



Louisiana

Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Policy # 00389

Original Effective Date: 11/20/2013

Current Effective Date: 01/11/2021

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: Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies is addressed separately in medical policy 00536.

Note: Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies is addressed separately in medical policy 00378.

Note: Genetic Testing for Facioscapulohumeral Muscular Dystrophy is addressed separately in medical policy 00392.

Note: Genetic Testing for Epilepsy is addressed separately in medical policy 00401.

Note: Genetic Testing for Limb-Girdle Muscular Dystrophies is addressed separately in medical policy 00489.

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 standard whole exome sequencing (WES), with trio testing when possible (see Policy Guidelines), for the evaluation of unexplained congenital or neurodevelopmental disorder in children to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility will be met for standard whole exome sequencing (WES), with trio testing when possible (see Policy Guidelines), for the evaluation of unexplained congenital or neurodevelopmental disorder in children when ALL of the following criteria are met:

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- 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; AND
- There is potential for a change in management and clinical outcome for the individual being tested; AND
- A genetic etiology is considered the most likely explanation for the phenotype despite previous genetic testing (e.g., 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 (e.g., muscle biopsy).

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 whole exome sequencing (WES) for the diagnosis of genetic disorders in all other situations to be **investigational**.*

Based on review of available data, the Company considers whole genome sequencing (WGS) for the diagnosis of genetic disorders in all situations to be **investigational**.*

Based on review of available data, the Company considers whole exome sequencing (WES) and whole genome sequencing (WGS) for screening for genetic disorders to be **investigational**.*

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.

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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 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 not limited to any of the following:

- Significant hypotonia; or
- Persistent seizures.

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- 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

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.

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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		

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	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives
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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.

Standard Whole Exome Sequencing or Whole Genome Sequencing

Standard WES or WGS turn-around time is usually 1 to 3 months.

Rapid Whole Exome Sequencing or Whole Genome Sequencing

Rapid means an average turnaround time of less than 14 days, but usually less than 7 days. Rapid results should be called to the clinician immediately if changes in management are likely.

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UltraRapid whole genome sequencing has an average turnaround time of 48-72 hours. It has the same indications as for rapid WGS. It is usually reserved for those infants in the first few days of life who are felt by their attending physician to be at immediate risk of death or long term disability, such as intractable seizures.

Note: Rapid WGS analysis has the ability to detect most Copy Number Variants (CNVs).

Background/Overview

Whole Exome Sequencing and Whole Genome Sequencing

Whole exome sequencing (WES) is targeted next-generation sequencing (NGS) of the subset of the human genome that contains functionally important sequences of protein-coding DNA, while whole genome sequencing (WGS) uses NGS techniques to sequence both coding and noncoding regions of the genome. WES and WGS have been proposed for use in patients presenting with disorders and anomalies not explained by standard clinical workup. Potential candidates for WES and 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 Exome Sequencing and Whole Genome Sequencing Technology

WES or WGS using NGS technology can facilitate obtaining a genetic diagnosis in patients efficiently. WES is limited to most of the protein-coding sequence of an individual ($\gg 85\%$), is composed of about 20000 genes and 180000 exons (protein-coding segments of a gene), and constitutes approximately 1% of the genome. It is believed that the exome contains about 85% of heritable disease-causing variants. WES has the advantage of speed and efficiency relative to Sanger sequencing of multiple genes. WES shares some limitations with Sanger sequencing. For example,

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it will not identify the following: intronic sequences or gene regulatory regions; chromosomal changes; large deletions; duplications; or rearrangements within genes, nucleotide repeats, or epigenetic changes. WGS uses techniques similar to WES but includes noncoding regions. WGS has a greater ability to detect large deletions or duplications in protein-coding regions compared with WES but requires greater data analytics.

Technical aspects of WES and 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 mutations. 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). WES 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.

Rationale/Source

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. WES and WGS have been proposed for use in patients presenting with disorders and

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anomalies not explained by standard clinical workup. Potential candidates for WES and WGS include patients who present with a broad spectrum of suspected genetic conditions.

For individuals who are children who are not critically ill with multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following standard workup who receive 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 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 a meaningful 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 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 the effects of the technology on health outcomes.

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For individuals who are children who are not critically ill with multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following 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 development delays of unknown etiology following 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. WGS may result in 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 the effects of the technology on health outcomes.

For individuals who are children with a suspected genetic disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following standard workup who receive 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. WGS 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 the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

American College of Medical Genetics and Genomics

In 2012, the American College of Medical Genetics and Genomics (ACMG) has 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:

- a. "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.

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- b. 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.
- c. A patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.
- d. 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—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."

In 2016, ACMG updated its recommendations on reporting incidental findings in WGS and WES testing. 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.

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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 (see Table 1).

Table 1. Guidelines on Limb-Girdle Muscular Dystrophy

Recommendation	LOE
<i>Diagnosis</i>	
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<i>Management of cardiac complications</i>	
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> If ECG or structural cardiac evaluation (eg, echocardiography) has abnormal results, or if the patient has episodes of syncope, near-syncope, or palpitations, 	B

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Recommendation	LOE
clinicians should order rhythm evaluation (eg, Holter monitor or event monitor) to guide appropriate management.	
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<i>Management of pulmonary complications</i>	
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> It is not obligatory for clinicians to refer patients with LGMD2B and LGMD2L for pulmonary evaluation unless they are symptomatic. 	C

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Recommendation	LOE
<ul style="list-style-type: none"> 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.

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 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
<i>Ongoing</i>			
NCT02826694	North Carolina Newborn Exome Sequencing for Universal Screening	400	Jun 2019(ongoing)
NCT03211039	Prenatal Precision Medicine (NSIGHT2): A Randomized, Blinded, Prospective Study of the Clinical Utility of Rapid Genomic Sequencing for Infants in the Acute-care Setting	1000	Aug 2019

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NCT03290469	NICUSeq: A Prospective Trial to Evaluate the Clinical Utility of Human Whole Genome Sequencing (WGS) Compared to Standard of Care in Acute Care Neonates and Infants	355	Jul 2019
NCT02699190	LeukoSEQ: Whole Genome Sequencing as a First-Line Diagnostic Tool for Leukodystrophies	450	Aug 2020
NCT03829176	Investigating the Feasibility and Implementation of Whole Genome Sequencing in Patients With Suspected Genetic Disorder	200	Jun 2020
NCT02422511	Genomic Sequencing for Childhood Risk and Newborn Illness (The BabySeq Project)	1440	Apr 2020
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 2021
NCT03548779	North Carolina Genomic Evaluation by Next-generation Exome Sequencing, 2	1700	May 2021
NCT03918707	Utility of Rapid Whole Genome Sequencing in the NICU: A Pilot Study	115	Jan 2022
NCT01736566	The MedSeq Project Pilot Study: Integrating Whole Genome Sequencing Into the Practice of Clinical Medicine	213	Apr 2022
NCT04170985	NeuroSeq: A Prospective Trial to Evaluate the Diagnostic Yield of Human Whole Genome Sequencing (WGS) Compared to Standard of Care in Adults With Suspected Genetic Neurological Disorders	100	Jun 2022

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NCT04154891	Genome Sequencing Strategies for Genetics Diagnosis of Patients With Intellectual Disability (DEFIDIAG)	3825	Nov 2023
NCT03632239	The Genomic Ascertainment Cohort (TGAC)	1000	Dec 2028
NCT00410241	ClinSeq: A Large-Scale Medical Sequencing Clinical Research Pilot Study	2650	Not reported
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	100000	Dec 2050
<i>Unpublished</i>			
NCT02380729	Mutation Exploration in Non-acquired, Genetic Disorders and Its Impact on Health Economy and Life Quality	200	Dec 2017 (completed)

NCT: national clinical trial.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, “Whole Exome and Whole Genome Sequencing for Diagnosis for Genetic Disorders”, 2.04.102, April 2020.
2. 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):138ra178. PMID 22700954
3. 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):405-424. PMID 25741868
4. 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.

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5. 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.*, 2018 May 16;21(1). PMID 29760485
6. Vissers L, 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
7. 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 Feb 2;13(2). PMID 29389947
8. 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.*, 2018 Mar 30;20(12). PMID 29595814
9. Powis Z, Farwell Hagman KD, Speare V, et al. Exome sequencing in neonates: diagnostic rates, characteristics, and time to diagnosis. *Genet. Med.*, 2018 Mar 23;20(11). PMID 29565416
10. 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.* Jan 11 2018. PMID 29323667
11. 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 4 2015;385(9975):1305-1314. PMID 25529582
12. 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
13. 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
14. Evers C, Stauffer 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
15. Nolan D, Carlson M. Whole exome sequencing in pediatric neurology patients: clinical implications and estimated cost analysis. *J Child Neurol.* Jun 2016;31(7):887-894. PMID 26863999
16. Allen NM, Conroy J, Shahwan A, et al. Unexplained early onset epileptic encephalopathy: Exome screening and phenotype expansion. *Epilepsia.* Jan 2016;57(1):e12-17. PMID 26648591

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Current Effective Date: 01/11/2021

17. Stark Z, Tan TY, Chong B, et al. A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders. *Genet Med*. Nov 2016;18(11):1090-1096. PMID 26938784
18. Tarailo-Graovac M, Shyr C, Ross CJ, et al. Exome sequencing and the management of neurometabolic disorders. *N Engl J Med*. Jun 9 2016;374(23):2246-2255. PMID 27276562
19. 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):578-586. PMID 25356970
20. Yang Y, Muzny DM, Xia F, et al. Molecular findings among patients referred for clinical whole-exome sequencing. *JAMA*. Nov 12 2014;312(18):1870-1879. PMID 25326635
21. Lee H, Deignan JL, Dorrani N, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. *JAMA*. Nov 12 2014;312(18):1880-1887. PMID 25326637
22. Iglesias A, Anyane-Yeboa K, Wynn J, et al. The usefulness of whole-exome sequencing in routine clinical practice. *Genet Med*. Dec 2014;16(12):922-931. PMID 24901346
23. 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 3 2014;6(265):265ra168. PMID 25473036
24. Srivastava S, Cohen JS, Vernon H, et al. Clinical whole exome sequencing in child neurology practice. *Ann Neurol*. Oct 2014;76(4):473-483. PMID 25131622
25. 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):1502-1511. PMID 24088041
26. 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
27. 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.e32. PMID 28330790
28. 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
29. 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
30. Posey JE, Rosenfeld JA, James RA, et al. Molecular diagnostic experience of whole-exome sequencing in adult patients. *Genet Med*. Jul 2016;18(7):678-685. PMID 26633545

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31. 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):1424-1432. PMID 26436962
32. 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.* Aug 2015;3:67. PMID 26284228
33. Wortmann SB, Koolen DA, Smeitink JA, et al. Whole exome sequencing of suspected mitochondrial patients in clinical practice. *J Inher Metab Dis.* May 2015;38(3):437-443. PMID 25735936
34. 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):1721-1726. PMID 24123792
35. 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
36. 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
37. 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
38. Hiatt SM, Amaral MD, Bowling KM, et al. Systematic reanalysis of genomic data improves quality of variant interpretation. *Clin. Genet.* 2018 Jul;94(1). PMID 29652076
39. 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
40. Gilissen C, Hehir-Kwa JY, Thung DT, et al. Genome sequencing identifies major causes of severe intellectual disability. *Nature.* Jul 17 2014;511(7509):344-347. PMID 24896178
41. Thiffault I, Farrow E, Zellmer L, et al. Clinical genome sequencing in an unbiased pediatric cohort. *Genet. Med.*, 2018 Jul 17;21(2). PMID 30008475
42. 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

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Current Effective Date: 01/11/2021

43. 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
44. 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):1143-1150. PMID 26872967
45. 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
46. Yuen RK, Thiruvahindrapuram B, Merico D, et al. Whole-genome sequencing of quartet families with autism spectrum disorder. *Nat Med.* Feb 2015;21(2):185-191. PMID 25621899
47. 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.* 2019 Nov;20(11). PMID 31261230
48. 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.* 2019 Aug;178(8). PMID 31172278
49. 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.* 2019 Nov. PMID 31780822
50. Stark Z, Lunke S, Brett GR, et al. Meeting the challenges of implementing rapid genomic testing in acute pediatric care. *Genet Med.* Mar 15 2018. PMID 29543227
51. 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 4 2017;171(12):e173438. PMID 28973083
52. French CE, Delon I, Dolling H, et al. Whole genome sequencing reveals that genetic conditions are frequent in intensively ill children. *Intensive Care Med.* 2019 Mar 9;45(5). PMID 30847515
53. Sanford EF, Clark MM, Farnaes L, et al. Rapid Whole Genome Sequencing Has Clinical Utility in Children in the PICU. *Pediatr Crit Care Med.* 2019 Jun 28. PMID 31246743
54. 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
55. 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

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56. 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
57. van Diemen CC, Kerstjens-Frederikse WS, Bergman KA, et al. Rapid Targeted Genomics in Critically Ill Newborns. *Pediatrics.* Oct 2017;140(4). PMID 28939701
58. 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):377-387. PMID 25937001
59. 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.* 2019 Oct;105(4). PMID 31564432
60. 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
61. ACMG Board of Directors. Points to consider in the clinical application of genomic sequencing. *Genet Med.* Aug 2012;14(8):759-761. PMID 22863877
62. 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):347-355. PMID 24651602
63. 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. *Feb 2017;19(2):249-255.* PMID 27854360
64. 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):1453-1463. PMID 25313375

Policy History

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11/07/2013 Medical Policy Committee review

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- 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:

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- 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.

Next Scheduled Review Date: 12/2021

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 2019 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.

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

Code Type	Code
CPT	0012U, 0094U, 81415, 81416, 81417, 81425, 81426, 81427, 81479 Add codes eff 10/1/2020: 0212U, 0214U, 0215U

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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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

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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.

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