



## FEP Medical Policy Manual

### FEP 2.04.102 Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

**Effective Policy Date: July 1, 2021**

**Original Policy Date: December 2013**

#### **Related Policies:**

- 2.04.105 - Genetic Testing for Facioscapulohumeral Muscular Dystrophy
- 2.04.109 - Genetic Testing for Epilepsy
- 2.04.132 - Genetic Testing for Limb-Girdle Muscular Dystrophies
- 2.04.59 - Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies
- 2.04.89 - Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

## Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

### Description

#### Description

Whole exome sequencing (WES) sequences the portion of the genome that contains protein-coding DNA, while whole genome sequencing (WGS) sequences both coding and noncoding regions of the genome. Whole exome sequencing and WGS have been proposed for use in patients presenting with disorders and anomalies not explained by a standard clinical workup. Potential candidates for WES and WGS include patients who present with a broad spectrum of suspected genetic conditions.

#### OBJECTIVE

The objective of this evidence review is to determine whether whole exome or whole genome sequencing improves the net health outcome in individuals with suspected genetic disorders.

## POLICY STATEMENT

Standard whole exome sequencing, with trio testing when possible (see Policy Guidelines), may be considered **medically necessary** for the evaluation of unexplained congenital or neurodevelopmental disorders in children when ALL of the following criteria are met:

1. Documentation that the patient has been evaluated by a clinician with expertise in clinical genetics, including at minimum a family history and phenotype description, and counseled about the potential risks of genetic testing.
2. There is potential for a change in management and clinical outcome for the individual being tested.
3. A genetic etiology is considered the most likely explanation for the phenotype despite previous genetic testing (eg, chromosomal microarray analysis and/or targeted single-gene testing), **OR** when previous genetic testing has failed to yield a diagnosis, and the affected individual is faced with invasive procedures or testing as the next diagnostic step (eg, muscle biopsy).

Rapid whole exome sequencing or rapid whole genome sequencing, with trio testing when possible (see Policy Guidelines), may be considered **medically necessary** for the evaluation of critically ill infants in neonatal or pediatric intensive care with a suspected genetic disorder of unknown etiology when BOTH of the following criteria are met:

1. At least one of the following criteria is met:
  1. Multiple congenital anomalies (see Policy Guidelines);
  2. An abnormal laboratory test or clinical features suggests a genetic disease or complex metabolic phenotype (see Policy Guidelines);
  3. An abnormal response to standard therapy for a major underlying condition;
2. None of the following criteria apply regarding the reason for admission to intensive care:
  1. An infection with normal response to therapy;
  2. Isolated prematurity;
  3. Isolated unconjugated hyperbilirubinemia;
  4. Hypoxic Ischemic Encephalopathy;
  5. Confirmed genetic diagnosis explains illness;
  6. Isolated Transient Neonatal Tachypnea; or
  7. Nonviable neonates.

Whole exome sequencing is considered **investigational** for the diagnosis of genetic disorders in all other situations.

Whole genome sequencing is considered **investigational** for the diagnosis of genetic disorders in all other situations.

Whole exome sequencing and whole genome sequencing are considered **investigational** for screening for genetic disorders.

## POLICY GUIDELINES

The policy statements are intended to address the use of whole exome and whole genome sequencing for the diagnosis of genetic disorders in patients with suspected genetic disorders and for population-based screening.

This policy does not address the use of whole exome and whole genome sequencing for preimplantation genetic diagnosis or screening, prenatal (fetal) testing, or testing of cancer cells.

### Rapid Sequencing

In the NSIGHT1 trial (Petrikin, 2018) rapid Whole Genome Sequencing (rWGS) provided time to provisional diagnosis by 10 days with time to final report of approximately 17 days although the trial required confirmatory testing of WGS results which lengthened the time to rWGS diagnosis by 7 - 10 days. The WGS was performed in "rapid run" mode with a minimum depth of 90 Gb per genome and average depth of coverage of 40X.

For rapid WES or WGS, the patient should be critically ill and in the NICU or PICU when the test is ordered but may be discharged before results are delivered.

Copy number variation (CNV) analysis should be performed in parallel with rWGS using chromosomal microarray analysis (CMA) or directly within rWGS if the test is validated for CNV analysis.

Examples of specific malformations highly suggestive of a genetic etiology, include but are not limited to any of the following :

- Choanal atresia
- Coloboma
- Hirschsprung disease
- Meconium ileus

Examples of an abnormal laboratory test suggesting a genetic disease or complex metabolic phenotype, include but are not limited to any of the following:

- Abnormal newborn screen
- Conjugated hyperbilirubinemia not due to total parental nutrition (TPN) cholestasis
- Hyperammonemia
- Lactic acidosis not due to poor perfusion
- Refractory or severe hypoglycemia

Examples of clinical features suggesting a genetic disease include but are not limited to any of the following:

- Significant hypotonia; or
- Persistent seizures.
- Infant with high risk stratification on evaluation for a Brief Resolved Unexplained Event (BRUE) (see below) with any of the following features:
  - Recurrent events without respiratory infection
  - Recurrent witnessed seizure like events
  - Required Cardiopulmonary Resuscitation (CPR)
  - Significantly abnormal chemistry including but not limited to electrolytes, bicarbonate or lactic acid, venous blood gas, glucose, or other tests that suggest an inborn error of metabolism
- Significantly abnormal electrocardiogram (ECG), including but not limited to possible channelopathies, arrhythmias, cardiomyopathies, myocarditis or structural heart disease

- Family history of:
  - Arrhythmia
  - BRUE in sibling
  - Developmental delay
  - Inborn error of metabolism or genetic disease
  - Long QT syndrome (LQTS)
  - Sudden unexplained death (including unexplained car accident or drowning) in first- or second-degree family members before age 35, and particularly as an infant

## Brief Resolved Unexplained Event (BRUE)

Brief Resolved Unexplained Event (BRUE) was previously known as Apparent Life Threatening Event (ALTE). In a practice guideline from the American Academy of Pediatrics (AAP), BRUE is defined as an event occurring in an infant younger than 1 year of age when the observer reports a sudden, brief (usually less than one minute), and now resolved episode of one or more of the following:

- Absent, decreased, or irregular breathing
- Altered level of responsiveness
- Cyanosis or pallor
- Marked change in tone (hyper- or hypotonia)

A BRUE is diagnosed only when there is no explanation for a qualifying event after conducting an appropriate history and physical examination. Note: More information is available at: <https://pediatrics.aappublications.org/content/137/5/e20160590>

## Trio Testing

The recommended option for testing when possible is testing of the child and both parents (trio testing). Trio testing increases the chance of finding a definitive diagnosis and reduces false-positive findings.

Trio testing is preferred whenever possible but should not delay testing of a critically ill patient when rapid testing is indicated. Testing of one available parent should be done if both are not immediately available and one or both parents can be done later if needed.

## Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organisation, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

**Table PG1. Nomenclature to Report on Variants Found in DNA**

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

**Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification**

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

## Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

## BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

## FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Whole exome sequencing or WGS tests as a clinical service are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

## RATIONALE

### Summary of Evidence

For individuals who are children who are not critically ill with multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup who receive whole exome sequencing, (WES) with trio testing when possible, the evidence includes large case series and within-subject comparisons. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. Patients who have multiple congenital anomalies or a developmental disorder with a suspected genetic etiology, but whose specific genetic alteration is unclear or unidentified by a standard clinical workup, may be left without a clinical diagnosis of their disorder, despite a lengthy diagnostic workup. For a substantial proportion of these patients, WES may return a likely pathogenic variant. Several large and smaller series have reported diagnostic yields of WES ranging from 25% to 60%, depending on the individual's age, phenotype, and previous workup. One comparative study found a 44% increase in yield compared with standard testing strategies. Many of the studies have also reported changes in patient management, including medication changes, discontinuation of or additional testing, ending the diagnostic odyssey, and family planning. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are children with a suspected genetic disorder other than multiple congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup who receive WES with trio testing when possible, the evidence includes small case series and prospective research studies. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. There is an increasing number of reports evaluating the use of WES to identify a molecular basis for disorders other than multiple congenital anomalies or neurodevelopmental disorders. The diagnostic yields in these studies range from as low as 3% to 60%. Some studies have reported on the use of a virtual gene panel with restricted analysis of disease-associated genes, and WES data allows reanalysis as new genes are linked to the patient phenotype. Overall, a limited number of patients have been studied for any specific disorder, and clinical use of WES for these disorders is at an early stage with uncertainty about changes in patient management. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are children who are not critically ill with multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup who receive WGS with trio testing when possible, the evidence includes case series. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. In studies of children with congenital abnormalities and developmental delays of unknown etiology following a standard clinical workup, the yield of WGS has been between 20% and 40%. Additional indirect evidence is available from studies reporting diagnostic yield and change in management results of WES in a similar population. Whole genome sequencing may result in a similar or better diagnostic yield for pathogenic or likely pathogenic variants as compared with WES but few direct comparisons are available. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are children with a suspected genetic disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup who receive WGS with trio testing when possible, the evidence includes case series. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. Whole genome sequencing has also been studied in other genetic conditions with yield ranging from 9% to 55%. Overall, a limited number of patients have been studied for any specific disorder, and clinical use of WGS as well as information regarding meaningful changes in management for these disorders is at an early stage. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are critically ill infants with a suspected genetic disorder of unknown etiology following a standard workup who receive rapid whole genome sequencing (rWGS) rapid whole exome sequencing (rWES) with trio testing when possible, the evidence includes randomized controlled trials (RCTs) and case series. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. One RCT comparing rWGS with standard genetic tests to diagnose suspected genetic disorders in critically ill infants was terminated early due to loss of equipoise. The rate of genetic diagnosis within 28 days of enrollment was higher for rWGS versus standard tests (31% vs. 3%;  $p=0.003$ ). Changes in management due to test results were reported in 41% vs. 21% ( $p=0.11$ ) of rWGS versus control patients; however, 73% of control subjects received broad genetic tests (eg, next-generation sequencing panel testing, WES, or WGS) as part of standard testing. A second RCT compared rWGS to rWES in seriously ill infants with diseases of unknown etiology from the neonatal intensive care unit, pediatric intensive care unit, and cardiovascular intensive care unit. Only the diagnostic outcomes have currently been reported. The diagnostic yield of rWGS and rWES was similar (19% vs. 20%, respectively), as was time (days) to result (median, 11 vs. 11 days). Several retrospective and prospective studies including more than 800 critically ill infants and children in total have reported on diagnostic yield for rWGS or rWES. These studies included phenotypically diverse but critically ill infants and had yields of between 30% and 60% for pathogenic or likely pathogenic variants. Studies have also reported associated changes in patient management for patients receiving a diagnosis from rWGS or rWES, including avoidance of invasive procedures, medication changes to reduce morbidity, discontinuation of or additional testing, and initiation of palliative care or reproductive planning. A chain of evidence linking meaningful improvements in diagnostic yield and changes in management expected to improve health outcomes supports the clinical value of rWGS or rWES. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

## SUPPLEMENTAL INFORMATION

### Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in "Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

#### American College of Medical Genetics and Genomics

In 2012, the American College of Medical Genetics and Genomics (ACMG) recommended that *diagnostic testing* with whole exome sequencing (WES) and whole genome sequencing (WGS) should be considered in the clinical diagnostic assessment of a phenotypically affected individual when:<sup>63</sup>

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."

ACMG has recommended that for *screening* purposes:

WGS/WES may be considered in preconception carrier screening, using a strategy to focus on genetic variants known to be associated with significant phenotypes in homozygous or hemizygous progeny.

ACMG has also recommended that WGS and WES not be used at this time as an approach to prenatal screening or as a first-tier approach for newborn screening.

In 2014, ACMG guidelines on the clinical evaluation and etiologic diagnosis of hearing loss stated that for individuals with findings suggestive of a syndromic genetic etiology for hearing loss, "pretest genetic counseling should be provided, and, with patient's informed consent, genetic testing, if available, should be ordered to confirm the diagnosis<97>this testing may include single-gene tests, hearing loss sequencing panels, WES, WGS, chromosome analysis, or microarray-based copy number analysis, depending on clinical findings."<sup>64</sup>

In 2016, ACMG updated its recommendations on reporting incidental findings in WGS and WES testing.<sup>65</sup> ACMG determined that reporting some incidental findings would likely have medical benefit for the patients and families of patients undergoing clinical sequencing, recommending that, when a report is issued for clinically indicated exome and genome sequencing, a minimum list of conditions, genes, and variants should be routinely evaluated and reported to the ordering clinician. The 2016 update added 4 genes and removed 1 gene resulting in an updated secondary findings minimum list including 59 medically actionable genes recommended for return in clinical genomic sequencing.

## American Academy of Neurology et al

In 2014, the American Academy of Neurology and American Association of Neuromuscular and Electrodiagnostic Medicine issued evidence-based guidelines on the diagnosis and treatment of limb-girdle and distal dystrophies, which made the following recommendations ( Table 1).<sup>66</sup>

**Table 1. Guidelines on Limb-Girdle Muscular Dystrophy**

Recommendation	LOE
<i>Diagnosis</i>	
<ul style="list-style-type: none"> <li>For patients with suspected muscular dystrophy, clinicians should use a clinical approach to guide genetic diagnosis based on the clinical phenotype, including the pattern of muscle involvement, inheritance pattern, age at onset, and associated manifestations (eg, early contractures, cardiac or respiratory involvement).</li> </ul>	B
<ul style="list-style-type: none"> <li>In patients with suspected muscular dystrophy in whom initial clinically directed genetic testing does not provide a diagnosis, clinicians may obtain genetic consultation or perform parallel sequencing of targeted exomes, whole-exome sequencing, whole-genome screening, or next-generation sequencing to identify the genetic abnormality.</li> </ul>	C
<i>Management of cardiac complications</i>	
<ul style="list-style-type: none"> <li>Clinicians should refer newly diagnosed patients with (1) limb-girdle muscular dystrophy (LGMD)1A, LGMD1B, LGMD1D, LGMD1E, LGMD2C - K, LGMD2M - P, ... or (2) muscular dystrophy without a specific genetic diagnosis for cardiology evaluation, including electrocardiogram (ECG) and structural evaluation (echocardiography or cardiac magnetic resonance imaging [MRI]), even if they are asymptomatic from a cardiac standpoint, to guide appropriate management.</li> </ul>	B
<ul style="list-style-type: none"> <li>If ECG or structural cardiac evaluation (eg, echocardiography) has abnormal results, or if the patient has episodes of syncope, near-syncope, or palpitations, clinicians should order rhythm evaluation (eg, Holter monitor or event monitor) to guide appropriate management.</li> </ul>	B
<ul style="list-style-type: none"> <li>Clinicians should refer muscular dystrophy patients with palpitations, symptomatic or asymptomatic tachycardia or arrhythmias, or signs and symptoms of cardiac failure for cardiology evaluation.</li> </ul>	B
<ul style="list-style-type: none"> <li>It is not obligatory for clinicians to refer patients with LGMD2A, LGMD2B, and LGMD2L for cardiac evaluation unless they develop overt cardiac signs or symptoms.</li> </ul>	B
<i>Management of pulmonary complications</i>	
<ul style="list-style-type: none"> <li>Clinicians should order pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright and, if normal, supine positions) or refer for pulmonary evaluation (to identify and treat respiratory insufficiency) in muscular dystrophy patients at the time of diagnosis, or if they develop pulmonary symptoms later in their course.</li> </ul>	B



<ul style="list-style-type: none"> <li>In patients with a known high risk of respiratory failure (eg, those with LGMD2I ...), clinicians should obtain periodic pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright position and, if normal, in the supine position) or evaluation by a pulmonologist to identify and treat respiratory insufficiency.</li> </ul>	B
<ul style="list-style-type: none"> <li>It is not obligatory for clinicians to refer patients with LGMD2B and LGMD2L for pulmonary evaluation unless they are symptomatic.</li> </ul>	C
<ul style="list-style-type: none"> <li>Clinicians should refer muscular dystrophy patients with excessive daytime somnolence, nonrestorative sleep (eg, frequent nocturnal arousals, morning headaches, excessive daytime fatigue), or respiratory insufficiency based on pulmonary function tests for pulmonary or sleep medicine consultation for consideration of noninvasive ventilation to improve quality of life.</li> </ul>	B

LOE: level of evidence; LGMD: limb-girdle muscular dystrophy.

## U.S. Preventive Services Task Force Recommendations

Not applicable.

## Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

## REFERENCES

- Dixon-Salazar TJ, Silhavy JL, Udpa N, et al. Exome sequencing can improve diagnosis and alter patient management. *Sci Transl Med*. Jun 13 2012; 4(138): 138ra78. PMID 22700954
- Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. May 2015; 17(5): 405-24. PMID 25741868
- Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Special Report: Exome Sequencing for Clinical Diagnosis of Patients with Suspected Genetic Disorders. TEC Assessments. 2013; Volume 28: Tab 3.
- Smith HS, Swint JM, Lalani SR, et al. Clinical Application of Genome and Exome Sequencing as a Diagnostic Tool for Pediatric Patients: a Scoping Review of the Literature. *Genet Med*. Jan 2019; 21(1): 3-16. PMID 29760485
- 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*. Sep 2017; 19(9): 1055-1063. PMID 28333917
- Cordoba M, Rodriguez-Quiroga SA, Vega PA, et al. Whole exome sequencing in neurogenetic odysseys: An effective, cost- and time-saving diagnostic approach. *PLoS One*. 2018; 13(2): e0191228. PMID 29389947
- Ewans LJ, Schofield D, Shrestha R, et al. Whole-exome sequencing reanalysis at 12 months boosts diagnosis and is cost-effective when applied early in Mendelian disorders. *Genet Med*. Dec 2018; 20(12): 1564-1574. PMID 29595814
- Powis Z, Farwell Hagman KD, Speare V, et al. Exome sequencing in neonates: diagnostic rates, characteristics, and time to diagnosis. *Genet Med*. Nov 2018; 20(11): 1468-1471. PMID 29565416
- 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*. Oct 2018; 20(10): 1216-1223. PMID 29323667
- Wright CF, Fitzgerald TW, Jones WD, et al. Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data. *Lancet*. Apr 04 2015; 385(9975): 1305-14. PMID 25529582
- Nambot S, Thevenon J, Kuentz P, et al. Clinical whole-exome sequencing for the diagnosis of rare disorders with congenital anomalies and/or intellectual disability: substantial interest of prospective annual reanalysis. *Genet Med*. Jun 2018; 20(6): 645-654. PMID 29095811
- Tsuchida N, Nakashima M, Kato M, et al. Detection of copy number variations in epilepsy using exome data. *Clin Genet*. Mar 2018; 93(3): 577-587. PMID 28940419
- Evers C, Staufner C, Granzow M, et al. Impact of clinical exomes in neurodevelopmental and neurometabolic disorders. *Mol Genet Metab*. Aug 2017; 121(4): 297-307. PMID 28688840

14. Nolan D, Carlson M. Whole Exome Sequencing in Pediatric Neurology Patients: Clinical Implications and Estimated Cost Analysis. *J Child Neurol.* Jun 2016; 31(7): 887-94. PMID 26863999
15. Allen NM, Conroy J, Shahwan A, et al. Unexplained early onset epileptic encephalopathy: Exome screening and phenotype expansion. *Epilepsia.* Jan 2016; 57(1): e12-7. PMID 26648591
16. Stark Z, Lunke S, Brett GR, et al. Meeting the challenges of implementing rapid genomic testing in acute pediatric care. *Genet Med.* Dec 2018; 20(12): 1554-1563. PMID 29543227
17. Tarailo-Graovac M, Shyr C, Ross CJ, et al. Exome Sequencing and the Management of Neurometabolic Disorders. *N Engl J Med.* Jun 09 2016; 374(23): 2246-55. PMID 27276562
18. Farwell KD, Shahmirzadi L, El-Khechen D, et al. Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families with undiagnosed genetic conditions. *Genet Med.* Jul 2015; 17(7): 578-86. PMID 25356970
19. Yang Y, Muzny DM, Xia F, et al. Molecular findings among patients referred for clinical whole-exome sequencing. *JAMA.* Nov 12 2014; 312(18): 1870-9. PMID 25326635
20. Lee H, Deignan JL, Dorrani N, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. *JAMA.* Nov 12 2014; 312(18): 1880-7. PMID 25326637
21. Iglesias A, Anyane-Yeboah K, Wynn J, et al. The usefulness of whole-exome sequencing in routine clinical practice. *Genet Med.* Dec 2014; 16(12): 922-31. PMID 24901346
22. Soden SE, Saunders CJ, Willig LK, et al. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. *Sci Transl Med.* Dec 03 2014; 6(265): 265ra168. PMID 25473036
23. Srivastava S, Cohen JS, Vernon H, et al. Clinical whole exome sequencing in child neurology practice. *Ann Neurol.* Oct 2014; 76(4): 473-83. PMID 25131622
24. Yang Y, Muzny DM, Reid JG, et al. Clinical whole-exome sequencing for the diagnosis of mendelian disorders. *N Engl J Med.* Oct 17 2013; 369(16): 1502-11. PMID 24088041
25. Kwong AK, Tsang MH, Fung JL, et al. Exome sequencing in paediatric patients with movement disorders. *Orphanet J Rare Dis.* Jan 15 2021; 16(1): 32. PMID 33446253
26. Gileles-Hillel A, Mor-Shaked H, Shoseyov D, et al. Whole-exome sequencing accuracy in the diagnosis of primary ciliary dyskinesia. *ERJ Open Res.* Oct 2020; 6(4). PMID 33447612
27. Kim SY, Jang SS, Kim H, et al. Genetic diagnosis of infantile-onset epilepsy in the clinic: Application of whole-exome sequencing following epilepsy gene panel testing. *Clin Genet.* Mar 2021; 99(3): 418-424. PMID 33349918
28. Hauer NN, Popp B, Schoeller E, et al. Clinical relevance of systematic phenotyping and exome sequencing in patients with short stature. *Genet Med.* Jun 2018; 20(6): 630-638. PMID 29758562
29. Rossi M, El-Khechen D, Black MH, et al. Outcomes of Diagnostic Exome Sequencing in Patients With Diagnosed or Suspected Autism Spectrum Disorders. *Pediatr Neurol.* May 2017; 70: 34-43.e2. PMID 28330790
30. Walsh M, Bell KM, Chong B, et al. Diagnostic and cost utility of whole exome sequencing in peripheral neuropathy. *Ann Clin Transl Neurol.* May 2017; 4(5): 318-325. PMID 28491899
31. Miller KA, Twigg SR, McGowan SJ, et al. Diagnostic value of exome and whole genome sequencing in craniosynostosis. *J Med Genet.* Apr 2017; 54(4): 260-268. PMID 27884935
32. Posey JE, Rosenfeld JA, James RA, et al. Molecular diagnostic experience of whole-exome sequencing in adult patients. *Genet Med.* Jul 2016; 18(7): 678-85. PMID 26633545
33. Ghaoui R, Cooper ST, Lek M, et al. Use of Whole-Exome Sequencing for Diagnosis of Limb-Girdle Muscular Dystrophy: Outcomes and Lessons Learned. *JAMA Neurol.* Dec 2015; 72(12): 1424-32. PMID 26436962
34. Valencia CA, Husami A, Holle J, et al. Clinical Impact and Cost-Effectiveness of Whole Exome Sequencing as a Diagnostic Tool: A Pediatric Center's Experience. *Front Pediatr.* 2015; 3: 67. PMID 26284228
35. Wortmann SB, Koolen DA, Smeitink JA, et al. Whole exome sequencing of suspected mitochondrial patients in clinical practice. *J Inherit Metab Dis.* May 2015; 38(3): 437-43. PMID 25735936
36. Neveling K, Feenstra I, Gilissen C, et al. A post-hoc comparison of the utility of sanger sequencing and exome sequencing for the diagnosis of heterogeneous diseases. *Hum Mutat.* Dec 2013; 34(12): 1721-6. PMID 24123792
37. Lionel AC, Costain G, Monfared N, et al. Improved diagnostic yield compared with targeted gene sequencing panels suggests a role for whole-genome sequencing as a first-tier genetic test. *Genet Med.* Apr 2018; 20(4): 435-443. PMID 28771251
38. 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.* May 2018; 26(5): 740-744. PMID 29453418
39. Stavropoulos DJ, Merico D, Jobling R, et al. Whole Genome Sequencing Expands Diagnostic Utility and Improves Clinical Management in Pediatric Medicine. *NPJ Genom Med.* Jan 13 2016; 1. PMID 28567303
40. Hiatt SM, Amaral MD, Bowling KM, et al. Systematic reanalysis of genomic data improves quality of variant interpretation. *Clin Genet.* Jul 2018; 94(1): 174-178. PMID 29652076
41. Bowling KM, Thompson ML, Amaral MD, et al. Genomic diagnosis for children with intellectual disability and/or developmental delay. *Genome Med.* May 30 2017; 9(1): 43. PMID 28554332
42. Gilissen C, Hehir-Kwa JY, Thung DT, et al. Genome sequencing identifies major causes of severe intellectual disability. *Nature.* Jul 17 2014; 511(7509): 344-7. PMID 24896178
43. Costain G, Walker S, Marano M, et al. Genome Sequencing as a Diagnostic Test in Children With Unexplained Medical Complexity. *JAMA Netw Open.* Sep 01 2020; 3(9): e2018109. PMID 32960281

44. Thiffault I, Farrow E, Zellmer L, et al. Clinical genome sequencing in an unbiased pediatric cohort. *Genet Med*. Feb 2019; 21(2): 303-310. PMID 30008475
45. Alfares A, Aloraini T, Subaie LA, et al. Whole-genome sequencing offers additional but limited clinical utility compared with reanalysis of whole-exome sequencing. *Genet Med*. Nov 2018; 20(11): 1328-1333. PMID 29565419
46. Carss KJ, Arno G, Erwood M, et al. Comprehensive Rare Variant Analysis via Whole-Genome Sequencing to Determine the Molecular Pathology of Inherited Retinal Disease. *Am J Hum Genet*. Jan 05 2017; 100(1): 75-90. PMID 28041643
47. Ellingford JM, Barton S, Bhaskar S, et al. Whole Genome Sequencing Increases Molecular Diagnostic Yield Compared with Current Diagnostic Testing for Inherited Retinal Disease. *Ophthalmology*. May 2016; 123(5): 1143-50. PMID 26872967
48. Taylor JC, Martin HC, Lise S, et al. Factors influencing success of clinical genome sequencing across a broad spectrum of disorders. *Nat Genet*. Jul 2015; 47(7): 717-726. PMID 25985138
49. Yuen RK, Thiruvahindrapuram B, Merico D, et al. Whole-genome sequencing of quartet families with autism spectrum disorder. *Nat Med*. Feb 2015; 21(2): 185-91. PMID 25621899
50. Petrikin JE, Cakici JA, Clark MM, et al. The NSIGHT1-randomized controlled trial: rapid whole-genome sequencing for accelerated etiologic diagnosis in critically ill infants. *NPJ Genom Med*. 2018; 3: 6. PMID 29449963
51. Wu ET, Hwu WL, Chien YH, et al. Critical Trio Exome Benefits In-Time Decision-Making for Pediatric Patients With Severe Illnesses. *Pediatr Crit Care Med*. Nov 2019; 20(11): 1021-1026. PMID 31261230
52. Elliott AM, du Souich C, Lehman A, et al. RAPIDOMICS: rapid genome-wide sequencing in a neonatal intensive care unit-successes and challenges. *Eur J Pediatr*. Aug 2019; 178(8): 1207-1218. PMID 31172278
53. Gubbels CS, VanNoy GE, Madden JA, et al. Prospective, phenotype-driven selection of critically ill neonates for rapid exome sequencing is associated with high diagnostic yield. *Genet Med*. Apr 2020; 22(4): 736-744. PMID 31780822
54. Meng L, Pammi M, Saronwala A, et al. Use of Exome Sequencing for Infants in Intensive Care Units: Ascertainment of Severe Single-Gene Disorders and Effect on Medical Management. *JAMA Pediatr*. Dec 04 2017; 171(12): e173438. PMID 28973083
55. French CE, Delon I, Dolling H, et al. Whole genome sequencing reveals that genetic conditions are frequent in intensively ill children. *Intensive Care Med*. May 2019; 45(5): 627-636. PMID 30847515
56. Sanford EF, Clark MM, Farnaes L, et al. Rapid Whole Genome Sequencing Has Clinical Utility in Children in the PICU. *Pediatr Crit Care Med*. Nov 2019; 20(11): 1007-1020. PMID 31246743
57. Hauser NS, Solomon BD, Vilboux T, et al. Experience with genomic sequencing in pediatric patients with congenital cardiac defects in a large community hospital. *Mol Genet Genomic Med*. Mar 2018; 6(2): 200-212. PMID 29368431
58. Farnaes L, Hildreth A, Sweeney NM, et al. Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization. *NPJ Genom Med*. 2018; 3: 10. PMID 29644095
59. Mestek-Boukhibar L, Clement E, Jones WD, et al. Rapid Paediatric Sequencing (RaPS): comprehensive real-life workflow for rapid diagnosis of critically ill children. *J Med Genet*. Nov 2018; 55(11): 721-728. PMID 30049826
60. van Diemen CC, Kerstjens-Frederikse WS, Bergman KA, et al. Rapid Targeted Genomics in Critically Ill Newborns. *Pediatrics*. Oct 2017; 140(4). PMID 28939701
61. Willig LK, Petrikin JE, Smith LD, et al. Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings. *Lancet Respir Med*. May 2015; 3(5): 377-87. PMID 25937001
62. Kingsmore SF, Cakici JA, Clark MM, et al. A Randomized, Controlled Trial of the Analytic and Diagnostic Performance of Singleton and Trio, Rapid Genome and Exome Sequencing in Ill Infants. *Am J Hum Genet*. Oct 03 2019; 105(4): 719-733. PMID 31564432
63. ACMG Board of Directors. Points to consider in the clinical application of genomic sequencing. *Genet Med*. Aug 2012; 14(8): 759-61. PMID 22863877
64. Alford RL, Arnos KS, Fox M, et al. American College of Medical Genetics and Genomics guideline for the clinical evaluation and etiologic diagnosis of hearing loss. *Genet Med*. Apr 2014; 16(4): 347-55. PMID 24651602
65. 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*. Feb 2017; 19(2): 249-255. PMID 27854360
66. Narayanaswami P, Weiss M, Selcen D, et al. Evidence-based guideline summary: diagnosis and treatment of limb-girdle and distal dystrophies: report of the guideline development subcommittee of the American Academy of Neurology and the practice issues review panel of the American Association of Neuromuscular Electrodiagnostic Medicine. *Neurology*. Oct 14 2014; 83(16): 1453-63. PMID 25313375

**POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:**

<b>Date</b>	<b>Action</b>	<b>Description</b>
December 2013	New policy	
December 3014	Replace policy	Policy updated with literature review. References 2, 4, 5, and 8-13 added. Whole genome sequencing added to policy statement; whole genome sequencing considered investigational.
December 2015	Replace policy	Policy updated with literature review through September 28, 2015. References 3, 5, 9, 15-16, 18-20, and 22-25 added. Policy statements unchanged.
March 2017	Replace policy	Policy updated with literature review through August 22, 2016; references 9, 11, 14, 16-18, and 20-22 added. Rationale revised. Whole exome sequencing considered medically necessary for children with multiple congenital anomalies or a neurodevelopmental disorder. All other uses of whole exome and whole genome sequencing are considered investigational. Policy statement added that whole exome and whole genome sequencing are considered investigational for screening.
December 2017	Replace policy	Policy updated with literature search through August 23, 2017; references 6-8, 19, 24-25, 27, and 30 added. Policy statements unchanged.
December 2018	Replace policy	Policy updated with literature search through August 6, 2018; references 12, 16-20, 28-29, 31, 35, and 37; references 36 and 38 updated. Policy statements unchanged.
June 2020	Replace policy	Policy updated with literature search through January 31, 2020. references added. Policy statements added to include rapid whole exome or genome sequencing with trio testing when possible as medically necessary for critically ill infants with suspected genetic disorder of unknown etiology following standard workup. Policy statement added to include whole genome sequencing with trio testing when possible for children who are not critically ill with multiple unexplained congenital anomalies or neurodevelopmental disorder of unknown etiology following standard workup.
June 2021	Replace policy	Policy updated with literature search through February 2, 2021; references added. Policy statements unchanged.