Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Policy #  00389
Original Effective Date:  11/20/2013
Current Effective Date:  08/01/2023

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.**
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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:

- Documentation that the individual 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).

Based on review of available data, the Company may consider rapid whole exome sequencing or 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 exome sequencing or 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);
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- 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 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 repeat whole exome sequencing (WES) and repeat whole genome sequencing (WGS) for the diagnosis of genetic disorders, including re-analysis of previous test results to be investigational.*

Based on review of available data, the Company considers whole genome sequencing (WGS) for the diagnosis of genetic disorders in all other 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 sequencing (WES) and whole genome sequencing (WGS) for the diagnosis of genetic disorders in individuals with suspected genetic disorders and for population-based screening.
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This policy does not address the use of whole exome and whole genome sequencing for preimplantation genetic diagnosis or screening, prenatal (fetal) testing, or testing of cancer cells.

Rapid Sequencing
In the NSIGHT1 trial (Petrikin, 2018) rapid 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 WES or 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

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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)
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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

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Variant</th>
<th>Change in the DNA sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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 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.
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of the genome. Whole exome sequencing and WGS have been proposed for use in patients presenting with disorders and anomalies not explained by a standard clinical workup. Potential candidates for WES and WGS include patients who present with a broad spectrum of suspected genetic conditions.

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

Whole exome sequencing or WGS using NGS technology can facilitate obtaining a genetic diagnosis in patients efficiently. Whole exome sequencing is limited to most of the protein-coding sequence of an individual (>85%), is composed of about 20,000 genes and 180,000 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. Whole exome sequencing has the advantage of speed and efficiency relative to Sanger sequencing of multiple genes. Whole exome sequencing shares some limitations with Sanger sequencing. For example, 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. Whole genome sequencing uses techniques similar to WES but includes noncoding regions. Whole genome sequencing 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 disease-associated variants. The variability contributed by the different
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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). Whole exome sequencing or WGS tests as a clinical service are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

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

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

For individuals who have previously received WES who receive repeat WES, including re-analysis of previous test results, the evidence includes nonrandomized studies and a systematic review. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making,
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and resource utilization. There is no direct evidence of clinical utility. In a meta-analysis of nonrandomized studies, re-analysis of WES data resulted in an 11% increase in diagnostic yield (95% confidence interval (CI), 8% to 14%) in individuals who were previously undiagnosed via WES. Three nonrandomized studies published after the meta-analysis had findings consistent with the meta-analysis. Conclusions were limited by heterogeneity across individual studies and a lack of detailed reporting on reasons for new diagnoses, changes in management based on new diagnoses, and the frequency of the identification of variants of uncertain significance (VUS). Therefore, a chain of evidence for clinical utility cannot be established. Additionally, the optimal timing of re-analysis has not been established, and there are no clear guidelines on what factors should prompt the decision to repeat testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are children who are not critically ill with multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup or WES who receive whole genome sequencing (WGS) with trio testing when possible, the evidence includes nonrandomized studies and a systematic review. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. In studies of children with congenital anomalies and developmental delays of unknown etiology following standard clinical workup, the yield of WGS has ranged between 20% and 40%. A majority of studies described methods for interpretation of WGS indicating that only pathogenic or likely pathogenic variants were included in the diagnostic yield and that VUS were frequently not reported. In a systematic review, the pooled (9 studies, N=648) diagnostic yield of WGS was 40% (95% CI, 32% to 49%). Although the diagnostic yield of WGS is at least as high as WES in individuals without a diagnosis following standard clinical workup, it is unclear if the additional yield results in actionable clinical management changes that improve health outcomes. Further, while reporting practices of VUS found on exome and genome sequencing vary across laboratories, WGS results in the identification of more VUS than WES. The clinical implications of this difference are uncertain as more VUS findings can be seen as potential for future VUS reclassification allowing a diagnosis. However, most VUS do not relate to the patient phenotype, the occurrence of medical mismanagement and patient stress based on misinterpretation of VUS is not well defined, and provider reluctance to interpret VUS information lessen the value of additional VUS identification by WGS. As such, higher yield and higher VUS from WGS currently have limited clinical utility. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.
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For individuals who are children with a suspected genetic disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup who receive WGS with trio testing when possible, the evidence includes case series. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. Whole genome sequencing has also been studied in other genetic conditions with yield ranging from 9% to 55%. Overall, a limited number of patients have been studied for any specific disorder, and clinical use of WGS as well as information regarding meaningful changes in management for these disorders is at an early stage. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are critically ill infants with a suspected genetic disorder of unknown etiology following a standard workup who receive rapid 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 or rWES, including avoidance of invasive procedures, medication changes to...
reduce morbidity, discontinuation of or additional testing, and initiation of palliative care or reproductive planning. A chain of evidence linking meaningful improvements in diagnostic yield and changes in management expected to improve health outcomes supports the clinical value of rWGS or rWES. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

**Supplemental Information**

**Practice Guidelines and Position Statements**

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

**American Academy of Neurology et al**

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

<table>
<thead>
<tr>
<th>Table 1. Guidelines on Limb-Girdle Muscular Dystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
</tr>
<tr>
<td>• 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).</td>
</tr>
<tr>
<td>• 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.</td>
</tr>
</tbody>
</table>
### Management of cardiac complications

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinicians should refer newly diagnosed patients with (1) limb-girdle muscular dystrophy (LGMD1A, 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.</td>
<td>B</td>
</tr>
<tr>
<td>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.</td>
<td>B</td>
</tr>
<tr>
<td>Clinicians should refer muscular dystrophy patients with palpitations, symptomatic or asymptomatic tachycardia or arrhythmias, or signs and symptoms of cardiac failure for cardiology evaluation.</td>
<td>B</td>
</tr>
<tr>
<td>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.</td>
<td>B</td>
</tr>
</tbody>
</table>

### Management of pulmonary complications

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>B</td>
</tr>
<tr>
<td>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.</td>
<td>B</td>
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<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• It is not obligatory for clinicians to refer patients with LGMD2B and LGMD2L for pulmonary evaluation unless they are symptomatic.</td>
<td>C</td>
</tr>
<tr>
<td>• 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.</td>
<td>B</td>
</tr>
</tbody>
</table>

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 exome sequencing (WES) and whole genome sequencing (WGS) and made the following recommendation: "We strongly recommend ES [exome sequencing] 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

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02699190</td>
<td>LeukoSEQ: Whole Genome Sequencing as a First-Line Diagnostic Tool for Leukodystrophies</td>
<td>450</td>
<td>Jul 2023</td>
</tr>
<tr>
<td>NCT03525431</td>
<td>Genomic Sequencing to Aid Diagnosis in Pediatric and Prenatal Practice: Examining Clinical Utility, Ethical Implications, Payer Coverage, and Data Integration in a Diverse Population</td>
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<td>North Carolina Genomic Evaluation by Next-generation Exome Sequencing, 2</td>
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<td>NCT04154891</td>
<td>Genome Sequencing Strategies for Genetics Diagnosis of Patients With Intellectual Disability (DEFIDIAG)</td>
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<td>The Genomic Ascertainment Cohort (TGAC)</td>
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<td>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</td>
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<td>Genome-based Management of Patients in Precision Medicine (Ge-Med) Towards a Genomic Health Program</td>
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<td>Identification of the Genetic Causes of Rare Diseases With Negative Exome Findings</td>
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Policy # 00389
Original Effective Date: 11/20/2013
Current Effective Date: 08/01/2023

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NCT: national clinical trial.

References
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Policy History
Original Effective Date:  11/20/2013
Current Effective Date:  08/01/2023
11/07/2013  Medical Policy Committee review
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
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...
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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
12/20/2021 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.

Next Scheduled Review Date:  05/2024
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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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*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.
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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.

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