Whole Genome Sequencing for Diagnosis of Genetic Disorders

Policy # 00389
Original Effective Date: 11/20/2013
Current Effective Date: 07/01/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: All Genetic Testing outside of Whole Genome Sequencing that is outlined in MP 00389 will be decisioned by Carelon and all genetic testing requests should be sent to Carelon per program requirements.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider rapid whole genome sequencing, with trio testing when possible (see Policy Guidelines) for the evaluation of critically ill infants in neonatal or pediatric intensive care with a suspected genetic disorder of unknown etiology to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility will be met for rapid whole genome sequencing, with trio testing when possible (see Policy Guidelines) for the evaluation of critically ill infants in neonatal or pediatric intensive care with a suspected genetic disorder of unknown etiology when **ALL** of the following criteria are met:

- Infant is one year of age or younger with a complex illness of unknown etiology and suspected of having a rare genetic condition that is not diagnosable by a standard clinical work-up; **AND**
- Timely identification of a molecular diagnosis is necessary to guide clinical decision-making and results may guide treatment or management of the infant's condition; **AND**
- At least **ONE** of the following criteria is met:
    - Multiple congenital anomalies (see Policy Guidelines);

  - Abnormal laboratory tests or clinical features suggest a genetic disease or complex metabolic phenotype (see Policy Guidelines);
  - An abnormal response to standard therapy for a major underlying condition; **AND**
- None of the following criteria apply regarding the reason for admission to intensive care:
  - An infection with normal response to therapy;
  - Isolated prematurity;
  - Isolated unconjugated hyperbilirubinemia;
  - Hypoxic Ischemic Encephalopathy;
  - Confirmed genetic diagnosis explains illness;
  - Isolated Transient Neonatal Tachypnea; or
  - Nonviable neonates.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers rapid whole genome sequencing (with or without trio testing) that does not meet patient selection criteria for the evaluation of critically ill infants in neonatal or pediatric intensive care with a suspected genetic disorder of unknown etiology to be **investigational.****

Policy Guidelines

The policy statements are intended to address the use of whole genome sequencing (WGS) for the diagnosis of genetic disorders in critically ill infants in neonatal or pediatric intensive care with a suspected genetic disorder.

This policy does not address the use of whole exome sequencing, and whole genome sequencing in other clinical situations including but not limited to use for preimplantation genetic diagnosis or screening, prenatal (fetal) testing, or testing of cancer cells. This is outside the scope of this policy and should be sent to Carelon.

Rapid Sequencing
In the NSIGHT1 trial (Petrikin, 2018) rapid WGS (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 to 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 40-fold.

For rapid WGS, the individual should be critically ill and in the neonatal or pediatric intensive care units (NICU, 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.
- 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
Brief Resolved Unexplained Event 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 individual 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

Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview

Whole Genome Sequencing

Whole genome sequencing (WGS) uses NGS techniques to sequence both coding and noncoding regions of the genome. Whole genome sequencing has been proposed for use in patients presenting with disorders and anomalies not explained by a standard clinical workup. Potential candidates for WGS include patients who present with a broad spectrum of suspected genetic conditions.

Given the variety of disorders and management approaches, there are a variety of potential health outcomes from a definitive diagnosis. In general, the outcomes of a molecular genetic diagnosis include (1) impacting the search for a diagnosis, (2) informing follow-up that can benefit a child by

reducing morbidity, and (3) affecting reproductive planning for parents and potentially the affected patient.

The standard diagnostic workup for patients with suspected Mendelian disorders may include combinations of radiographic, electrophysiologic, biochemical, biopsy, and targeted genetic evaluations. The search for a diagnosis may thus become a time-consuming and expensive process.

Whole Genome Sequencing Technology
WGS using NGS technology can facilitate obtaining a genetic diagnosis in patients efficiently. Whole genome sequencing has ability to detect large deletions or duplications in protein-coding regions but requires greater data analytics.

Technical aspects WGS are evolving, including the development of databases such as the National Institutes of Health's ClinVar database (http://www.ncbi.nlm.nih.gov/clinvar/) to catalog variants, uneven sequencing coverage, gaps in exon capture before sequencing, and difficulties with narrowing the large initial number of variants to manageable numbers without losing likely candidate disease-associated variants. The variability contributed by the different platforms and procedures used by different clinical laboratories offering exome sequencing as a clinical service is unknown.

In 2013, the American College of Medical Genetics and Genomics, Association for Molecular Pathology, and College of American Pathologists convened a workgroup to standardize terminology for describing sequence variants. In 2015, guidelines developed by this workgroup describe criteria for classifying pathogenic and benign sequence variants based on 5 categories of data: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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). 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.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Whole genome sequencing (WGS) sequences both coding and noncoding regions of the genome. WGS has been proposed for use in patients presenting with disorders and anomalies not explained by a standard clinical workup.

Summary of Evidence

For individuals who are critically ill infants with a suspected genetic disorder of unknown etiology following a standard workup who receive rapid WGS (rWGS) or rapid WES (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=.003). Changes in management due to test results were reported in 41% (p=.11) of rWGS versus 21% of 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. The diagnostic yield of rWGS and rWES was similar (19% vs. 20%, respectively), as was time to result (median, 11 vs. 11 days). The NICUSeq RCT compared rWGS (test results returned in 15 days) to a delayed reporting group (WGS with test results returned in 60 days) in 354 infants admitted to an intensive care unit with a suspected genetic disease. Diagnostic yield was higher in the rWGS group (31.0%; 95% CI, 25.5% to 38.7% vs. 15.0%; 95% CI, 10.2% to 21.3%). Additionally, significantly more infants in the rWGS group had a change in management compared with the delayed arm

(21.1% vs. 10.3%; p=.009; odds ratio, 2.3; 95% CI, 1.22 to 4.32). 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, 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. 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 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).

Table 1. Guidelines on Limb-Girdle Muscular Dystrophy

Recommendation	LOE
Diagnosis	
• 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).	B

Recommendation	LOE
• 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.	C
Management of cardiac complications	
• 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.	B
• 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.	B
• Clinicians should refer muscular dystrophy patients with palpitations, symptomatic or asymptomatic tachycardia or arrhythmias, or signs and symptoms of cardiac failure for cardiology evaluation.	B
• 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.	B
Management of pulmonary complications	
• 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.	B

Recommendation	LOE
• 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.	B
• It is not obligatory for clinicians to refer patients with LGMD2B and LGMD2L for pulmonary evaluation unless they are symptomatic.	C
• 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.	B

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

American College of Medical Genetics and Genomics
In 2021, the American College of Medical Genetics and Genomics (ACMG) published a clinical practice guideline for the use of whole genome sequencing (WGS) and made the following recommendation: "We strongly recommend and GS [genome sequencing] as a first-tier or second-tier test (guided by clinical judgment and often clinician-patient/family shared decision making after CMA [chromosomal microarray] or focused testing) for patients with one or more CAs [congenital anomalies] prior to one year of age or for patients with DD/ID [developmental delay/intellectual disability] with onset prior to 18 years of age." The recommendation was informed by a systematic evidence review and a health technology assessment conducted by Ontario Health.

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.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02699190	LeukoSEQ: Whole Genome Sequencing as a First-Line Diagnostic Tool for Leukodystrophies	450	Jul 2023
NCT03525431	Genomic Sequencing to Aid Diagnosis in Pediatric and Prenatal Practice: Examining Clinical Utility, Ethical Implications, Payer Coverage, and Data Integration in a Diverse Population	800	May 2022 (Results submitted, quality control review not concluded)
NCT03548779	North Carolina Genomic Evaluation by Next-generation Exome Sequencing, 2	806	May 2023
NCT04154891	Genome Sequencing Strategies for Genetics Diagnosis of Patients With Intellectual Disability (DEFIDIAG)	3825	May 2024
NCT03632239	The Genomic Ascertainment Cohort (TGAC)	1000	Dec 2028
NCT03385876	Rapid Whole Genome Sequencing (rWGS): Rapid Genomic Sequencing for Acutely Ill Patients and the Collection, Storage, Analysis, and Distribution of Biological Samples, Genomic and Clinical Data	100,000	Dec 2050

NCT04760522	Genome-based Management of Patients in Precision Medicine (Ge-Med) Towards a Genomic Health Program	12,000	Jul 2027
NCT04315727	Identification of the Genetic Causes of Rare Diseases With Negative Exome Findings	100	Dec 2024
NCT04586075	UW Undiagnosed Genetic Diseases Program	500	Oct 2025
Unpublished			
NCT03829176	Investigating the Feasibility and Implementation of Whole Genome Sequencing in Patients With Suspected Genetic Disorder	200	Oct 2020
NCT03954652	Whole Genome Trio Sequencing as a Standard Routine Test in Patients With Rare Diseases - "GENOME FIRST APPROACH"	1350	Oct 2022

NCT: national clinical trial.

References

1. 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
2. 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
3. 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
4. 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

5. 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
6. 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
7. 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
8. 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
9. 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
10. 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
11. 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
12. 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
13. 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
14. 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
15. 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
16. 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
17. 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
18. 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
19. 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

20. 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
21. 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
22. 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
23. 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
24. 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
25. 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
26. 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
27. Dai P, Honda A, Ewans L, et al. Recommendations for next generation sequencing data reanalysis of unsolved cases with suspected Mendelian disorders: A systematic review and meta-analysis. Genet Med. Aug 2022; 24(8): 1618-1629. PMID 35550369
28. 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
29. 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
30. 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: 15012-. PMID 28567303
31. 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

32. 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
33. 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
34. 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
35. 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
36. 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
37. 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
38. 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
39. 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
40. 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
41. 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
42. 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
43. van Diemen CC, Kerstjens-Frederikse WS, Bergman KA, et al. Rapid Targeted Genomics in Critically Ill Newborns. Pediatrics. Oct 2017; 140(4). PMID 28939701

44. 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
45. 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
46. Dimmock DP, Clark MM, Gaughran M, et al. An RCT of Rapid Genomic Sequencing among Seriously Ill Infants Results in High Clinical Utility, Changes in Management, and Low Perceived Harm. Am J Hum Genet. Nov 05 2020; 107(5): 942-952. PMID 33157007
47. Krantz ID, Medne L, Weatherly JM, et al. Effect of Whole-Genome Sequencing on the Clinical Management of Acutely Ill Infants With Suspected Genetic Disease: A Randomized Clinical Trial. JAMA Pediatr. Dec 01 2021; 175(12): 1218-1226. PMID 34570182
48. 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

Original Effective Date: 11/20/2013
Current Effective Date: 07/01/2024

11/07/2013	Medical Policy Committee review
11/20/2013	Medical Policy Implementation Committee approval. New policy.
12/04/2014	Medical Policy Committee review
12/17/2014	Medical Policy Implementation Committee approval. Title changed from "Whole Exome Sequencing" to "Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders." The policy investigational section was revised to clarify that the intent of the policy is limited to the diagnosis of genetic disorders.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015	Medical Policy Committee review
12/16/2015	Medical Policy Implementation Committee approval. No change to coverage eligibility.

12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Added eligibility statement for WES with criteria and INV statement for WES and WGS in screening for genetic disorders.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
08/01/2017	Coding update
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/17/2019	Coding update
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/11/2020	Coding update
09/22/2020	Coding update
12/03/2020	Medical Policy Committee review
12/09/2020	Medical Policy Implementation Committee approval. Additions made to the first eligible for coverage statement to include whole standard exome 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. Reference made to Policy Guidelines. First criteria bullet for this coverage statement revised to read as follows: • 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.
09/30/2021	Coding update
12/02/2021	Medical Policy Committee review
12/08/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/20/2021	Coding update
02/04/2022	Coding update
03/25/2022	Coding update
09/01/2022	Medical Policy Committee review

09/14/2022 Medical Policy Implementation Committee approval. Added "rapid whole exome sequencing or rapid whole genome sequencing, with trio testing when possible for the evaluation of critically ill infants in neonatal or pediatric intensive care with a suspected genetic disorder of unknown etiology" may be eligible for coverage with criteria. Added two additional bullets to the criteria. Added "Payment for services provided during approved inpatient stay is all inclusive." to the end of the Policy Guidelines section.
09/20/2022 Coding Update
05/04/2023 Medical Policy Committee review
05/10/2023 Medical Policy Implementation Committee approval. Replaced "patient" with "individual" in the Patient Selection Criteria. Added an investigational statement for repeat whole exome sequencing (WES) and repeat whole genome sequencing (WGS) for the diagnosis of genetic disorders, including re-analysis of previous test results.
12/14/2023 Coding update
06/06/2024 Medical Policy Committee review
06/12/2024 Medical Policy Implementation Committee approval. Title changed from "Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders" to "Whole Genome Sequencing for Diagnosis of Genetic Disorders". Removed everything except Whole Genome Sequencing for Diagnosis of Genetic Disorders. All genetic testing is being moved to Carelon as of 07/01/2024. This policy will only be utilized for rapid whole genome sequencing, with trio testing, when possible, for the evaluation of critically ill infants in neonatal or pediatric intensive care with a suspected genetic disorder of unknown etiology.

Next Scheduled Review Date: 06/2025

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0094U, 0425U, 0426U
HCPCS	No codes
ICD-10 Diagnosis	All related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or

diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

Whole Genome Sequencing for Diagnosis of Genetic Disorders

Policy # 00389
Original Effective Date: 11/20/2013
Current Effective Date: 07/01/2024

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.