BSC_CON_2.02	Genetic Testing: Exome and Genome Sequencing For The Diagnosis Of Genetic Disorders		
Original Policy Date:	June 1, 2022	**Effective Date:**	March 1, 2024
Section:	2.0 Medicine	**Page:**	Page 1 of 21

Example Test Table

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
Standard Exome Sequencing	Genomic Unity® Exome Plus Analysis - Proband (Variantyx Inc.)	0214U
	Genomic Unity® Exome Plus Analysis - Comparator (Variantyx Inc.)	0215U
	XomeDx (GeneDx)	81415, 81416, 81417
	Invitae Boosted Exome (Invitae)	
	ExomeNext (Ambry Genetics)	
	PGxome (PreventionGenetics)	
	Whole Exome Sequencing (PerkinElmer Genomics)	
	Exome (Quest Diagnostics)	
	Whole Exome Sequencing (LabCorp)	
Rapid Exome Sequencing	XomeDxXpress (GeneDx)	81415, 81416, 81417
	XExomeNext-Rapid (Ambry)	
	PGxome RAPID (PreventionGenetics)	
	STAT Whole Exome Sequencing (PerkinElmer Genomics)	
Standard Genome Sequencing	Genomic Unity® Whole Genome Analysis - Proband (Variantyx Inc.)	0212U
	Genomic Unity® Whole Genome Analysis - Comparator (Variantyx Inc.)	0213U
	GenomeSeqDx (GeneDx)	81425, 81426, 81427
	TruGenome Trio (Illumina)	
	Whole Genome Sequencing (PerkinElmer Genomics)	
	MNGenome (MNG Laboratories)	0094U
	MatePair Targeted Rearrangements, Congenital (Mayo Medical Laboratories)	0012U *(deleted code effective 10/01/2022)*
	CNGnome (PerkinElmer Genomics)	0209U
	Praxis Whole Genome Sequencing (Praxis Genomics LLC)	0265U

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
	Praxis Combined Whole Genome Sequencing and Optical Genome Mapping (Praxis Genomics LLC)	0267U
Rapid Genome Sequencing	Rapid Whole Genome Sequencing (Rady Children's Institute for Genomic Medicine)	0094U

Policy Statement

Standard Exome Sequencing

I. Standard exome sequencing (81415, 81416, 81417, 0214U, 0215U), with trio testing when possible, may be considered **medically necessary** when **all** of the following criteria are met:
   A. The member has unexplained epilepsy at any age
   B. The member has an unexplained congenital or neurodevelopmental disorder, AND
   C. The member has been evaluated by a clinician with expertise in clinical genetics, including but not limited to:
      1. Board-Certified or Board-Eligible Medical Geneticist
      2. Certified Genetic Counselor
      3. Advanced practice practitioner (e.g., Advanced practice registered nurse (APRN) or Physician's Assistant) in genetics; AND
   D. Documentation submitted includes **all** of the following:
      1. A complete family history of at least 3 generations when available (or notation why it is not)
      2. Complete and detailed description of the proband phenotype
      3. Any previous genetic testing results (e.g., chromosomal microarray/CMA, single gene or small panels)
      4. If no previous testing has been done, that the member's clinical presentation does not fit a well-described syndrome for which specific testing (e.g., single-gene testing, CMA) is available
      5. Any invasive testing that might be avoided by exome testing
      6. Why a genetic etiology is a likely explanation for the clinical and historical findings

II. **Standard genome sequencing** (81425, 81426, 81427, 0209U, 0212U, 0213U, 0265U, 0267U) is considered **investigational**.

III. **Repeat standard exome sequencing** (not reanalysis*) for the above indications may be considered **medically necessary** when **all** of the following criteria are met:
   A. The member has been re-evaluated by a Board-Certified or Board-Eligible Medical Geneticist, a Certified Genetic Counselor, an advanced practice practitioner (e.g., APRN or Physician's Assistant) in genetics, who is not employed by a commercial genetic testing laboratory that recommends repeat exome sequencing, AND
   B. There have been improvements in technology/chemistry (e.g., new methods for DNA capture and/or sequencing), bioinformatics advancements, or new information regarding the genetic etiology of a condition that could explain the patient's clinical features and would not have been able to be detected by the previous exome sequencing the patient underwent.

IV. Repeat standard exome sequencing (81415, 81416, 0214U, 0215U) is considered **investigational** for all other indications.

V. Repeat standard genome sequencing sequencing (81425, 81426, 81427, 0209U, 0212U, 0213U, 0265U, 0267U) is considered **investigational** for all indications including but not limited to those considered medically necessary for repeat exome testing.

VI. Standard exome and genome sequencing is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

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Rapid and ultra-rapid Exome or Genome Sequencing

VII. Rapid or ultra-rapid exome or genome sequencing (rES, urES, rGS or urGS), with trio testing when possible, may be considered **medically necessary** when **all** of the following are met:
- A. For the evaluation of hospitalized critically ill infants or children (NICU or PICU) less than 18 years of age with an illness of unknown etiology
- B. Documentation that supports **both** of the following:
  1. At least **one** of the following:
     - a. Multiple congenital anomalies affecting unrelated organ systems
     - b. Specific malformations highly suggestive of a genetic etiology, including but not limited to **one or more** of the following:
       - i. Choanal atresia
       - ii. Coloboma
       - iii. Hirschsprung disease
       - iv. Meconium ileus
     - c. An abnormal laboratory test suggests a genetic disease or complex metabolic phenotype, including but not limited to **one or more** of the following:
       - i. Abnormal newborn screen
       - ii. Conjugated hyperbilirubinemia not due to total parental nutrition (TPN) cholestasis
       - iii. Hyperammonemia
       - iv. Lactic acidosis not due to poor perfusion
       - v. Refractory or severe hypoglycemia
     - d. An abnormal response to standard therapy for a major underlying condition
     - e. Significant hypotonia
     - f. Persistent seizures
     - g. Infant with high risk stratification on evaluation for a Brief Resolved Unexplained Event (BRUE) with **one or more** of the following:
       - i. Recurrent events without respiratory infection
       - ii. Recurrent witnessed seizure like events
       - iii. Required Cardiopulmonary Resuscitation (CPR)
       - iv. 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
       - v. Significantly abnormal electrocardiogram (ECG), including but not limited to possible channelopathies, arrhythmias, cardiomyopathies, myocarditis or structural heart disease
       - vi. Family history of **one or more** of the following:
         - 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

2. **All** of the following have been excluded a reason for admission:
   a. An infection with normal response to therapy
   b. Confirmed genetic diagnosis explains illness
   c. Hypoxic Ischemic Encephalopathy (HIE) with a clear precipitating event
   d. Isolated prematurity
   e. Isolated meconium aspiration
   f. Isolated Transient Tachypnea of the Newborn (TTN)
   g. Isolated unconjugated hyperbilirubinemia
   h. Nonviable neonates

VIII. Rapid or ultra-rapid exome and genome sequencing (rES, urES, rGS and urGS) are considered **investigational** for the diagnosis of genetic disorders in all other situations.

IX. Standard, rapid and ultra-rapid-exome or genome sequencing (ES, rES, urES, GS, rGS, and urGS) are considered **investigational** when screening for genetic disorders.

X. Copy Number Variation (CNV) analysis (e.g., using Chromosomal Microarray Analysis [CMA]) may be considered **medically necessary** when **either** of the following are met:
   A. Performed at the same time as rES OR
   B. The results of the rES are insufficient to explain the clinical presentation

XI. Separate CMA testing is considered **investigational** with rGS or urGS analysis.

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NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Note: The terms *whole* exome and *whole* genome have previously been in common use. However, it is increasingly common to delete the term "whole" as it is understood that exome and genome testing are for the entire sequence. For the purposes of this document whole exome is meant to mean the same as exome and the same for whole genome and genome.

The policy statements are intended to address the use of exome and genome sequencing for the diagnosis of suspected genetic disorders.

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

Clinical Considerations
Standard vs. rapid vs. ultra-rapid

Standard Exome Sequencing (ES)
Standard ES turn-around time is usually 1 to 3 months, and is indicated only for stable patients who are unlikely to be harmed by standard timing

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

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

Note: rGS and urGS analysis has the ability to detect most CNVs and separate CMA testing is not needed.

Trio Testing

Testing of the child (proband) and both parents can increase the chance of finding a definitive diagnosis and better interpretation of results. 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.

While trio sequencing is preferred and recommended, an alternative method referred to as "Patient Plus" by PreventionGenetics may be considered. "Patient Plus" involves sequencing and copy number variant (CNV) analysis of the patient, and then targeted testing for the key variants found in the patient is performed on parental specimens. This approach permits detection of de novo variants and phasing of variants in recessive genes to increase diagnostic yield from a singleton sample in situations where full trio sequencing may not be feasible or preferable.

BRUE

Brief Resolved Unexplained Event (BRUE) was previously known as Apparent Life Threatening Event (ALTE). In a practice guideline from the American Academy of Pediatrics (AAP), BRUE is defined as an event occurring in an infant younger than 1 year of age when the observer reports a sudden, brief (usually less than one minute), and now resolved episode of one or more of the following:

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

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

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

Organ Transplantation

Rapid GS and ES may be considered for approval in some cases prior to undergoing organ transplantation when documentation supports the urgent need for testing.

For rapid ES or GS, the patient should be critically ill and in the Neonatal Intensive Care Unit (NICU) or Pediatric Intensive Care Unit (PICU) when the test is ordered, but may be discharged before the results are delivered.

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.

Incidental or secondary findings
Exome or genome sequencing can reveal incidental findings or secondary findings. These findings are defined as results that are not related to the indication for undergoing the sequencing, but may be of medical value or utility. Disclosure of these findings has been a topic of intense debate within the medical genetics community. In 2013, American College of Medical Genetics (ACMG) published recommendations for reporting secondary findings that included a list of conditions to be included. The list currently includes 59 genes that confer highly-penetrant and medically actionable conditions.

Pre-test and post-test genetic counseling that facilitates informed decision-making, the possibility to identify secondary finding with the option to 'opt out' of receiving these results, elicits patient preferences regarding secondary and/or incidental findings if possible, and formulates a plan for returning such results before testing occurs is strongly advised.

***Note**: repeat exome or variant analysis (not sequencing) is usually provided by the laboratory without additional charge when there are significant changes in symptoms or findings (phenotype) or the gene database over time.

If a genetic diagnosis is not found by exome sequencing or genome sequencing, periodic reanalysis of the previously obtained genomic sequence is recommended. Reevaluation can occur on the variant-level or case-level. When appropriate, re-sequencing (retesting)may be considered (see Policy Statement above). Any variants identified and reported prior to the current ACMG variant classification standards should be reevaluated using the current ACMG standards.

Variant-level reanalysis should be considered in the following circumstances:
- Availability of a new community resource (e.g., gnomAD)
- Publication and/or adoption of a novel/updated methodology for variant assessment
- Publication of evidence supporting new gene–disease relationships and/or mechanisms of disease

Case-level reanalysis should be considered in the following circumstances:
- Significant changes in clinical and family history occur
- Significant improvements have been made to the bioinformatics handling of the data

Notes and Definitions:
- **Exome Sequencing (ES)** is a genomic technique for sequencing all of the protein-coding regions of genes in the genome (also known as the exome).
- **Genome Sequencing (GS)** is a genomic technique for sequencing the complete DNA sequence, which includes protein coding as well as non-coding DNA elements.
- **Trio Testing** includes testing of the child and both parents and increases the chances of finding a definitive diagnosis, while reducing false-positive findings.
- **Comparator Exome Sequencing** is used only for comparison with the proband (individual undergoing exome sequencing) and is used to inform the pathogenicity of variants. A comparator exome is typically one or both parents to the proband.
- **Congenital anomalies** according to ACMG are multiple anomalies not specific to a well-delineated genetic syndrome. These anomalies are structural or functional abnormalities usually evident at birth, or shortly thereafter, and can be consequential to an individual's life expectancy, health status, physical or social functioning, and typically require medical intervention.

- **Developmental delay** is a slow-to-meet or not reaching milestones in one or more of the areas of development (communication, motor, cognition, social-emotional, or adaptive skills) in the expected way for a child's age
- **Intellectual disability** (ID) is defined by the DSM-V as:
  - Deficits in intellectual functions, such as reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and learning from experience, confirmed by both clinical assessment and individualized, standardized intelligence testing.
  - Deficits in adaptive functioning that result in failure to meet developmental and sociocultural standards for personal independence and social responsibility. Without ongoing support, the adaptive deficits limit functioning in one or more activities of daily life, such as communication, social participation, and independent living, across multiple environments, such as home, school, work, and community.
  - Onset of intellectual and adaptive deficits during the developmental period.

Coding

The following CPT codes are specific for this testing:

- **0094U**: Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis
- **81415**: Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
- **81416**: Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (e.g., parents, siblings) (List separately in addition to code for primary procedure)
- **81417**: Exome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (e.g., updated knowledge or unrelated condition/syndrome)
- **81425**: Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
- **81426**: Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (e.g., parents, siblings) (List separately in addition to code for primary procedure)
- **81427**: Genome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (e.g., updated knowledge or unrelated condition/syndrome)

Description

Exome sequencing (ES) (also known as 'whole exome sequencing (WES)') involves sequencing and often copy number variant (CNV) analysis of the portion of the genome that contains protein-coding DNA, which are termed exons. Together, all of the exons in a genome are known as the exome, which constitutes approximately 1% of the genome and is currently estimated to contain about 85% of heritable disease-causing variants.

Genome sequencing (GS) (also known as 'whole genome sequencing (WGS)') is a comprehensive method that sequences both coding and noncoding regions of the genome. GS has typically been limited to use in the research setting, but is emerging in the clinical setting and has a greater ability to detect large deletions or duplications in protein-coding regions compared with ES. GS requires greater data analysis but less DNA preparation prior to sequencing.

ES and GS have been proposed for use in patients presenting with disorders and anomalies not immediately explained by standard clinical workup. Potential candidates for ES and GS include patients who present with a broad spectrum of suspected genetic conditions.

Rapid exome sequencing (rES) and rapid genome (rGS) sequencing involves sequencing of the exome or genome, respectively, in an accelerated time frame. Preliminary results can typically be returned in less than 7 days, and a final report in less than two weeks. Studies suggest that the use of rES or rGS in acutely-ill infants presenting with complex phenotypes that are likely rare genetic conditions, can identify a genetic diagnosis more quickly, allowing clinicians and family members to change acute medical or surgical management options and end the diagnostic odyssey. Ultra-rapid GS involves sequencing of the genome typically in less than 72 hours and is currently considered investigational.

Related Policies

This policy document provides coverage criteria for exome and genome sequencing for the diagnosis of genetic disorders in patients with suspected genetic disorders and for population-based screening. Please refer to:

- ***Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies*** for coverage criteria related to exome and genome sequencing of solid tumors and hematologic malignancies.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to diagnostic genetic testing performed after a child has been born. ***(to be published)***
- ***Genetic Testing: Prenatal and Preconception Carrier Screening*** for coverage criteria related to prenatal carrier screening, preimplantation genetic testing, or preconception carrier screening.
- ***Genetic Testing: Prenatal Diagnosis (via Amniocentesis, CVS, or PUBS) and Pregnancy Loss*** for coverage related to prenatal exome sequencing.
- ***Genetic Testing: General Approach to Genetic Testing*** for coverage criteria related to exome and genome sequencing that is not specifically discussed in this or another non-general policy. ***(to be published)***

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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 Act. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Act for high-complexity testing.

Rationale

Standard Exome Sequencing

American College of Medical Genetics and Genomics (ACMG)

In 2021, ACMG published an evidence-based clinical practice guideline on exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability (Manickam, 2021).

- ACMG recommends using exome or genome sequencing as a first- or second-tier test for patients diagnosed with one or more congenital anomalies before the age of 1, or with intellectual disability/developmental delay before the age of 18. (p. 2031)
- ACMG recommends exome or genome sequencing for active and long-term clinical management of the proband, as well as for implications on family-focused and reproductive outcomes. (p. 2032)
- These guidelines also recommend consideration of exome sequencing after the results of chromosome microarray or focused genetic testing are uninformative for a patient with one or more congenital anomaly or patients with developmental delay/intellectual disability. (p. 2031)

ACMG also released a systematic evidence-based review (Malinowski, 2020) of 167 published studies examining the clinical impact of exome sequencing (ES) and genome sequencing (GS) in individuals with congenital anomalies (CA), developmental delay (DD), and intellectual disability (ID). This systematic review "provide[d] indirect evidence of the clinical and personal utility of ES/GS for patients with CA/DD/ID and their family members," noting that a "change in clinical management" resulted in over half of the patients examined as a result of their ES/GS results.

In regards to repeat exome sequencing, ACMG published a statement in 2019 recommending that repeat testing be considered when significant changes occur in the patient's personal and/or family histories, or if there have been improvements in testing methodologies, ability to analyze data, or understanding of the genetic etiology of disease (p. 1296) (Deignan, 2019).

In 2022, ACMG published ACMG SF v3.1, an updated list of genes included in the secondary findings (SF), which added an additional 5 genes bringing the total up to 78 genes (Miller, Lee, Gordon, 2021). ACMG also published a policy statement regarding updated recommendations for reporting of secondary findings in clinical exome and genome sequencing, which clarified that ACMG supports the continued research and discussion around population screening for the genes included in the secondary findings list. However, "ACMG has made it clear that the ACMG SF is not validated for general population screening" (Miller, Lee, Chung, 2021).

National Society for Genetic Counselors

The National Society for Genetic Counselors (NSGC) released a position statement (2013, updated 2020) stating the following in regard to secondary and incidental findings in genetic testing:
"The National Society of Genetic Counselors strongly advises pre-test counseling that facilitates informed decision-making, elicits patient preferences regarding secondary and/or incidental findings if possible, and formulates a plan for returning such results before testing occurs.

Germline and somatic genetic testing, in both clinical and research contexts, may identify secondary findings and incidental findings as a part of the test performed. Secondary findings are purposely analyzed as part of the test, but unrelated to the primary testing indication. Incidental findings are detected unexpectedly during the analysis, and also unrelated to the primary testing indication. Both of these types of variants may be disclosed as a part of the return-of-results process.

The pre-test counseling process should establish clear expectations for what categories of results will and will not be returned. Healthcare practitioners conducting the informed consent and return-of-

results processes for broad genomic testing and screening should ensure that their patients have access to practitioners with genetic expertise, such as genetic counselors."

UpToDate

UpToDate is an evidence-based clinical decision support resource that is expert-authored and goes through a multi-layered review and consensus process.

Intellectual disability in children: Evaluation for a cause

"Whole exome sequencing — WES should be considered for patients with moderate to severe ID in whom other standard tests (including CMA) have failed to identify the cause. The diagnostic yield of WES in this setting is approximately 16 to 33 percent. The diagnostic yield is likely lower in patients with mild ID without additional findings and the role of WES testing in this population is not defined. WES testing should be performed with consultation of a clinical geneticist and should include appropriate pretest counseling to discuss the risk of incidental findings unrelated to the child's ID that may be medically actionable (eg, BRCA1 or BRCA2 mutation). Incidental findings can be minimized if a focused analysis is conducted. Due to the falling costs of sequencing and its high diagnostic yield, WES is rapidly becoming a clinical tool for the evaluation of ID, especially at specialty centers. Adoption of WES testing into the diagnostic process will depend on its cost, availability, access to expert interpretation, and the allocation of resources within each health care setting."

National Society of Genetic Counselors

The National Society of Genetic Counselors (NSGC) published evidence-based practice guidelines for individuals with unexplained epilepsy (Smith et al, 2022). The NSGC recommendations are as follows (p. 4):

- Individuals with unexplained epilepsy should be offered genetic testing, without limitation of age.
- Multi-gene, comprehensive testing, such as exome sequencing, genome sequencing or a multigene panel as a first-tier test is strongly recommended

Patient-centered Laboratory Utilization Guidance (PLUGS)

PLUGS developed an expert-written exome sequencing coverage policy as part of their insurance alignment focus. Their policy includes the following criteria for exome sequencing:

- The patient and family history have been evaluated by a Board -Certified or Board -Eligible Medical Geneticist, or an Advanced Practice Nurse in Genetics (APGN) credentialed by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) **AND**
- A genetic etiology is considered the most likely explanation for the phenotype, based on EITHER of the following **AND**
    - Multiple congenital abnormalities affecting unrelated organ systems
    - **TWO** of the following criteria are met:
        - abnormality affecting at minimum a single organ system significant neurodevelopmental disorder (e.g., global developmental delay, intellectual disability , and/or period of unexplained developmental regression)
        - symptoms of a complex neurological condition (e.g. , dystonia, hemiplegia, spasticity, epilepsy, myopathy, muscular dystrophy)
        - severe neuropsychiatric condition (e.g. , schizophrenia, bipolar disorder, Tourette syndrome, self -injurious behavior, reverse sleep -wake cycles)
        - family history strongly suggestive of a genetic etiology, including consanguinity
        - laboratory findings suggestive of an inborn error of metabolism
- Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection), **AND**

- Clinical presentation does not fit a well -described syndrome for which single - gene or targeted panel testing (e.g., comparative genomic hybridization [CGH]/chromosomal microarray analysis [CMA]) is available, **AND**
- WES is more efficient and economical than the separate single -gene tests or panels that would be recommended based on the differential diagnosis (e.g., genetic conditions that demonstrate a high degree of genetic heterogeneity), **AND**
- A diagnosis cannot be made by standard clinical work -up, excluding invasive procedures such as muscle biopsy, **AND**
- Predicted impact on health outcomes, as above, **AND**
- Pre- and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), such as an American Board of Medical Genetics or American Board of Genetic Counseling -certified Genetic Counselor

Rapid Exome Sequencing
Kingsmore SF, Cakici JA, Clark MM et al. 2019
This report is from the NSIGHT2 study, a prospective randomized, controlled, blinded trial (RCT) in acutely ill infants, primarily from the NICU, PICU, and CVICU at Rady Children's Hospital, San Diego (RCHSD) to compare the effectiveness and outcomes between rWGS and rWES, with analysis as singleton probands and familial trios. The inclusion criteria for the 1,248 ill infants defined the maximum age at the time of admission as four months. They found that 24% of infants undergoing rapid exome sequencing had genetic disease. They conclude that diagnostic testing in infants with diseases of unknown etiology, rapid genomic sequencing, including rapid exome sequencing can be performed as a first tier test in infants with diseases of unknown etiology at time of admission to ICUs. In unstable infants and in those whom a genetic diagnosis was likely to impact immediate management, rapid genomic sequencing had optimal analytic and diagnostic performance by virtue of shortest time to results. (p. 725)

Patient-centered Laboratory Utilization Guidance (PLUGS)
The PLUGS Exome Sequencing policy acknowledges that exome sequencing "is typically not an appropriate first -tier test, but can be appropriate if initial testing is unrevealing, or if there is no single-gene or panel test available for the particular condition, or if a rapid diagnosis for a critically-ill child is indicated. (p. 1)

Standard Genome Sequencing
American College of Medical Genetics and Genomics (ACMG) 2021 revision on Next-generation sequencing for constitutional variants in the clinical laboratory states the following:

> "… Exome Sequencing or Genome Sequencing provide[s] a broad approach to match detected variants with the clinical phenotype assessed by the laboratory and health-care provider. Exome Sequencing may be performed with the intention of restricting interpretation and reporting to variants in genes with specific disease associations with an option to expand the analysis to the rest of the exome if the initial analysis is nondiagnostic. Exome Sequencing/Genome Sequencing approaches are most appropriate in the following scenarios: (1) when the phenotype is complex and genetically heterogeneous; (2) when the phenotype has unusual features, an atypical clinical course, or unexpected age of onset; (3) when the phenotype is associated with recently described disease genes for which disease-targeted testing is unavailable; (4) when focused testing has been performed and was nondiagnostic; (5) when sequential testing could cause therapeutic delays; or (6) when the phenotype does not match an identified genetic condition, suggesting the possibility of more than one genetic diagnosis, which has been documented in 4–7% of positive cases. When Exome Sequencing/Genome Sequencing does not establish a diagnosis, the data can be reanalyzed (section E.6). The potential impact of secondary findings with Exome Sequencing/Genome Sequencing should also be considered (section E.3)." (p. 1400-1401)

Rapid Genome Sequencing

Patient-centered Laboratory Utilization Guidance (PLUGS)

PLUGS developed an expert-written rapid genome sequencing coverage policy as part of their insurance alignment focus. This policy references multiple primary research publications with examples of clinical presentations that result in evidence of clinical utility. (p. 3)

They recommend rapid whole genome testing criteria to include acutely ill infants 12 months of age or younger whose features suggest an unknown genetic etiology and have a complex phenotype which may include a combination of multiple congenital anomalies, encephalopathy, symptoms of a complex neurodevelopmental disorder, family history suggestive of genetic etiology, laboratory findings suggestive of an inborn error of metabolism and an abnormal response to therapy. The clinical presentation should not fit a well-described syndrome for which rapid single gene or targeted panel testing is available. They suggest that there should be predicted impact on health outcomes, including immediate impact on medical management based on the molecular results. (p. 3-4)

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Genetics and Genomics (ACMG). *Genet Med*. 2021;23(8):1399-1415. doi:10.1038/s41436-021-01139-4

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Documentation for Clinical Review

Please provide the following documentation for standard exome testing:

- History and physical and/or consultation notes including:
  - Type of test and reason for test including why a genetic cause for problems is considered to be likely
  - Family history and phenotype
  - Any invasive procedures that could be avoided by exome or genome testing
- Previous lab results pertaining to genetic testing, including CMA (chromosomal microarray) or previous exome testing
- For repeat standard exome testing
  - Evaluation and or consultation notes from the clinician with expertise in clinical genetics
  - Why repeat sequencing is thought to be needed
- Name of the test being requested or the Concert Genetics GTU identifier
  The Concert Genetics GTU can be found at https://app.concertgenetics.com

Post Service (in addition to the above, please include the following):

- Laboratory report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0094U	Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis
	0209U	Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities
	0212U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband

Type	Code	Description
	0213U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator genome (e.g., parent, sibling)
	0214U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband
	0215U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator exome (e.g., parent, sibling)
	0265U	Rare constitutional and other heritable disorders, whole genome and mitochondrial DNA sequence analysis, blood, frozen and formalin-fixed paraffin-embedded (FFPE) tissue, saliva, buccal swabs or cell lines, identification of single nucleotide and copy number variants
	0267U	Rare constitutional and other heritable disorders, identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping and whole genome sequencing
	0425U	Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis, each comparator genome (e.g., parents, siblings) ***(Code effective 1/1/2024)***
	0426U	Genome (e.g., unexplained constitutional or heritable disorder or syndrome), ultra-rapid sequence analysis ***(Code effective 1/1/2024)***
	81415	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
	81416	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (e.g., parents, siblings) (List separately in addition to code for primary procedure
	81417	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (e.g., updated knowledge or unrelated condition/syndrome)
	81425	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
	81426	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (e.g., parents, siblings) (List separately in addition to code for primary procedure)
	81427	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (e.g., updated knowledge or unrelated condition/syndrome)
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
06/01/2022	New policy.
11/01/2022	Coding update.
12/01/2022	Administrative update.
03/01/2023	Coding update.
06/01/2023	Annual review. Policy statement, guidelines and literature updated.
03/01/2024	Coding update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. 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 covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Genetic Testing: Exome and Genome Sequencing For The Diagnosis Of Genetic Disorders BSC_CON_2.02 **Policy Statement:** **Standard Exome Sequencing** I. Standard exome sequencing (81415, 81416, 81417, 0214U, 0215U), with trio testing when possible, may be considered **medically necessary** when **all** of the following criteria are met: A. The member has unexplained epilepsy at any age B. The member has an unexplained congenital or neurodevelopmental disorder, AND C. The member has been evaluated by a clinician with expertise in clinical genetics, including but not limited to: 1. Board-Certified or Board-Eligible Medical Geneticist 2. Certified Genetic Counselor 3. Advanced practice practitioner (e.g., Advanced practice registered nurse (APRN) or Physician's Assistant) in genetics; AND D. Documentation submitted includes **all** of the following: 1. A complete family history of at least 3 generations when available (or notation why it is not) 2. Complete and detailed description of the proband phenotype 3. Any previous genetic testing results (e.g., chromosomal microarray/CMA, single gene or small panels) 4. If no previous testing has been done, that the member's clinical presentation does not fit a well-described syndrome for which specific testing (e.g., single-gene testing, CMA) is available 5. Any invasive testing that might be avoided by exome testing 6. Why a genetic etiology is a likely explanation for the clinical and historical findings	**Genetic Testing: Exome and Genome Sequencing For The Diagnosis Of Genetic Disorders BSC_CON_2.02** **Policy Statement:** **Standard Exome Sequencing** I. Standard exome sequencing (81415, 81416, 81417, 0214U, 0215U), with trio testing when possible, may be considered **medically necessary** when **all** of the following criteria are met: A. The member has unexplained epilepsy at any age B. The member has an unexplained congenital or neurodevelopmental disorder, AND C. The member has been evaluated by a clinician with expertise in clinical genetics, including but not limited to: 1. Board-Certified or Board-Eligible Medical Geneticist 2. Certified Genetic Counselor 3. Advanced practice practitioner (e.g., Advanced practice registered nurse (APRN) or Physician's Assistant) in genetics; AND D. Documentation submitted includes **all** of the following: 1. A complete family history of at least 3 generations when available (or notation why it is not) 2. Complete and detailed description of the proband phenotype 3. Any previous genetic testing results (e.g., chromosomal microarray/CMA, single gene or small panels) 4. If no previous testing has been done, that the member's clinical presentation does not fit a well-described syndrome for which specific testing (e.g., single-gene testing, CMA) is available 5. Any invasive testing that might be avoided by exome testing 6. Why a genetic etiology is a likely explanation for the clinical and historical findings

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
II. **Standard genome sequencing** (81425, 81426, 81427, 0209U, 0212U, 0213U, 0265U, 0267U) is considered **investigational**. III. **Repeat standard exome sequencing** (not reanalysis*) for the above indications may be considered **medically necessary** when **all** of the following criteria are met: A. The member has been re-evaluated by a Board-Certified or Board-Eligible Medical Geneticist, a Certified Genetic Counselor, an advanced practice practitioner (e.g., APRN or Physician's Assistant) in genetics, who is not employed by a commercial genetic testing laboratory that recommends repeat exome sequencing, AND B. There have been improvements in technology/chemistry (e.g., new methods for DNA capture and/or sequencing), bioinformatics advancements, or new information regarding the genetic etiology of a condition that could explain the patient's clinical features and would not have been able to be detected by the previous exome sequencing the patient underwent. IV. Repeat standard exome sequencing (81415, 81416, 0214U, 0215U) is considered **investigational** for all other indications. V. Repeat standard genome sequencing (81425, 81426, 81427, 0212U, 0213U, 0265U, 0267U) is considered **investigational** for all indications including but not limited to those considered medically necessary for repeat exome testing. VI. Standard exome and genome sequencing is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders. back to top	II. **Standard genome sequencing** (81425, 81426, 81427, 0209U, 0212U, 0213U, 0265U, 0267U) is considered **investigational**. III. **Repeat standard exome sequencing** (not reanalysis*) for the above indications may be considered **medically necessary** when **all** of the following criteria are met: A. The member has been re-evaluated by a Board-Certified or Board-Eligible Medical Geneticist, a Certified Genetic Counselor, an advanced practice practitioner (e.g., APRN or Physician's Assistant) in genetics, who is not employed by a commercial genetic testing laboratory that recommends repeat exome sequencing, AND B. There have been improvements in technology/chemistry (e.g., new methods for DNA capture and/or sequencing), bioinformatics advancements, or new information regarding the genetic etiology of a condition that could explain the patient's clinical features and would not have been able to be detected by the previous exome sequencing the patient underwent. IV. Repeat standard exome sequencing (81415, 81416, 0214U, 0215U) is considered **investigational** for all other indications. V. Repeat standard genome sequencing (81425, 81426, 81427, 0212U, 0213U, 0265U, 0267U) is considered **investigational** for all indications including but not limited to those considered medically necessary for repeat exome testing. VI. Standard exome and genome sequencing is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders. back to top
Rapid and ultra-rapid Exome or Genome Sequencing	**Rapid and ultra-rapid Exome or Genome Sequencing**

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
VII. Rapid or ultra-rapid exome or genome sequencing (rES, urES, rGS or urGS), with trio testing when possible, may be considered **medically necessary** when **all** of the following are met: A. For the evaluation of hospitalized critically ill infants or children (NICU or PICU) less than 18 years of age with an illness of unknown etiology B. Documentation that supports **both** of the following: 1. At least **one** of the following: a. Multiple congenital anomalies affecting unrelated organ systems b. Specific malformations highly suggestive of a genetic etiology, including but not limited to **one or more** of the following: i. Choanal atresia ii. Coloboma iii. Hirschsprung disease iv. Meconium ileus c. An abnormal laboratory test suggests a genetic disease or complex metabolic phenotype, including but not limited to **one or more** of the following: i. Abnormal newborn screen ii. Conjugated hyperbilirubinemia not due to total parental nutrition (TPN) cholestasis iii. Hyperammonemia iv. Lactic acidosis not due to poor perfusion v. Refractory or severe hypoglycemia d. An abnormal response to standard therapy for a major underlying condition e. Significant hypotonia f. Persistent seizures g. Infant with high risk stratification on evaluation for a Brief Resolved Unexplained Event (BRUE) with **one or more** of the following: i. Recurrent events without respiratory infection ii. Recurrent witnessed seizure like events iii. Required Cardiopulmonary Resuscitation (CPR)	VII. Rapid or ultra-rapid exome or genome sequencing (rES, urES, rGS or urGS), with trio testing when possible, may be considered **medically necessary** when **all** of the following are met: A. For the evaluation of hospitalized critically ill infants or children (NICU or PICU) less than 18 years of age with an illness of unknown etiology B. Documentation that supports **both** of the following: 1. At least **one** of the following: a. Multiple congenital anomalies affecting unrelated organ systems b. Specific malformations highly suggestive of a genetic etiology, including but not limited to **one or more** of the following: i. Choanal atresia ii. Coloboma iii. Hirschsprung disease iv. Meconium ileus c. An abnormal laboratory test suggests a genetic disease or complex metabolic phenotype, including but not limited to **one or more** of the following: i. Abnormal newborn screen ii. Conjugated hyperbilirubinemia not due to total parental nutrition (TPN) cholestasis iii. Hyperammonemia iv. Lactic acidosis not due to poor perfusion v. Refractory or severe hypoglycemia d. An abnormal response to standard therapy for a major underlying condition e. Significant hypotonia f. Persistent seizures g. Infant with high risk stratification on evaluation for a Brief Resolved Unexplained Event (BRUE) with **one or more** of the following: i. Recurrent events without respiratory infection ii. Recurrent witnessed seizure like events iii. Required Cardiopulmonary Resuscitation (CPR)

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
iv. 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 v. Significantly abnormal electrocardiogram (ECG), including but not limited to possible channelopathies, arrhythmias, cardiomyopathies, myocarditis or structural heart disease vi. Family history of **one or more** of the following: • 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 2. **All** of the following have been excluded a reason for admission: a. An infection with normal response to therapy b. Confirmed genetic diagnosis explains illness c. Hypoxic Ischemic Encephalopathy (HIE) with a clear precipitating event d. Isolated prematurity e. Isolated meconium aspiration f. Isolated Transient Tachypnea of the Newborn (TTN) g. Isolated unconjugated hyperbilirubinemia h. Nonviable neonates	iv. 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 v. Significantly abnormal electrocardiogram (ECG), including but not limited to possible channelopathies, arrhythmias, cardiomyopathies, myocarditis or structural heart disease vi. Family history of **one or more** of the following: • 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 2. **All** of the following have been excluded a reason for admission: a. An infection with normal response to therapy b. Confirmed genetic diagnosis explains illness c. Hypoxic Ischemic Encephalopathy (HIE) with a clear precipitating event d. Isolated prematurity e. Isolated meconium aspiration f. Isolated Transient Tachypnea of the Newborn (TTN) g. Isolated unconjugated hyperbilirubinemia h. Nonviable neonates

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
VIII. Rapid or ultra-rapid exome and genome sequencing (rES, urES, rGS and urGS) are considered **investigational** for the diagnosis of genetic disorders in all other situations.	VIII. Rapid or ultra-rapid exome and genome sequencing (rES, urES, rGS and urGS) are considered **investigational** for the diagnosis of genetic disorders in all other situations.
IX. Standard, rapid and ultra-rapid-exome or genome sequencing (ES, rES, urES, GS, rGS, and urGS) are considered **investigational** when screening for genetic disorders.	IX. Standard, rapid and ultra-rapid-exome or genome sequencing (ES, rES, urES, GS, rGS, and urGS) are considered **investigational** when screening for genetic disorders.
X. Copy Number Variation (CNV) analysis (e.g., using Chromosomal Microarray Analysis [CMA]) may be considered **medically necessary** when **either** of the following are met: A. Performed at the same time as rES OR B. The results of the rES are insufficient to explain the clinical presentation	X. Copy Number Variation (CNV) analysis (e.g., using Chromosomal Microarray Analysis [CMA]) may be considered **medically necessary** when **either** of the following are met: A. Performed at the same time as rES OR B. The results of the rES are insufficient to explain the clinical presentation
XI. Separate CMA testing is considered **investigational** with rGS or urGS analysis.	XI. Separate CMA testing is considered **investigational** with rGS or urGS analysis.