BSC_CON_2.02	Genetic Testing: Exome and Genome Sequencing For The Diagnosis Of Genetic Disorders		
Original Policy Date:	June 1, 2022	**Effective Date:**	July 1, 2024
Section:	2.0 Medicine	**Page:**	Page 1 of 27

Example Test Table

The tests and associated laboratories and CPT codes contained within this document serve only as examples to help users navigate claims and corresponding coverage criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the Concert Genetics Platform for a comprehensive list of registered tests.

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
Standard Exome Sequencing	Genomic Unity Exome Plus Analysis - Proband (Variantyx)	0214U
	Genomic Unity Exome Plus Analysis - Comparator (Duo or Trio) (Variantyx Inc.)	0215U
	XomeDx - Proband (GeneDx)	81415
	Exome - Proband Only (Invitae)	
	XomeDx - Duo (GeneDx)	81415, 81416
	XomeDX - Trio (GeneDx)	
	Exome - Duo (Invitae)	
	Exome - Trio (Invitae)	
Reanalysis of Exome or Genome Sequencing Data	Exome Reanalysis (Ambry)	81417
	Whole Genome Reanalysis (ARUP)	81427
Rapid Exome Sequencing	XomeDxXpress (GeneDx)	81415, 81416
	ExomeNext-Rapid (Ambry)	
	PGxome RAPID Exome Test (PreventionGenetics, part of Exact Sciences)	
	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
	TruGenome Trio (Illumina)	
	Whole Genome Sequencing (PerkinElmer Genomics)	
	MNGenome (MNG Laboratories)	

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
	Praxis Whole Genome Sequencing (Praxis Genomics LLC)	0265U
Rapid Genome Sequencing	Rapid Whole Genome Sequencing (Rady Children's Institute for Genomic Medicine)	0094U
	Rapid Whole Genome Sequencing, Comparator Genome (Rady Children's Institute for Genomic Medicine)	0425U
	Ultra-Rapid Whole Genome Sequencing (Rady Children's Institute for Genomic Medicine)	0426U
	STAT Whole Genome Sequencing (PerkinElmer Genomics)	81425, 81426
	MNGenome STAT (Labcorp/MNG Laboratories)	

Policy Statement

Standard Exome Sequencing

I. Standard exome sequencing (81415, 81416, 0214U, 0215U), with trio testing when possible, may be considered **medically necessary** when **all** of the following criteria are met:
   A. The member has not previously had genome sequencing
   B. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity)
   C. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available
   D. The member's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN)
   E. The member meets at least **one** of the following clinical findings:
      1. The member has unexplained epilepsy diagnosed at any age
      2. The member has global developmental delay or intellectual disability with onset prior to age 18 years
      3. The member was diagnosed with at least one congenital anomaly (functional and/or structural)
      4. The member has at least **TWO** of the following:
         a. Bilateral sensorineural hearing loss of unknown etiology, **OR**
         b. Symptoms of a complex neurological disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, myopathy, muscular dystrophy), **OR**
         c. Family history suggestive of a genetic etiology, including consanguinity, **OR**
         d. Clinical or laboratory findings suggestive of an inborn error of metabolism, **OR**
         e. Autism, **OR**
         f. Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles), **OR**
         g. Period of unexplained developmental regression (unrelated to epilepsy or autism).

II. Repeat standard exome sequencing (81415, 81416, 0214U, 0215U) is considered **investigational**.

III. Standard exome sequencing (81415, 81416, 0214U, 0215U) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

Reanalysis of Exome or Genome Sequencing Data

IV. Reanalysis of exome or genome sequencing data (81417, 81427) may be considered **medically necessary** when*:
   A. The member had exome or genome sequencing at least 18 months ago, **OR**
   B. The member's phenotype has expanded to include clinical findings** that were not present at the time of the initial exome or genome sequencing analysis, **AND**
      1. Results of prior exome or genome sequencing do not explain these new clinical findings.

V. Reanalysis of exome or genome sequencing data (81417, 81427) is considered **investigational** for all other indications.

*If reanalysis of exome data is not possible, see the genome sequencing criteria for additional coverage information.

**See Standard Exome Sequencing or Standard Genome Sequencing criteria for qualifying clinical findings.

Rapid Exome Sequencing

VI. Rapid exome sequencing (81415, 81416), with trio testing when possible, may be considered **medically necessary** when **all** of the following are met:
   A. The member is an acutely-ill infant (12 months of age or younger)
   B. The member has not previously had genome sequencing
   C. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity)
   D. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available
   E. The member's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN)
   F. The member meets at least **one** of the following clinical findings:
      1. The member has unexplained epilepsy
      2. The member has global developmental delay
      3. The member was diagnosed with at least one congenital anomaly (functional and/or structural)
      4. The member has at least **TWO** of the following:
         a. Bilateral sensorineural hearing loss of unknown etiology
         b. Symptoms of a complex neurological disorder (e.g., dystonia, hemiplegia, spasticity, myopathy, muscular dystrophy)
         c. Family history suggestive of a genetic etiology, including consanguinity
         d. Clinical or laboratory findings suggestive of an inborn error of metabolism
         e. Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles)
         f. Period of unexplained developmental regression (unrelated to epilepsy or autism).

VII. Rapid exome sequencing (81415, 81416) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

Standard Genome Sequencing

VIII. Standard genome sequencing (81425, 81426, 0212U, 0213U, 0265U) may be considered **medically necessary** when **all** of the following are met:
   A. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity)
   B. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available

C. The member's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN)
D. The member meets at least **one** of the following clinical findings:
   1. The member previously had uninformative exome sequencing (ES), **AND**
      a. ES reanalysis is not possible
   2. The member has unexplained epilepsy diagnosed at any age
   3. The member has global developmental delay or intellectual disability with onset prior to age 18 years
   4. The member was diagnosed with at least one congenital anomaly (functional and/or structural)
   5. The member has at least **TWO** of the following:
      a. Bilateral sensorineural hearing loss of unknown etiology
      b. Symptoms of a complex neurological disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, myopathy, muscular dystrophy)
      c. Family history suggestive of a genetic etiology, including consanguinity
      d. Clinical or laboratory findings suggestive of an inborn error of metabolism
      e. Autism
      f. Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles)
      g. Period of unexplained developmental regression (unrelated to epilepsy or autism).

IX. Repeat standard genome sequencing (81425, 81426, 0212U, 0213U, 0265U) is considered **investigational**.

X. Standard genome sequencing (81425, 81426, 0212U, 0213U, 0265U) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

Note: When genome sequencing is performed, the mitochondrial genome is assumed to be included as a part of the analysis.

Rapid Genome Sequencing

XI. Rapid genome sequencing (rGS) (81425, 81426, 0094U, 0425U, 0426U), with trio testing when possible, may be considered **medically necessary** when **all** of the following are met:
A. The member is an acutely-ill infant (12 months of age or younger)
B. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity)
C. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available
D. The member's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN)
E. The member meets at least **one** of the following clinical findings:
   1. The member has multiple congenital abnormalities (functional and/or structural) affecting unrelated organ systems
   2. The member has epileptic encephalopathy
   3. The member has at least **TWO** of the following:
      a. Abnormality affecting at least one organ system
      b. Symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia, myopathy, muscular dystrophy, global developmental delay, intellectual disability)
      c. Family history suggestive of a genetic etiology, including consanguinity
      d. Laboratory findings suggestive of an inborn error of metabolism
      e. Abnormal response to standard therapy.

XII. Rapid genome sequencing (rGS) (81425, 81426, 0094U, 0425U, 0426U) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

Note: When genome sequencing is performed, the mitochondrial genome is assumed to be included as a part of the analysis.
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NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Definitions

1. **Exome Sequencing (ES)**: A genomic technique for sequencing all of the protein-coding regions of genes in the genome (also known as the exome).
2. **Genome Sequencing (GS)**: A genomic technique for sequencing the complete DNA sequence, which includes protein coding as well as non-coding DNA elements.
3. **Trio Testing**: Testing of the child and both biological/genetic parents and increases the chances of finding a definitive diagnosis, while reducing false-positive findings.
4. **Comparator Exome Sequencing:** 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 biological/genetic parents to the proband.
5. **Congenital anomalies:** According to ACMG, congenital anomalies 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.
6. **Global Developmental delay:** An individual that is slow-to-meet or not reaching milestones in the expected way for a child's age in at least two of the areas of development (communication, gross/fine motor, cognition, social-emotional, or adaptive skills)
7. **Intellectual disability (ID):** Defined by the DSM-V as:
   a. 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.
   b. 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.
   c. Onset of intellectual and adaptive deficits during the developmental period.
8. **Exome sequencing (ES) reanalysis** may not be possible in some situations. Sequencing platforms may have changed substantially enough that the performing lab can no longer use the data from the original ES in their pipeline. Specifically, ES reanalysis may not be possible if there have been improvements in technology/chemistry (e.g., new methods for DNA capture and/or sequencing), bioinformatics advancements, or there is 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.

Clinical Considerations

Trio testing is preferred whenever possible. Testing of one available parent is a valid alternative if both are not immediately available and one or both parents can be done later if needed. Exome sequencing 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, 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.
If a genetic diagnosis is not found by ES or GS, periodic reanalysis of the previously obtained genomic sequence is recommended. Reevaluation can occur on the variant-level or case-level. Any variants identified and reported prior to the current ACMG variant classification standards should be reevaluated using the current ACMG standards.

Coding
See the Codes table for details.

Description

Exome sequencing (ES) (also known as 'whole exome sequencing (WES)') involves sequencing and 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. GS has been shown to have a higher diagnostic yield compared to ES when used as a first line test. ES reanalysis is often performed approximately 18 months to 2 years following initial, uninformative ES. Studies have shown that the diagnostic yield of ES reanalysis is comparable to performing GS after an uninformative ES.

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.

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 and Molecular 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

State:
SB 496 requires health plans licensed under the Knox-Keene Act ("Plans"), Medi-Cal managed care plans ("MCPS"), and health insurers ("Insurers") to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed. The bill does not require coverage of biomarker testing for screening purposes. Restricted or denied use of biomarker testing for these purposes is subject to state and federal grievance and appeal processes. Where biomarker testing is deemed medically necessary, Plans and Insurers must ensure that the testing is provided in a way that limits disruptions in care.

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), which included the following:

- 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 for patients 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)

Of note, ACMG states that "Isolated autism without ID or congenital malformation is formally out of scope for this recommendation but evaluation of exome/genome studies is ongoing." (p. 2034)

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. (p. 1001)
In their clinical practice resource for the clinical evaluation of hearing loss published in 2022 by Li et al, ACMG states that first-line genetic testing for individuals with exam findings that suggest a syndromic hearing loss etiology may include a variety of tests, including genome sequencing, depending on clinical presentation. For individuals without physical findings that suggest a syndromic hearing loss etiology, they recommend a tiered approach, starting with comprehensive hearing loss gene panel testing unless a more specific genetic etiology is evident for which targeted testing is appropriate. (p. 1400)

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"
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 Services
In the PLUGS July 2023 guidelines entitled "Genomic Sequencing for Rare Disease," the following clinical criteria are recommended, in part, for exome sequencing and genome sequencing.
"Exome sequencing or genome sequencing (ES/GS) is considered medically necessary when ALL of the following criteria are met: …

1. The etiology of the patient's features is not known, and a genetic etiology is considered a likely explanation for the phenotype, based on… the following…
    a. Epilepsy of unexplained etiology with onset at any age, OR
    b. Confirmed bilateral sensorineural hearing loss of unknown etiology and panel testing is unrevealing, OR
    c. Intellectual disability, following formal assessment by a developmental pediatrician or neurologist, defined as moderate/severe/profound by Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, diagnosed by 18 years of age, OR
    d. Global developmental delay, following formal assessment by a developmental pediatrician or neurologist, defined as significant delay in younger children, under age five years, in at least two of the major developmental domains: gross or fine motor; speech and language; cognition; social and personal development; and activities of daily living, OR
    e. Multiple congenital anomalies affecting unrelated organ systems, OR
    f. At least TWO of the following criteria are met:
        i. Abnormality affecting at minimum a single organ system
        ii. Autism
        iii. Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles)
        iv. Symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, hypotonia, myopathy, muscular dystrophy)

   v. Family history strongly suggestive of a genetic etiology, including consanguinity
   vi. Period of unexplained developmental regression (unrelated to epilepsy or autism)
   vii. Laboratory findings suggestive of an inherited metabolic disorder
2. Alternate etiologies have been considered and ruled out, when possible (e.g., MRI abnormalities/brain malformations, environmental exposure, injury, infection, isolated prematurity), AND
3. Clinical presentation does not fit a well-described syndrome for which more targeted testing is available." (p. 7)

Rehm et al (2023)
Traditional genetic testing strategies have included single gene analysis or multi-gene panels as a first line test, which may still be the most appropriate test for a patient. However, there is increasing evidence that exome or genome sequencing may be more elucidating options. A 2023 paper by Rehm et al on behalf of the Medical Genome Initiative, which analyzed the rate of variants of uncertain significance (VUS) in 1,463,812 multigene panels, 42,165 exome sequencing tests, and 6,329 genome sequencing tests across 19 North American clinical laboratories, demonstrated that exome and genome sequencing had a significantly lower VUS rate (22.5%) compared to multigene panels (32.6%). (p. 5 and 6)

Belanger, et al
A review of the evaluation of children with global developmental delay and intellectual disability by Belanger et al (2018) defines global developmental delay (GDD) as the following:

- Significant delay (at least 2 standard deviations below the mean) in at least two developmental domains (gross or fine motor, speech/language, cognition, social/personal or activities of daily living. (p. 404)

Reanalysis of Exome or Genome Sequencing Data
Tan, et al
A study from 2020 examined data from 58 unsolved cases referred for any indication to evaluate the systematic reanalysis of singleton exome sequencing (ES). The authors performed a reanalysis at multiple timepoints following initial testing, and ultimately suggest that an interval of greater than 18 months from the original report may be optimal for reanalysis. (p. 1)

Alfares, et al.
This study from 2018 compared the detection rates of whole-exome sequencing (WES) and whole-genome sequencing (WGS) in a clinical setting. The study included 108 patients with negative array CGH and negative or inconclusive WES results. WGS was performed on all patients, and the results of the study showed that 30% of the positive cases identified by WGS could be identified by reanalyzing WES raw data, and WGS achieved an only 7% higher detection rate. (p. 1328) The paper concluded that, although WGS is a more powerful tool than WES, in this study, "we showed that WGS has additional, but limited, clinical utility compared with reanalyzing WES data, and until the cost of WGS approximates that of WES, reanalyzing WES raw data is recommended before performing WGS." (p. 1333)

American College of Medical Genetics
A statement from ACMG (Deignan, 2019) included considerations for case-level exome re-analysis, which include the following:

- Significant improvements have been made to bioinformatics handling of the data (alignment/variant calling and/or the automated filtering processes)
- Updated clinical and family history information, which may result in the identification of additional variants that are associated with the indication(s) for testing. (p. 1269)

Patient-Centered Laboratory Utilization Guidance Services
The PLUGS July 2023 guidelines entitled "Genomic Sequencing for Rare Disease" state the following regarding reanalysis of exome or genome sequencing data: "Periodic reanalysis of previously obtained exome or genome sequence has the potential for additional diagnostic yield because of expanding variant databases, as well as periodic novel gene discovery and publication. A review of twenty-seven peer-reviewed articles revealed a median new diagnosis rate via reanalysis of 15% and median reanalysis timeframe of 22 months. The authors suggest that an interval of greater than 18 months from the original report may be optimal for reanalysis." (p. 3)

The guidelines also state: "Re-analysis of previously obtained exome or genome sequence has the potential for additional diagnostic yield because of expanding variant databases, as well as periodic novel gene discovery and publication. Re-analysis could be considered prior to additional genomic sequencing, particularly if there has been onset or identification of additional symptoms that broadens the clinical phenotype assessed during the original ES/GS analysis…" (p. 8)

Rapid 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), which included the following:

- 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 for patients with intellectual disability/developmental delay before the age of 18. (p. 2031)
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In their clinical practice resource for the clinical evaluation of hearing loss published in 2022 by Li et al, ACMG states that first-line genetic testing for individuals with exam findings that suggest a syndromic hearing loss etiology may include a variety of tests, including genome sequencing, depending on clinical presentation. For individuals without physical findings that suggest a syndromic hearing loss etiology, they recommend a tiered approach, starting with comprehensive hearing loss gene panel testing unless a more specific genetic etiology is evident for which targeted testing is appropriate. (p. 1400)

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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:
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    b. Confirmed bilateral sensorineural hearing loss of unknown etiology and panel testing is unrevealing, OR
    c. Intellectual disability, following formal assessment by a developmental pediatrician or neurologist, defined as moderate/severe/profound by Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, diagnosed by 18 years of age, OR
    d. Global developmental delay, following formal assessment by a developmental pediatrician or neurologist, defined as significant delay in younger children, under age five years, in at least two of the major developmental domains: gross or fine motor; speech and language; cognition; social and personal development; and activities of daily living, OR
    e. Multiple congenital anomalies affecting unrelated organ systems, OR
    f. At least TWO of the following criteria are met:
        i. Abnormality affecting at minimum a single organ system
        ii. Autism
        iii. Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles)
        iv. Symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, hypotonia, myopathy, muscular dystrophy)
        v. Family history strongly suggestive of a genetic etiology, including consanguinity
        vi. Period of unexplained developmental regression (unrelated to epilepsy or autism)
        vii. Laboratory findings suggestive of an inherited metabolic disorder
2. Alternate etiologies have been considered and ruled out, when possible (e.g., MRI abnormalities/brain malformations, environmental exposure, injury, infection, isolated prematurity), AND
3. Clinical presentation does not fit a well-described syndrome for which more targeted testing is available." (p. 7)

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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)

Belanger, et al
A review of the evaluation of children with global developmental delay and intellectual disability by Belanger et al (2018) defines global developmental delay (GDD) as the following:

- Significant delay (at least 2 standard deviations below the mean) in at least two developmental domains (gross or fine motor, speech/language, cognition, social/personal or activities of daily living. (p. 404)

Standard Genome 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), which included the following:

- 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 for patients 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)

Of note, ACMG states that "Isolated autism without ID or congenital malformation is formally out of scope for this recommendation but evaluation of exome/genome studies is ongoing." (p. 2034)
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. (p. 1001)

In their clinical practice resource for the clinical evaluation of hearing loss published in 2022 by Li et al, ACMG states that first-line genetic testing for individuals with exam findings that suggest a syndromic hearing loss etiology may include a variety of tests, including genome sequencing, depending on clinical presentation. For individuals without physical findings that suggest a syndromic hearing loss etiology, they recommend a tiered approach, starting with comprehensive hearing loss gene panel testing unless a more specific genetic etiology is evident for which targeted testing is appropriate. (p. 1400)

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."

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 Services
In the PLUGS July 2023 guidelines entitled "Genomic Sequencing for Rare Disease," the following clinical criteria are recommended, in part, for exome sequencing and genome sequencing.
"Exome sequencing or genome sequencing (ES/GS) is considered medically necessary when ALL of the following criteria are met:

1. The etiology of the patient's features is not known, and a genetic etiology is considered a likely explanation for the phenotype, based on… the following…
    a. Epilepsy of unexplained etiology with onset at any age, OR
    b. Confirmed bilateral sensorineural hearing loss of unknown etiology and panel testing is unrevealing, OR
    c. Intellectual disability, following formal assessment by a developmental pediatrician or neurologist, defined as moderate/severe/profound by Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, diagnosed by 18 years of age, OR
    d. Global developmental delay, following formal assessment by a developmental pediatrician or neurologist, defined as significant delay in younger children, under age five years, in at least two of the major developmental domains: gross or fine motor; speech and language; cognition; social and personal development; and activities of daily living, OR
    e. Multiple congenital anomalies affecting unrelated organ systems, OR
    f. At least TWO of the following criteria are met:
        i. Abnormality affecting at minimum a single organ system
        ii. Autism
        iii. Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles)
        iv. Symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, hypotonia, myopathy, muscular dystrophy)
        v. Family history strongly suggestive of a genetic etiology, including consanguinity
        vi. Period of unexplained developmental regression (unrelated to epilepsy or autism)
        vii. Laboratory findings suggestive of an inherited metabolic disorder
2. Alternate etiologies have been considered and ruled out, when possible (e.g., MRI abnormalities/brain malformations, environmental exposure, injury, infection, isolated prematurity), AND
3. Clinical presentation does not fit a well-described syndrome for which more targeted testing is available." (p. 7)

Rehm et al (2023)
Traditional genetic testing strategies have included single gene analysis or multi-gene panels as a first line test, which may still be the most appropriate test for a patient. However, there is increasing evidence that exome or genome sequencing may be more elucidating options. A 2023 paper by Rehm et al on behalf of the Medical Genome Initiative, which analyzed the rate of variants of uncertain significance (VUS) in 1,463,812 multigene panels, 42,165 exome sequencing tests, and 6,329 genome sequencing tests across 19 North American clinical laboratories, demonstrated that exome and genome sequencing had a significantly lower VUS rate (22.5%) compared to multigene panels (32.6%). (p. 5 and 6)

Belanger, et al
A review of the evaluation of children with global developmental delay and intellectual disability by Belanger et al (2018) defines global developmental delay (GDD) as the following:

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Rapid Genome Sequencing
Patient-Centered Laboratory Utilization Guidance Services
In the PLUGS June 2022 guidelines entitled "Rapid Genome Sequencing," the following clinical criteria are recommended for coverage for "acutely-ill individuals" who meet "ALL of the following criteria":
"1. The etiology of the patient's features is not known and a genetic etiology is considered a likely explanation for the phenotype, based on one of the following
a) Multiple congenital abnormalities affecting unrelated organ systems, OR
b) Epileptic encephalopathy, OR
c) TWO of the following criteria are met:

- abnormality affecting at minimum a single organ system
- symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia, myopathy, muscular dystrophy, global developmental delay, intellectual disability)
- family history strongly suggestive of a genetic etiology, including consanguinity
- laboratory findings suggestive of an inborn error of metabolism
- abnormal response to standard therapy

2. Alternate etiologies have been considered and ruled out when possible (e.g., MRI abnormalities/brain malformations, environmental exposure, injury, infection, isolated prematurity), AND
3. rGS 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)…" (p. 3 and 4)

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."

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- 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.

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)

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Documentation for Clinical Review

Please provide the following documentation:

- Name of the test being requested or the Concert Genetics GTU identifier.
  The Concert Genetics GTU can be found at https://app.concertgenetics.com
- CPT codes to be billed for the particular genetic test (GTU required for unlisted codes)
- History and physical and/or consultation notes including:
  - Clinical findings:
    - Signs/symptoms leading to a suspicion of genetic condition
    - Family history if applicable
  - Prior evaluation/treatment:
    - Previous test results (i.e., imagining, lab work, etc.) related to reason for genetic testing
    - Family member's genetic test result, if applicable
  - Rationale
    - Reason for performing test
    - How test result will impact clinical decision making

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

- Results/reports of tests performed

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
	0213U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence

Type	Code	Description
		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.
07/01/2024	Annual review. Policy statement, guidelines and literature updated.

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	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
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	**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, 0214U, 0215U), with trio testing when possible, may be considered **medically necessary** when **all** of the following criteria are met: A. The member has not previously had genome sequencing B. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity) C. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available D. The member's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN) E. The member meets at least **one** of the following clinical findings: 1. The member has unexplained epilepsy diagnosed at any age 2. The member has global developmental delay or intellectual disability with onset prior to age 18 years 3. The member was diagnosed with at least one congenital anomaly (functional and/or structural) 4. The member has at least **TWO** of the following: a. Bilateral sensorineural hearing loss of unknown etiology, **OR** b. Symptoms of a complex neurological disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, myopathy, muscular dystrophy), **OR** c. Family history suggestive of a genetic etiology, including consanguinity, **OR**

POLICY STATEMENT	
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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.	d. Clinical or laboratory findings suggestive of an inborn error of metabolism, **OR** e. Autism, **OR** f. Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles), **OR** g. Period of unexplained developmental regression (unrelated to epilepsy or autism).

POLICY STATEMENT	
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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. back to top	II. Repeat standard exome sequencing (81415, 81416, 0214U, 0215U) is considered **investigational**. III. Standard exome sequencing (81415, 81416, 0214U, 0215U) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders. back to top **Reanalysis Of Exome Or Genome Sequencing Data** IV. Reanalysis of exome or genome sequencing data (81417, 81427) may be considered **medically necessary** when*: C. The member had exome or genome sequencing at least 18 months ago, **OR** D. The member's phenotype has expanded to include clinical findings** that were not present at the time of the initial exome or genome sequencing analysis, **AND** 1. Results of prior exome or genome sequencing do not explain these new clinical findings. V. Reanalysis of exome or genome sequencing data (81417, 81427) is considered **investigational** for all other indications. *If reanalysis of exome data is not possible, see the genome sequencing criteria for additional coverage information. **See Standard Exome Sequencing or Standard Genome Sequencing criteria for qualifying clinical findings. back to top

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
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	**Rapid Exome Sequencing** VI. Rapid exome sequencing (81415, 81416), with trio testing when possible, may be considered **medically necessary** when **all** of the following are met: A. The member is an acutely-ill infant (12 months of age or younger) B. The member has not previously had genome sequencing C. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity) D. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available E. The member's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN) F. The member meets at least **one** of the following clinical findings: 1. The member has unexplained epilepsy 2. The member has global developmental delay 3. The member was diagnosed with at least one congenital anomaly (functional and/or structural) 4. The member has at least **TWO** of the following: a. Bilateral sensorineural hearing loss of unknown etiology b. Symptoms of a complex neurological disorder (e.g., dystonia, hemiplegia, spasticity, myopathy, muscular dystrophy) c. Family history suggestive of a genetic etiology, including consanguinity d. Clinical or laboratory findings suggestive of an inborn error of metabolism e. Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles) f. Period of unexplained developmental regression (unrelated to epilepsy or autism).

POLICY STATEMENT	
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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.	VII. Rapid exome sequencing (81415, 81416) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders. back to top

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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. back to top	**Standard Genome Sequencing** VIII. Standard genome sequencing (81425, 81426, 0212U, 0213U, 0265U) may be considered **medically necessary** when **all** of the following are met: A. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity) B. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available C. The member's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN) D. The member meets at least **one** of the following clinical findings: 1. The member previously had uninformative exome sequencing (ES), **AND** a. ES reanalysis is not possible 2. The member has unexplained epilepsy diagnosed at any age 3. The member has global developmental delay or intellectual disability with onset prior to age 18 years 4. The member was diagnosed with at least one congenital anomaly (functional and/or structural) 5. The member has at least **TWO** of the following: a. Bilateral sensorineural hearing loss of unknown etiology b. Symptoms of a complex neurological disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, myopathy, muscular dystrophy) c. Family history suggestive of a genetic etiology, including consanguinity d. Clinical or laboratory findings suggestive of an inborn error of metabolism e. Autism

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	f. Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles) g. Period of unexplained developmental regression (unrelated to epilepsy or autism). IX. Repeat standard genome sequencing (81425, 81426, 0212U, 0213U, 0265U) is considered **investigational**. X. Standard genome sequencing (81425, 81426, 0212U, 0213U, 0265U) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders. **Note**: When genome sequencing is performed, the mitochondrial genome is assumed to be included as a part of the analysis. back to top **Rapid Genome Sequencing** XI. Rapid genome sequencing (rGS) (81425, 81426, 0094U, 0425U, 0426U), with trio testing when possible, may be considered **medically necessary** when **all** of the following are met: A. The member is an acutely-ill infant (12 months of age or younger) B. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity) C. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available D. The member's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN) E. The member meets at least **one** of the following clinical findings:

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	1. The member has multiple congenital abnormalities (functional and/or structural) affecting unrelated organ systems 2. The member has epileptic encephalopathy 3. The member has at least **TWO** of the following: a. Abnormality affecting at least one organ system b. Symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia, myopathy, muscular dystrophy, global developmental delay, intellectual disability) c. Family history suggestive of a genetic etiology, including consanguinity d. Laboratory findings suggestive of an inborn error of metabolism e. Abnormal response to standard therapy. XII. Rapid genome sequencing (rGS) (81425, 81426, 0094U, 0425U, 0426U) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders. **Note**: When genome sequencing is performed, the mitochondrial genome is assumed to be included as a part of the analysis.