BSC_CON_2.02	Genetic Testing: Exome and Genome Sequencing For The Diagnosis Of Genetic Disorders		
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Section:	2.0 Medicine	**Page:**	Page 1 of 19

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
	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
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:

I. The member has an unexplained congenital or neurodevelopmental disorder, AND
II. The member has been evaluated by a clinician with expertise in clinical genetics, including but not limited to:
   A. Board-Certified or Board-Eligible Medical Geneticist
   B. Certified Genetic Counselor
   C. Advanced practice practitioner (e.g., Advanced practice registered nurse (APRN) or Physician's Assistant) in genetics; AND
III. Documentation submitted includes **all** of the following:
   A. A complete family history of at least 3 generations when available (or notation why it is not)
   B. Complete and detailed description of the proband phenotype
   C. Any previous genetic testing results (e.g., chromosomal microarray/CMA, single gene or small panels)
   D. 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
   E. Any invasive testing that might be avoided by exome testing
   F. Why a genetic etiology is a likely explanation for the clinical and historical findings

Standard genome sequencing (81425, 81426, 81427, 0012U, 0209U, 0212U, 0213U, 0265U, 0267U) is considered **investigational**.

Repeat standard exome sequencing (not reanalysis*) for the above indications may be considered **medically necessary** when **all** of the following criteria are met:

I. 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
II. 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.

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

Repeat standard genome sequencing (81425, 81426, 81427, 0012U, 0209U, 0212U, 0213U, 0265U, 0267U) is considered **investigational** for all indications including but not limited to those considered medically necessary for repeat exome testing.

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

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:

I. 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
II. Documentation that supports **both** of the following:
    A. At least **one** of the following:
        1. Multiple congenital anomalies affecting unrelated organ systems
        2. Specific malformations highly suggestive of a genetic etiology, including but not limited to **one or more** of the following:
            a. Choanal atresia
            b. Coloboma
            c. Hirschsprung disease
            d. Meconium ileus
        3. An abnormal laboratory test suggests a genetic disease or complex metabolic phenotype, including but not limited to **one or more** of the following:
            a. Abnormal newborn screen
            b. Conjugated hyperbilirubinemia not due to total parental nutrition (TPN) cholestasis
            c. Hyperammonemia
            d. Lactic acidosis not due to poor perfusion
            e. Refractory or severe hypoglycemia
        4. An abnormal response to standard therapy for a major underlying condition
        5. Significant hypotonia
        6. Persistent seizures
        7. Infant with high risk stratification on evaluation for a Brief Resolved Unexplained Event (BRUE) with **one or more** of the following:
            a. Recurrent events without respiratory infection
            b. Recurrent witnessed seizure like events
            c. Required Cardiopulmonary Resuscitation (CPR)
            d. 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
            e. Significantly abnormal electrocardiogram (ECG), including but not limited to possible channelopathies, arrhythmias, cardiomyopathies, myocarditis or structural heart disease
            f. Family history of **one or more** of the following:
                i. Arrhythmia
                ii. BRUE in sibling
                iii. Developmental delay
                iv. Inborn error of metabolism or genetic disease
                v. Long QT syndrome (LQTS)
                vi. Sudden unexplained death (including unexplained car accident or drowning) in first- or second-degree family members before age 35, and particularly as an infant
    B. **All** of the following have been excluded a reason for admission:
        1. An infection with normal response to therapy
        2. Confirmed genetic diagnosis explains illness
        3. Hypoxic Ischemic Encephalopathy (HIE) with a clear precipitating event
        4. Isolated prematurity
        5. Isolated meconium aspiration
        6. Isolated Transient Tachypnea of the Newborn (TTN)

7. Isolated unconjugated hyperbilirubinemia
8. Nonviable neonates

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.

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

Copy Number Variation (CNV) analysis (e.g., using Chromosomal Microarray Analysis [CMA]) may be considered **medically necessary** when **either** of the following are met:

I. Performed at the same time as rES OR
II. The results of the rES are insufficient to explain the clinical presentation

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.

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.
- ***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.

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

Practice Guidelines and Position Statements
American College of Medical Genetics and Genomics
The American College of Medical Genetics and Genomics (ACMG) (2012) published a position statement on clinical application of exome and genome testing. ACMG recommends considering ES/GS sequencing in the clinical diagnostic assessment of a phenotypically affected individual when:

- "The phenotype or family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test is available."
- "A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WES or WGS analysis of multiple genes simultaneously a more practical approach."
- "A patient presents with a likely genetic disorder, but specific genetic tests available for that phenotype have failed to arrive at a diagnosis."
- "A fetus with a likely genetic disorder in which specific genetic tests, including targeted sequencing tests, available for that phenotype have failed to arrive at a diagnosis."

In 2013, ACMG published the following recommendations for reporting of incidental findings in clinical exome and genome sequencing:

1. "Constitutional mutations found in the genes on the minimum list (Table 1) should be reported by the laboratory to the ordering clinician, regardless of the indication for which the clinical sequencing was ordered.
    - Additional genes may be analyzed for incidental variants, as deemed appropriate by the laboratory.
    - Incidental variants should be reported regardless of the age of the patient.
    - Incidental variants should be reported for any clinical sequencing conducted on a constitutional (but not tumor) tissue. This includes the normal sample of a tumor-normal sequenced dyad and unaffected members of a family trio."
2. "The Working Group recommends that laboratories seek and report only the types of variants within these genes that we have delineated (Table 1).
    - For most genes, only variants that have been previously reported and are a recognized cause of the disorder or variants that are previously unreported but are of

the type that is expected to cause the disorder, as defined by prior ACMG guidelines,20 should be reported.
    - For some genes, predicted loss-of-function variants are not relevant (e.g., COL3A1 and most hypertrophic cardiomyopathy genes).
    - For some genes (e.g., APOB), laboratories should only report variants for certain associated conditions."
3. "It is the responsibility of the ordering clinician/team to provide comprehensive pre and posttest counseling to the patient.
    - Clinicians should be familiar with the basic attributes and limitations of clinical sequencing.
    - Clinicians should alert patients to the possibility that clinical sequencing may generate incidental findings that could require further evaluation.
    - Given the complexity of genomic information, the clinical geneticist should be consulted at the appropriate time, which may include ordering, interpreting, and communicating genomic testing. "
4. "These recommendations reflect limitations of current technology and are therefore focused on disorders that are caused by point mutations and small insertions and deletions, not those primarily caused by structural variants, repeat expansions, or copy-number variations."
5. "The Working Group recommends that the ACMG, together with content experts and other professional organizations, refine and update this list at least annually."

In 2016, ACMG updated its recommendations on reporting secondary findings in WGS and WES testing. ACMG determined that reporting some secondary findings would likely have medical benefit for the patients and families of patients undergoing clinical sequencing, recommending that, when a report is issued for clinically indicated exome and genome sequencing, a minimum list of conditions, genes, and variants should be routinely evaluated and reported to the ordering clinician. The 2016 update added 4 genes and removed 1 gene resulting in an updated secondary findings minimum list including 59 medically actionable genes recommended for return in clinical genomic sequencing.

In 2018, ACMG published points to consider encouraging engagement of older children and adolescents being considered for exome and/or genome sequencing, and that:

- "The purpose of the engagement process is to ensure that the mature older child is actively involved in conversation to understand the goals and implications of genomic testing and potential findings and to consider its personal benefits and limitations while having the opportunity to express their feelings and opinions".
- "It is critical to engage the child as much as possible in this process, which includes the assent of the child whenever reasonable."
- "Children as young as 8 years of age should be part of an active engagement process to the extent that they are considered by the clinician and parent to be psychologically and cognitively capable."

In 2019, ACMG published points to consider around exome or genome reanalysis and retesting (discussed in Clinical Considerations). These considerations include points to consider for variant-level reanalysis, case-level reanalysis, and retesting for laboratories and clinicians.

In 2021, ACMG published ACMG SF v3.0, an updated list of genes included in the secondary findings, which added an additional 14 genes bringing the total up to 73 genes. 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".

Additionally, the following policy recommendations were made regarding consenting and reporting practices:

- "The SF list is intended as a "minimum list" of actionable secondary findings."
- "Providing the opportunity for an informed decision and opt out, if desired, at the time of consent should continue to be the standard for secondary findings."
- "The option to receive SFs should be offered regardless of the age of the patient. The best interest of the child should still be prioritized when disclosing risk for adult-onset conditions in minors."
- "The option to opt out of SFs should also be presented to the individual in the context of prenatal ES/GS."
- "The consent process should include discussion of the categories of reportable gene–phenotype pairs related to the ACMG SF list."
- "Thoughtful consideration of the context of a positive SF result during results disclosure, and when making related medical management recommendations, is necessary."
- "If laboratories report apparent somatic mosaicism, the consent process should address this."
- "Pre-test and post-test genetic counseling should be provided to any person receiving SF results in order to discuss the types of possible results, limitations of testing, and medical implications of any results."

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."

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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

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
	0012U	Germline disorders, gene rearrangement detection by whole genome next-generation sequencing, DNA, whole blood, report of specific gene rearrangement(s)
	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
	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

Type	Code	Description
		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
	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.

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 (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.

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	
BEFORE **Red font: Verbiage removed**	**AFTER** **Blue font: Verbiage Changes/Additions**
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders 2.04.102 **Policy Statement:** A standard whole exome sequencing (WES), with trio testing when possible, may be considered **medically necessary** when **all** of the following are met: I. Testing is for the evaluation of unexplained congenital or neurodevelopmental disorder in children when **all** of the following criteria are met: A. Documentation that the patient has been evaluated by a clinician with expertise in clinical genetics, and **all** of the following: 1. Evaluation includes at least a family history and phenotype description 2. Patient and family (if applicable) have been counseled about the potential risks of genetic testing II. Previous genetic testing (e.g., chromosomal microarray analysis [CMA] and/or targeted single-gene testing) has failed to yield a diagnosis III. Documentation of **one or more** of the following: A. A genetic etiology is considered the most likely explanation for the phenotype B. The affected individual is faced with invasive procedures or testing (e.g., muscle biopsy) as the next diagnostic step Standard whole genome sequencing (WGS) is considered **investigational** for the diagnosis of genetic disorders.	**Genetic Testing: Exome and Genome Sequencing For The Diagnosis Of Genetic Disorders BSC_CON_2.02** **Policy Statement:** **Standard Exome Sequencing** 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: I. The member has an unexplained congenital or neurodevelopmental disorder, AND II. The member has been evaluated by a clinician with expertise in clinical genetics, including but not limited to: A. Board-Certified or Board-Eligible Medical Geneticist B. Certified Genetic Counselor C. Advanced practice practitioner (e.g., Advanced practice registered nurse (APRN) or Physician's Assistant) in genetics; AND III. Documentation submitted includes **all** of the following: A. A complete family history of at least 3 generations when available (or notation why it is not) B. Complete and detailed description of the proband phenotype C. Any previous genetic testing results (e.g., chromosomal microarray/CMA, single gene or small panels) D. 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 E. Any invasive testing that might be avoided by exome testing F. Why a genetic etiology is a likely explanation for the clinical and historical findings **Standard genome sequencing** (81425, 81426, 81427, 0012U, 0209U, 0212U, 0213U, 0265U, 0267U) is considered **investigational**.

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	Repeat standard exome sequencing (not reanalysis*) for the above indications may be considered **medically necessary** when **all** of the following criteria are met: I. 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 II. 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. Repeat standard exome sequencing (81415, 81416, 0214U, 0215U) is considered **investigational** for all other indications. Repeat standard genome sequencing (81425, 81426, 81427, 0012U, 0209U, 0212U, 0213U, 0265U, 0267U) is considered **investigational** for all indications including but not limited to those considered medically necessary for repeat exome testing.
Standard whole exome sequencing is considered **investigational** for the diagnosis of genetic disorders in all other situations.	Standard exome and genome sequencing is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders. back to top
Rapid whole exome or rapid whole genome sequencing (rWES or rWGS), with trio testing when possible, may be considered **medically necessary** when **all** of the following are met: I. For the evaluation of critically ill infants or children less than 18 years of age II. Hospitalized in neonatal or pediatric intensive care with illness of unknown etiology III. Documentation that supports **both** of the following:	**Rapid and ultra-rapid Exome or Genome Sequencing** 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: I. 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

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A. At least **one** of the following: 1. Multiple congenital anomalies 2. Specific malformations highly suggestive of a genetic etiology, including but not limited to **one or more** of the following: a. Choanal atresia b. Coloboma c. Hirschsprung disease d. Meconium ileus 3. An abnormal laboratory test suggests a genetic disease or complex metabolic phenotype, including but not limited to **one or more** of the following: a. Abnormal newborn screen b. Conjugated hyperbilirubinemia not due to total parental nutrition (TPN) cholestasis c. Hyperammonemia d. Lactic acidosis not due to poor perfusion e. Refractory or severe hypoglycemia 4. An abnormal response to standard therapy for a major underlying condition 5. Significant hypotonia 6. Persistent seizures 7. Infant with high risk stratification on evaluation for a Brief Resolved Unexplained Event (BRUE) with **one or more** of the following: a. Recurrent events without respiratory infection b. Recurrent witnessed seizure like events c. Required Cardiopulmonary Resuscitation (CPR) d. 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 e. Significantly abnormal electrocardiogram (ECG), including but not limited to possible channelopathies, arrhythmias, cardiomyopathies, myocarditis or structural heart disease f. Family history of **one or more** of the following: i. Arrhythmia	II. Documentation that supports **both** of the following: A. At least **one** of the following: 1. Multiple congenital anomalies affecting unrelated organ systems 2. Specific malformations highly suggestive of a genetic etiology, including but not limited to **one or more** of the following: a. Choanal atresia b. Coloboma c. Hirschsprung disease d. Meconium ileus 3. An abnormal laboratory test suggests a genetic disease or complex metabolic phenotype, including but not limited to **one or more** of the following: a. Abnormal newborn screen b. Conjugated hyperbilirubinemia not due to total parental nutrition (TPN) cholestasis c. Hyperammonemia d. Lactic acidosis not due to poor perfusion e. Refractory or severe hypoglycemia 4. An abnormal response to standard therapy for a major underlying condition 5. Significant hypotonia 6. Persistent seizures 7. Infant with high risk stratification on evaluation for a Brief Resolved Unexplained Event (BRUE) with **one or more** of the following: a. Recurrent events without respiratory infection b. Recurrent witnessed seizure like events c. Required Cardiopulmonary Resuscitation (CPR) d. 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 e. Significantly abnormal electrocardiogram (ECG), including but not limited to possible channelopathies, arrhythmias, cardiomyopathies, myocarditis or structural heart disease

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ii. BRUE in sibling iii. Developmental delay iv. Inborn error of metabolism or genetic disease v. Long QT syndrome (LQTS) vi. Sudden unexplained death (including unexplained car accident or drowning) in first- or second-degree family members before age 35, and particularly as an infant B. **All** of the following have been excluded a reason for admission: 1. An infection with normal response to therapy 2. Confirmed genetic diagnosis explains illness 3. Hypoxic Ischemic Encephalopathy (HIE) with a clear precipitating event 4. Isolated prematurity 5. Isolated Transient Tachypnea of the Newborn (TTN) 6. Isolated unconjugated hyperbilirubinemia 7. Nonviable neonates	f. Family history of **one or more** of the following: i. Arrhythmia ii. BRUE in sibling iii. Developmental delay iv. Inborn error of metabolism or genetic disease v. Long QT syndrome (LQTS) vi. Sudden unexplained death (including unexplained car accident or drowning) in first- or second-degree family members before age 35, and particularly as an infant B. **All** of the following have been excluded a reason for admission: 1. An infection with normal response to therapy 2. Confirmed genetic diagnosis explains illness 3. Hypoxic Ischemic Encephalopathy (HIE) with a clear precipitating event 4. Isolated prematurity 5. Isolated meconium aspiration 6. Isolated Transient Tachypnea of the Newborn (TTN) 7. Isolated unconjugated hyperbilirubinemia 8. Nonviable neonates
Rapid whole exome sequencing and rapid whole genome sequencing (rWES and rWGS) is considered **investigational** for the diagnosis of genetic disorders in all other situations.	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.
Standard and rapid whole exome sequencing (WES and rWES) and standard and rapid whole genome sequencing (WGS and rWGS)are considered **investigational** when screening for genetic disorders.	Standard, rapid and ultra-rapid-exome or genome sequencing (ES, rES, urES, GS, rGS, and urGS) are considered **investigational** when screening for genetic disorders.
Copy Number Variation (CNV) analysis (e.g., using Chromosomal Microarray Analysis [CMA]) may be considered **medically necessary** when **all** of the following are met: I. Performed at the same time as rWES or later II. The results of the rWES are insufficient to explain the clinical presentation	Copy Number Variation (CNV) analysis (e.g., using Chromosomal Microarray Analysis [CMA]) may be considered **medically necessary** when **either** of the following are met: I. Performed at the same time as rES OR II. The results of the rES are insufficient to explain the clinical presentation

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Separate CMA testing is considered **not medically necessary** with rWGS analysis.	Separate CMA testing is considered **investigational** with rGS or urGS analysis.