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Medical Benefit		Effective Date: 06/01/21	Next Review Date: 03/23
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Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

RELATED PROTOCOLS

Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

Genetic Testing for Epilepsy

Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> Who are children with multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following standard workup 	Interventions of interest are: <ul style="list-style-type: none"> Whole exome sequencing with trio testing when possible 	Comparators of interest are: <ul style="list-style-type: none"> Standard clinical workup without whole exome sequencing 	Relevant outcomes include: <ul style="list-style-type: none"> Test validity Functional outcomes Changes in reproductive decision making Resource utilization
Individuals: <ul style="list-style-type: none"> Who are children with a suspected genetic disorder other than multiple congenital anomalies or a neurodevelopmental of unknown etiology following standard workup 	Interventions of interest are: <ul style="list-style-type: none"> Whole exome sequencing with trio testing when possible 	Comparators of interest are: <ul style="list-style-type: none"> Standard clinical workup without whole exome sequencing 	Relevant outcomes include: <ul style="list-style-type: none"> Test validity Functional outcomes Changes in reproductive decision making Resource utilization
Individuals: <ul style="list-style-type: none"> Who are children who are not critically ill with multiple congenital anomalies or a neurodevelopmental disorder of unknown etiology following standard workup 	Interventions of interest are: <ul style="list-style-type: none"> Whole exome sequencing with trio testing when possible 	Comparators of interest are: <ul style="list-style-type: none"> Standard clinical workup without whole exome sequencing Whole exome sequencing with trio testing when possible 	Relevant outcomes include: <ul style="list-style-type: none"> Test validity Functional outcomes Changes in reproductive decision making Resource utilization

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> Who are children with a suspected genetic disorder other than multiple congenital anomalies or a neurodevelopmental of unknown etiology following standard workup 	Interventions of interest are: <ul style="list-style-type: none"> Whole genome sequencing with trio testing when possible 	Comparators of interest are: <ul style="list-style-type: none"> Standard clinical workup without whole genome sequencing Whole exome sequencing with trio testing when possible 	Relevant outcomes include: <ul style="list-style-type: none"> Test validity Functional outcomes Changes in reproductive decision making Resource utilization
Individuals: <ul style="list-style-type: none"> Who are critically ill infants with a suspected genetic disorder of unknown etiology following standard workup 	Interventions of interest are: <ul style="list-style-type: none"> Rapid whole exome or genome sequencing with trio testing when possible 	Comparators of interest are: <ul style="list-style-type: none"> Standard clinical workup without exome or whole genome sequencing 	Relevant outcomes include: <ul style="list-style-type: none"> Test validity Functional outcomes Changes in reproductive decision making Resource utilization

DESCRIPTION

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

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 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 phe-

notype. Overall, a limited number of patients have been studied for any specific disorder, and clinical use of WES for these disorders is at an early stage with uncertainty about changes in patient management. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

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

POLICY

Standard whole exome sequencing (WES), with trio testing when possible (see Policy Guidelines), may be con-

sidered **medically necessary** for the evaluation of unexplained congenital or neurodevelopmental disorder in children when ALL of the following criteria are met:

1. Documentation that the patient has been evaluated by a clinician with expertise in clinical genetics, including at minimum a family history and phenotype description, and counseled about the potential risks of genetic testing.
2. There is potential for a change in management and clinical outcome for the individual being tested.
3. A genetic etiology is considered the most likely explanation for the phenotype despite previous genetic testing (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).

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

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

WES is considered **investigational** for the diagnosis of genetic disorders in all other situations.

Whole genome sequencing (WGS) is considered **investigational** for the diagnosis of genetic disorders.

WES and WGS are considered **investigational** for screening for genetic disorders.

POLICY GUIDELINES

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

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

RAPID SEQUENCING

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

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

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

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

- Choanal atresia
- Coloboma
- Hirschsprung disease
- Meconium ileus

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

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

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

- Significant hypotonia
- 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

BRUE

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

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

A BRUE is diagnosed only when there is no explanation for a qualifying event after conducting an appropriate history and physical examination.

Note: More information is available at: <https://pediatrics.aappublications.org/content/137/5/e20160590>

TRIO TESTING

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

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

GENETICS NOMENCLATURE UPDATE

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical protocol updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Genome Project, the HUMAN Genome Organization, 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 Variant	Disease-associated change in the DNA sequence Change in the DNA sequence

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

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

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

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

GENETIC COUNSELING

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

MEDICARE ADVANTAGE

Whole exome sequencing and whole genome sequencing are unlikely to impact therapeutic decision-making in the clinical management of the patient and are considered **not medically necessary**.

BACKGROUND

WHOLE EXOME SEQUENCING AND WHOLE GENOME SEQUENCING

Whole exome sequencing (WES) is targeted next-generation sequencing (NGS) of the subset of the human genome that contains functionally important sequences of protein-coding DNA, while whole genome sequencing (WGS) uses NGS techniques to sequence both coding and noncoding regions of the genome. 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.¹ 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 mutations. The variability contributed by the different platforms and procedures used by different clinical laboratories offering exome sequencing as a clinical service is unknown.

In 2013, the American College of Medical Genetics and Genomics, Association for Molecular Pathology, and College of American Pathologists convened a workgroup to standardize terminology for describing sequence variants. In 2015, guidelines developed by this workgroup describe criteria for classifying pathogenic and benign sequence variants based on 5 categories of data: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign.²

REGULATORY STATUS

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

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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67. National Government Services, Inc. (Primary Geographic Jurisdiction 06 & K - Illinois, Minnesota, Wisconsin, Connecticut, New York - Entire State, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont) Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000).
68. National Government Services, Inc. (Primary Geographic Jurisdiction 06 & K - Illinois, Minnesota, Wisconsin, Connecticut, New York - Entire State, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont) Local Coverage Article: Billing and Coding: Molecular Pathology Procedures (A56199), Revision Effective Date 01/01/2022.