub 2018 May 11. PubMed PMID: 29750358.
- 13 Johansen Taber KA, Dickinson BD, Wilson M. The promise and challenges of next-generation genome sequencing for clinical care. *JAMA Intern Med*. 2014 Feb 1;174(2):275-80. PubMed PMID: 24217348.
- 14 Jurgens J, Ling H, Hetrick K, et al. Assessment of incidental findings in 232 whole-exome sequences from the Baylor-Hopkins Center for Mendelian Genomics. *Genet Med*. 2015 Oct;17(10):782-8. Epub 2015 Jan 8. PubMed PMID: 25569433.
- 15 Kremer LS, Bader DM, Mertes C, et al. Genetic diagnosis of Mendelian disorders via RNA sequencing. *Nat Commun*. 2017 Jun 12;8:15824. PubMed PMID: 28604674.
- 16 Kurian AW, Hare EE, Mills MA, et al. Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. *J Clin Oncol*. 2014 Jul 1;32(19):2001-9. Epub 2014 Apr 14. PubMed PMID: 24733792.
- 17 Michelucci et al., Genetics of epilepsy and relevance to current practice. *Current Neurology and Neuroscience Reports*, August 2012, Volume 12, Issue 4, pp 445-55. PubMed PMID: 22618127.
- 18 Myers KA, Johnstone DL, Dyment DA. Epilepsy genetics: Current knowledge, applications, and future directions. *Clin Genet*. 2018 Jul 10. doi: 10.1111/cge.13414. [Epub ahead of print] Review. PubMed PMID: 29992546.
- 19 Nolan D, Fink J. Genetics of epilepsy. *Handb Clin Neurol*. 2018;148:467-91. PubMed PMID: 29992546.
- 20 Palmer EE, Schofield D, Shrestha R, et al. Integrating exome sequencing into a diagnostic pathway for epileptic encephalopathy: Evidence of clinical utility and cost effectiveness. *Mol Genet Genomic Med*. 2018 Mar;6(2):186-99. Epub 2018 Jan 4. PubMed PMID: 29314763.
- 21 Shashi V, McConkie-Rosell A, Rosell B, et al. The utility of the traditional medical genetics diagnostic evaluation in the context of next-generation sequencing for undiagnosed genetic disorders. *Genet Med*. 2014 Feb;16(2):176-82. Epub 2013 Aug 29. PubMed PMID: 23928913.
- 22 Sheidley BR, Smith LA, and KL Helbig, et al. Genetics of epilepsy in the era of precision medicine: implications for testing, treatment, and genetic counseling. *Curr Genet Med Rep*. 2018; 6(2): 73-8. <https://doi.org/10.1007/s40142-018-0139-8>.
- 23 Van El CG, Cornel MC, Borry P, et al. Whole-genome sequencing in health care: recommendations of the European Society of Human Genetics. *Eur J Hum Genet*. 2013 Jun;21(6):580-4. PubMed PMID: 23676617.
- 24 Vassy JL, Christensen KD, Schonman EF, et al. The impact of whole-genome sequencing on the primary care and outcomes of healthy adult patients: A pilot randomized trial. *Ann Intern Med*. 2017;167(3):159-69. PubMed PMID: 28654958.
- 25 Vissers LELM, van Nimwegen KJM, Schieving JH, et al. A clinical utility study of exome sequencing versus conventional genetic testing in pediatric neurology. *Genet Med*. 2017 Sep;19(9):1055-63. Epub 2017 Mar 23. PubMed PMID: 28333917.
- 26 Weber YG, Biskup S, Helbig KL, et al. The role of genetic testing in epilepsy diagnosis and management. *Expert Rev Mol Diagn*. 2017 Aug;17(8):739-50. Epub 2017 Jun 26. PubMed PMID: 28548558.
- 27 Wenger AM, Guturu H, Bernstein JA, et al. Systematic reanalysis of clinical exome data yields additional diagnoses: implications for providers. *Genet Med*. 2017 Feb;19(2):209-14. Epub 2016 Jul 21. PubMed PMID: 27441994.
- 28 Winand R, Hens K, Dondorp W, et al. In vitro screening of embryos by whole-genome sequencing: now, in the future or never? *Hum Reprod*. 2014 Apr;29(4):842-51. Epub 2014 Feb 2. PubMed PMID: 24491297.
- 29 Wright CF, McRae JF, Clayton S, et al. Making new genetic diagnoses with old data: iterative reanalysis and reporting from genome-wide data in 1,133 families with developmental disorders. *Genet Med*. 2018 Jan 11. PubMed PMID: 29323667
- 30 Yang Y, Muzny DM, Reid JG, et al. Clinical whole-exome sequencing for the diagnosis of Mendelian disorders. *N Engl J Med*. 2013 Oct 17;369(16):1502-11. Epub 2013 Oct 2. PubMed PMID: 24088041.
- 31 Zawati MH, Parry D, Thorogood A, et al. Reporting results from whole-genome and whole-exome sequencing in clinical practice: a proposal for Canada? *J Med Genet*. 2014 Jan;51(1):68-70. Epub 2013 Sep 27. PubMed PMID: 24078715.

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Revision History

Medical Advisory Board Review:

v2.2019 05/23/2019: No Criteria Changes

v1.2019 11/07/2018: Reviewed

v1.2018 03/31/2018: Reviewed

Clinical Steering Committee Review:

v2.2019 04/03/2019: Approved

v1.2019 10/03/2018: Approved

v1.2018 02/28/2018: Approved

v1.2017 01/25/2017: Approved

Revisions:

Version	Date	Editor	Description
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, professional society guidelines and references updated.

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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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