

## Rapid Whole Genome Sequencing for Diagnosis of Genetic Disorders

**Policy # 00389**

Original Effective Date: 11/20/2013

Current Effective Date: 07/01/2026

*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.*

*Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.*

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

### When Services May Be Eligible for Coverage

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

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

Based on review of available data, the Company may consider rapid whole genome sequencing to be **eligible for coverage\*\*** when **ALL** of the following criteria are met:

- Request is for rapid whole genome sequencing with trio testing when possible (*see Notes for Trio Testing below<sup>1</sup>*); **AND**
- Request is for the evaluation of critically ill infants in neonatal or pediatric intensive care with a suspected genetic disorder of unknown etiology; **AND**
- 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; examples of specific malformations highly suggestive of a genetic etiology, include but are not limited to **ANY** of the following:
    - Choanal atresia; **OR**
    - Coloboma; **OR**
    - Hirschsprung disease; **OR**
    - Meconium ileus; **OR**
    - Any other malformation suggesting a genetic disease; **OR**

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- An abnormal laboratory test suggesting a genetic disease or complex metabolic phenotype; examples include but are not limited to **ANY** of the following:
  - Abnormal newborn screen; **OR**
  - Conjugated hyperbilirubinemia not due to total parental nutrition (TPN) cholestasis; **OR**
  - Hyperammonemia; **OR**
  - Lactic acidosis not due to poor perfusion; **OR**
  - Refractory or severe hypoglycemia; **OR**
  - Any other abnormal lab test suggesting a genetic disease; **OR**
- Clinical features suggesting a genetic disease; examples include but are not limited to **ANY** of the following:
  - Significant hypotonia; **OR**.
  - Persistent seizures; **OR**
  - Infant with high-risk stratification on evaluation for a Brief Resolved Unexplained Event (BRUE) (*see Notes for BRUE below*<sup>2</sup>) with **ANY** of the following features:
    - ❖ Recurrent events without respiratory infection; **OR**
    - ❖ Recurrent witnessed seizure like events; **OR**
    - ❖ Required cardiopulmonary resuscitation (CPR); **OR**
    - ❖ 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; **OR**
  - Significantly abnormal electrocardiogram (ECG), including but not limited to possible channelopathies, arrhythmias, cardiomyopathies, myocarditis, or structural heart disease; **OR**
  - Family history of:
    - ❖ Arrhythmia; **OR**
    - ❖ BRUE in sibling; **OR**
    - ❖ Developmental delay; **OR**
    - ❖ Inborn error of metabolism or genetic disease; **OR**
    - ❖ Long QT syndrome (LQTS); **OR**
    - ❖ Sudden unexplained death (including unexplained car accident or drowning) in first- or second-degree family members before age 35, and particularly as an infant; **OR**
- 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; **OR**
  - Isolated prematurity; **OR**
  - Isolated unconjugated hyperbilirubinemia; **OR**
  - Hypoxic Ischemic Encephalopathy; **OR**
  - Confirmed genetic diagnosis explains illness; **OR**
  - Isolated Transient Neonatal Tachypnea; **OR**
  - Nonviable neonates.

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## <sup>1</sup> **Notes for 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.*

## <sup>2</sup> **Notes for Brief Resolved Unexplained Event (BRUE):**

*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; **OR***
- *Altered level of responsiveness; **OR***
- *Cyanosis or pallor; **OR***
- *Marked change in tone (hyper- or hypotonia).*

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

## **When Services Are Considered Not Medically Necessary**

The use of rapid whole genome sequencing (with or without trio testing) for the evaluation of critically ill infants in neonatal or pediatric intensive care with a suspected genetic disorder of unknown etiology when patient selection criteria are not met is considered to be **not medically necessary**.\*\*

## **Policy Guidelines**

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

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

## **Rapid Sequencing**

In the NSIGHT1 trial (Petrikin, 2018) rapid WGS (rWGS) provided time to provisional diagnosis by 10 days with time to final report of approximately 17 days although the trial required confirmatory testing of WGS results which lengthened the time to rWGS diagnosis by 7 to 10 days. The WGS

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was performed in 'rapid run' mode with a minimum depth of 90 Gb per genome and average depth of coverage of 40-fold.

For rapid WGS, the individual should be critically ill and in the neonatal or pediatric intensive care units (NICU, PICU) when the test is ordered but may be discharged before results are delivered.

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

### Genetics Nomenclature Update

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

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

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

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

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

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

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|        |                                   |
|--------|-----------------------------------|
| Benign | Benign change in the DNA sequence |
|--------|-----------------------------------|

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

## Genetic Counseling

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

## Background/Overview

### Whole Genome Sequencing

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

Given the variety of disorders and management approaches, there are a variety of potential health outcomes from a definitive diagnosis. In general, the outcomes of a molecular genetic diagnosis include (1) impacting the search for a diagnosis, (2) informing follow-up that can benefit a child by reducing morbidity, and (3) affecting reproductive planning for parents and potentially the affected patient.

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

### Whole Genome Sequencing Technology

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

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

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procedures used by different clinical laboratories offering exome sequencing as a clinical service is unknown.

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

## **FDA or Other Governmental Regulatory Approval**

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

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

## **Rationale/Source**

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

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

### **Summary of Evidence**

For individuals who are critically ill infants with a suspected genetic disorder of unknown etiology following a standard workup who receive rapid WGS (rWGS) or rapid WES (rWES) with trio testing when possible, the evidence includes randomized controlled trials (RCTs) and case series. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. One RCT comparing rWGS with standard genetic tests to diagnose suspected genetic disorders in critically ill infants was terminated early due to loss of equipoise. The rate of genetic diagnosis within 28 days of enrollment was higher for rWGS versus standard tests (31% vs. 3%;  $p=.003$ ). Changes in management due to test results were reported in 41% ( $p=.11$ ) of rWGS versus 21% of control patients; however, 73% of control subjects received broad genetic tests (eg, next-generation sequencing panel testing, WES, or WGS) as part of standard testing. A second RCT compared rWGS to rWES in seriously ill infants with diseases of unknown etiology from the neonatal intensive care unit, pediatric intensive care unit, and cardiovascular intensive care unit. The diagnostic yield of rWGS and rWES was similar (19% vs. 20%, respectively), as was time to result

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(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%;  $p=0.009$ ; odds ratio, 2.3; 95% CI, 1.22 to 4.32). Several retrospective and prospective studies including more than 800 critically ill infants and children in total have reported on diagnostic yield for rWGS or rWES. These studies included phenotypically diverse but critically ill infants and had yields of between 30% and 60% for pathogenic or likely pathogenic variants. Studies have also reported associated changes in patient management for patients receiving a diagnosis from rWGS, including avoidance of invasive procedures, medication changes to reduce morbidity, discontinuation of or additional testing, and initiation of palliative care or reproductive planning. A chain of evidence linking meaningful improvements in diagnostic yield and changes in management expected to improve health outcomes supports the clinical value of rWGS. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

## **Supplemental Information**

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

### **American Academy of Neurology et al**

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

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

| <b>Recommendation</b>                                                                                                                                                                                                                                                                                                                                                                              | <b>LOE</b> |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| <i>Diagnosis</i>                                                                                                                                                                                                                                                                                                                                                                                   |            |
| <ul style="list-style-type: none"> <li>For patients with suspected muscular dystrophy, clinicians should use a clinical approach to guide genetic diagnosis based on the clinical phenotype, including the pattern of muscle involvement, inheritance pattern, age at onset, and associated manifestations (eg, early contractures, cardiac or respiratory involvement).</li> </ul>                | B          |
| <ul style="list-style-type: none"> <li>In patients with suspected muscular dystrophy in whom initial clinically directed genetic testing does not provide a diagnosis, clinicians may obtain genetic consultation or perform parallel sequencing of targeted exomes, whole-exome sequencing, whole-genome screening, or next-generation sequencing to identify the genetic abnormality.</li> </ul> | C          |

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| Recommendation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | LOE |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| <i>Management of cardiac complications</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |     |
| <ul style="list-style-type: none"> <li>Clinicians should refer newly diagnosed patients with (1) limb-girdle muscular dystrophy (LGMD)1A, LGMD1B, LGMD1D, LGMD1E, LGMD2C–K, LGMD2M–P, ... or (2) muscular dystrophy without a specific genetic diagnosis for cardiology evaluation, including electrocardiogram (ECG) and structural evaluation (echocardiography or cardiac magnetic resonance imaging [MRI]), even if they are asymptomatic from a cardiac standpoint, to guide appropriate management.</li> </ul> | B   |
| <ul style="list-style-type: none"> <li>If ECG or structural cardiac evaluation (eg, echocardiography) has abnormal results, or if the patient has episodes of syncope, near-syncope, or palpitations, clinicians should order rhythm evaluation (eg, Holter monitor or event monitor) to guide appropriate management.</li> </ul>                                                                                                                                                                                    | B   |
| <ul style="list-style-type: none"> <li>Clinicians should refer muscular dystrophy patients with palpitations, symptomatic or asymptomatic tachycardia or arrhythmias, or signs and symptoms of cardiac failure for cardiology evaluation.</li> </ul>                                                                                                                                                                                                                                                                 | B   |
| <ul style="list-style-type: none"> <li>It is not obligatory for clinicians to refer patients with LGMD2A, LGMD2B, and LGMD2L for cardiac evaluation unless they develop overt cardiac signs or symptoms.</li> </ul>                                                                                                                                                                                                                                                                                                  | B   |
| <i>Management of pulmonary complications</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |     |
| <ul style="list-style-type: none"> <li>Clinicians should order pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright and, if normal, supine positions) or refer for pulmonary evaluation (to identify and treat respiratory insufficiency) in muscular dystrophy patients at the time of diagnosis, or if they develop pulmonary symptoms later in their course.</li> </ul>                                                                                                 | B   |
| <ul style="list-style-type: none"> <li>In patients with a known high risk of respiratory failure (eg, those with LGMD2I ...), clinicians should obtain periodic pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright position and, if normal, in the supine position) or evaluation by a pulmonologist to identify and treat respiratory insufficiency.</li> </ul>                                                                                                         | B   |
| <ul style="list-style-type: none"> <li>It is not obligatory for clinicians to refer patients with LGMD2B and LGMD2L for pulmonary evaluation unless they are symptomatic.</li> </ul>                                                                                                                                                                                                                                                                                                                                 | C   |
| <ul style="list-style-type: none"> <li>Clinicians should refer muscular dystrophy patients with excessive daytime somnolence, nonrestorative sleep (eg, frequent nocturnal arousals, morning headaches, excessive daytime fatigue), or respiratory insufficiency based on pulmonary function tests for pulmonary or sleep medicine consultation for consideration of noninvasive ventilation to improve quality of life.</li> </ul>                                                                                  | B   |

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

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### Rapid Sequencing

#### American College of Medical Genetics and Genomics

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

#### U.S. Preventive Services Task Force Recommendations

Not applicable.

#### Medicare National Coverage

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

#### Ongoing and Unpublished Clinical Trials

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

**Table 2. Summary of Key Trials**

| NCT No.        | Trial Name                                                                                                                                                                                          | Planned Enrollment | Completion Date                    |
|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|------------------------------------|
| <i>Ongoing</i> |                                                                                                                                                                                                     |                    |                                    |
| NCT06549218    | Shortening the Path to Rare Disease Diagnosis by Using Newborn Genetic Screening and Digital Technologies (SCREEN4CARE): Genetic Newborn Screening for Rare Diseases Within the Screen4Care Project | 20,000             | Dec 2025                           |
| NCT03385876    | Rapid Whole Genome Sequencing (rWGS): Rapid Genomic Sequencing for Acutely Ill Patients and the Collection, Storage, Analysis, and Distribution of Biological Samples, Genomic and Clinical Data    | 100,000            | Dec 2050 (enrolling by invitation) |
| NCT04760522    | Genome-based Management of Patients in Precision Medicine (Ge-Med) Towards a Genomic Health Program                                                                                                 | 12,000             | Jul 2027                           |
| NCT07102966    | MAGNET: Making Genomics Accessible For Newborns In Texas                                                                                                                                            | 410                | Jul 2029                           |

NCT: national clinical trial.

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

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|            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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: <ul style="list-style-type: none"><li>• 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.</li></ul> |
| 09/30/2021 | Coding update                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 12/02/2021 | Medical Policy Committee review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 12/08/2021 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 12/20/2021 | Coding update                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 02/04/2022 | Coding update                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 03/25/2022 | Coding update                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 09/01/2022 | Medical Policy Committee review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 09/14/2022 | Medical Policy Implementation Committee approval. Added “rapid whole exome sequencing or rapid whole genome sequencing, with trio testing when possible for the evaluation of critically ill infants in neonatal or pediatric intensive care with a suspected genetic disorder of unknown etiology” may be eligible for coverage with criteria. Added two additional bullets to the criteria. Added “Payment for services provided during approved inpatient stay is all inclusive.” to the end of the Policy Guidelines section.                                                                                                                                                                                                                                     |
| 09/20/2022 | Coding Update                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 05/04/2023 | Medical Policy Committee review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

## Rapid Whole Genome Sequencing for Diagnosis of Genetic Disorders

Policy # 00389

Original Effective Date: 11/20/2013

Current Effective Date: 07/01/2026

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|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 05/10/2023 | Medical Policy Implementation Committee approval. Replaced “patient” with “individual” in the Patient Selection Criteria. Added an investigational statement for repeat whole exome sequencing (WES) and repeat whole genome sequencing (WGS) for the diagnosis of genetic disorders, including re-analysis of previous test results.                                                                                                                                                                                                                                                                                       |
| 12/14/2023 | Coding update                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 06/06/2024 | Medical Policy Committee review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 06/12/2024 | Medical Policy Implementation Committee approval. Title changed from “Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders” to “Whole Genome Sequencing for Diagnosis of Genetic Disorders”. Removed everything except Whole Genome Sequencing for Diagnosis of Genetic Disorders. All genetic testing is being moved to Carelon as of 07/01/2024. This policy will only be utilized for rapid whole genome sequencing, with trio testing, when possible, for the evaluation of critically ill infants in neonatal or pediatric intensive care with a suspected genetic disorder of unknown etiology. |
| 06/05/2025 | Medical Policy Committee review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 06/11/2025 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 06/04/2026 | Medical Policy Committee review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 06/10/2026 | Medical Policy Implementation Committee review                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 08/20/2026 | Medical Quality Management Committee approval. Moved and reformatted some content from Policy Guidelines to the When Services May Be Eligible for Coverage section. Changed the investigational statement and section to not medically necessary. Title clarification renamed “Rapid Whole Genome Sequencing for Diagnosis of Genetic Disorders”                                                                                                                                                                                                                                                                            |

Next Scheduled Review Date: 06/2027

### **Coding**

*The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2025 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

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

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*contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.*

CPT is a registered trademark of the American Medical Association.

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

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

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

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

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

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

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

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

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

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**NOTICE:** If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan's authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan's pharmacy benefit.