Exome and Genome Sequencing for Rare Disease

Executive Summary:

This medical coverage policy focuses on the use of genomic sequencing, specifically exome sequencing (ES) and genome sequencing (GS), for individuals with rare genetic conditions. Rare diseases affect approximately 1 in 10 Americans, and many of these conditions have genetic origins. ES/GS are powerful diagnostic tools for individuals with rare genetic conditions, offering higher diagnostic yields, improved clinical management, and potential cost savings. ES/GS is considered medically necessary for individuals who meet specific criteria, including when the underlying genetic cause is unknown and other possible causes have been ruled out. ES/GS can provide valuable information for people with various conditions, such as birth defects, developmental disorders, seizures (epilepsy), hearing loss, and inherited metabolic disorders. GS is preferred over ES due to its technical advantages. Including samples from the individual and both parents (i.e., trio testing) can increase the chance of reaching a diagnosis. The policy emphasizes the importance of pre- and post-test counseling by certified genetic counselors.

Criteria:

Exome Sequencing or 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 ONE of the following, AND
   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 (functional and/or structural) affecting unrelated organ systems, OR
   f) Findings suggestive of inborn error of immunity (e.g., infections requiring hospitalizations and/or IV antibiotics)
   g) At least TWO of the following criteria are met, OR
      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, cerebral palsy)
      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., environmental exposure, injury, infection, isolated prematurity), AND
3) Clinical presentation does not fit a well-described syndrome for which more targeted testing is available.

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Other Considerations:

- While ES and GS are similar diagnostic tools in the evaluation of individuals with rare disease, there are clear technical advantages of GS that support increased diagnostic yield and efficiencies. As such, if given a choice, GS is the preferred diagnostic test in individuals who meet the above criteria.
- GS is preferred when a mitochondrial disorder is suspected, due to analysis of both the nuclear and mitochondrial genome.
- ES/GS is appropriate as a first-tier genetic test instead of CMA or targeted testing for individuals with epilepsy, congenital anomalies, and/or ID/GDD based on clinical practice guidelines and peer-reviewed evidence. ES/GS may also be an appropriate first-tier test for other indications based on clinician judgement and current clinical practice.
- Pre- and post-test counseling by an appropriate provider, such as an American Board of Medical Genetics and Genomics or American Board of Genetic Counseling-certified Genetic Counselor, is strongly recommended.
- The patient and the patient's family history have been evaluated by a board-certified/board-eligible specialist with expertise in the conditions and genes for which testing is being considered, such as a geneticist, neurologist, developmental pediatrician, or immunologist. Restricting the policy to a geneticist-only requirement creates significant access barriers.
- Trio samples are preferred for ES/GS. Use of family trio samples in genomic sequencing analysis helps reduce the time to diagnosis, the rate of uncertain findings, and improves the clinical sensitivity and efficiency regarding the interpretation of clinically novel genes, and increases the diagnostic yield of ES/GS
- 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 an onset or identification of additional symptoms that broadens the clinical phenotype assessed during the original ES/GS analysis, and/or there has been a change in the family history that expands the clinical picture, such as the birth or diagnosis of a similarly affected first-degree relative.
- ES/GS in the setting of prenatal genetic diagnosis or screening is not addressed in this policy.
- Ideal sample type should be considered based on the clinical presentation (e.g., mosaicism is suspected based on pigmentary anomalies, consider skin fibroblast as ideal sample type).
- Rapid genome sequencing (rGS), defined as return of preliminary positive results in <7 days and final report in <14 days, may be indicated for acutely ill individuals. Criteria for rGS testing can be found in the Rapid Genome Sequencing Policy.

Background:

Approximately 1 in 10 Americans, an estimated 30 million individuals, are affected by rare disease. It is estimated that 71.9% of rare diseases have identified genetic origins.[1] The average time to get an accurate diagnosis is approximately 4 to 5 years, but may take over 10 years.[2] The diagnostic evaluation of an individual suspected of having a rare genetic condition may include combinations of radiographic, biochemical, electrophysiologic, and genetic testing. Genetic testing strategies include targeted approaches, such as single-gene analysis, and/or a targeted gene panel, chromosomal microarrays, as well as broad genomic sequencing, including exome sequencing (ES) and genome sequencing (GS). ES/GS are particularly useful for evaluating genetic conditions that demonstrate a high degree of genetic heterogeneity. When compared to serial genetic testing strategies, ES/GS are superior due to broader coverage, reduced cost and improved efficiencies.[3-9]

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Identifying a molecularly confirmed diagnosis in a timely manner for an individual with a rare genetic condition can have a variety of health outcomes including but not limited to:[10-16]

- guiding prognosis and improving clinical decision-making via
    - application of specific treatments, as well as withholding of contraindicated treatments for certain rare genetic conditions
    - planning or avoidance of surgical interventions
    - surveillance for comorbidities
    - initiation of palliative care
    - withdrawal of care
- reducing the psychological and financial impact of diagnostic uncertainty and the diagnostic odyssey (e.g., eliminating lower yield testing and additional screening testing that may later be proven unnecessary once a diagnosis is achieved)
- informing genetic counseling for other living relatives (i.e., siblings), as well as recurrence risk counseling and prenatal diagnosis options for the family

Technical Information:

Genomic sequencing technologies currently utilized in clinical practice include exome sequencing and genome sequencing. ES and GS are similar diagnostic tools in the evaluation of individuals with rare disease, but there are clear technical advantages of GS that support increased diagnostic yield and efficiencies as outlined below. As such, GS will likely supplant ES to become the preferred diagnostic test, particularly as access to GS increases.[2]

Exome sequencing (ES) is a capture-based method that targets the DNA sequence of coding regions (exons) and flanking intronic regions of 1% of the genome. ES is associated with technical and analytical variability, including uneven sequencing coverage and gaps in exon capture before sequencing. In contrast, genome sequencing (GS) involves shearing and sequencing all intergenic and intragenic regions, eliminating the need for a capture step, which increases efficiency and minimizes PCR-based artifacts. Both ES and GS can identify the following categories of pathogenic variants: missense, nonsense, splice-site, and small deletions or insertions. GS is advantageous as a diagnostic tool due to uniformity of coverage, including GC-rich regions, as well as the ability to detect variants that may be missed by ES, such as some copy-number variants (CNV), mid-size insertions and deletions (ca. 10-500 bp), nucleotide repeat expansion mutations, deeper intronic mutations, structural variants (e.g., translocations, inversions), variants in the mitochondrial genome, and variants that result in methylation defects and uniparental disomy.[17-21]

Several studies have compared ES to GS and demonstrate improved diagnostic yield with GS. Lionel et al examined a cohort of participants (N=70) who received both GS and ES.[6] In this cohort, GS had a diagnostic yield of 50% compared to 37% for ES. GS detected all diagnostic variants found by ES in addition to revealing several diagnostic variants not apparent in ES data. Examples of variants “missed” by ES included deep intronic SNVs, small CNVs, and SNVs in noncoding RNA.

In addition, GS has shown incremental diagnostic yield in individuals with non-diagnostic ES. In a cohort of heavily pre-investigated patients, GS was able to provide a diagnosis in 13% of patients in whom ES results were inconclusive.[22] Another study of 50 patients with severe intellectual disability and non-diagnostic CMA ES demonstrated that GS had a diagnostic yield of 42%.[17] Bertoli-Avella et al showed that up to 29.6% of ES negative cases could benefit from GS testing (14.5% with pathogenic or likely pathogenic results, and 15.1% with VUS).[23] The majority of genetic diagnoses made by GS in ES negative cases could be attributed to its superior technical performance; GS detected 79 noncoding variants, 41 of which were classified as pathogenic/likely

pathogenic. The diagnostic yield of GS in a cohort of 822 families who had previously undergone genetic testing was 8%, including several types of pathogenic variants that were undetectable by previous ES and other techniques.[24]

The use of family trio samples in genomic sequencing analysis helps reduces the time to diagnosis, the rate of uncertain findings, and improves the clinical sensitivity and efficiency with regard to the interpretation of clinically novel genes, and increases the diagnostic yield of ES/GS.[25] As part of a meta-analysis, five studies that conducted within-cohort comparisons of diagnostic utility of singleton and trio ES/GS found the pooled odds of diagnosis for trios was twice that of singletons (P<0.0001).[26]

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.[20,27-29] 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.[29] The authors suggest that an interval of greater than 18 months from the original report may be optimal for reanalysis. The majority of new diagnoses from re-analysis of ES result from newly discovered genes, with additional diagnostic yield from expanded phenotypic spectrum and upgraded classification of variants in previously known genes.[30] Reanalysis can be improved by thorough clinical reassessment and systematic reevaluation of the patient by the ordering provider.[31]

Guidelines and Evidence:

The American College of Medical Genetics and Genomics (ACMG) has several relevant policy statements that offer guidance on: the clinical application of ES/GS,[9,32] informed consent for ES/GS,[33] technical standards to ensure quality results and the interpretation and reporting of variants,[34] reporting of secondary findings in clinical ES/GS,[35,36] and re-analysis.[37]

A statement from the ACMG includes the following indications for diagnostic testing using ES/GS in assessment of phenotypically affected individuals when:[32]

> "a. 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 targeting a specific gene is available on a clinical basis."
> "b. 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."
> "c. A patient presents with a likely genetic disorder, but specific genetic tests available for that phenotype have failed to arrive at a diagnosis."
> "d. 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."

The ACMG issued an evidence-based clinical practice guideline for the use of exome sequencing and genome sequencing (ES/GS) in 2021.[9] The guideline supports the clinical utility of ES/GS as a first- or second-tier test for individuals with one or more congenital anomalies with onset prior to age 1 year, or developmental delay, or intellectual disability with onset prior to 18 years. ES/GS has a higher diagnostic yield compared with standard genetic testing and may be more cost-effective when ordered earlier in the diagnostic evaluation.

In 2021, the ACMG Secondary Findings Working Group published an updated policy statement with recommendations for reporting of secondary findings in clinical ES and GS.[35] This policy statement provides guidance on consenting, scope of secondary finding reporting based on test type, and proposes a framework for

annual updates to the secondary findings list. The goal of the secondary findings gene list is to provide updated guidance to clinical laboratories on which medically actionable genes unrelated to the indication for testing should be evaluated as part of clinical ES/GS.[36] Included in this list are several genes associated with heritable cardiovascular disease. The American Heart Association published a consensus statement to guide clinicians regarding counseling for incidentally identified genetic variants in monogenic cardiovascular disease genes and to assist them in the interpretation and clinical application of variants.[38]

Recommendations for obtaining informed consent for clinical ES/GS, including secondary findings, have also been outlined by the ACMG.[33] A medical geneticist or genetic counselor should perform pre-test counseling and consent documentation.

The ACMG Laboratory Quality Assurance Committee issued points to consider in the reevaluation and reanalysis of genomic test results,[37] including general considerations, considerations for variant-level reevaluation and case-level reanalysis, and reporting. This statement also suggests considerations for reanalysis versus retesting using new methodologies, including:

- Time elapsed since the previous testing occurred
- Improvements in technology/chemistry (e.g., new methods for DNA capture and sequencing)
- Bioinformatics advancements
- New information regarding the genetic etiology of a condition
- Additional patient phenotypes or family history that developed in the interim

ES/GS are powerful diagnostic tools for individuals with rare genetic conditions in which the specific genetic etiology is unclear or unidentified by standard clinical evaluation. While the diagnostic yield of ES/GS varies depending upon the individual's age, phenotype, previous workup, and inclusion of comparators, the efficacy is well established. Further, the diagnostic yield of ES/GS is higher when used earlier in the diagnostic work-up.[39] A review of publications from 2009-2017 revealed median diagnostic yield of ES/GS in aggregate analyses was 33.2%, but varied by broad clinical categories and test type.[12] The 100,000 Genomes Project demonstrated that GS had an overall diagnostic yield of 25% in 2183 probands—many of whom were heavily pre-tested.[40] Notably, diagnostic yields for intellectual disability, hearing disorders, and vision disorders ranged from 40 to 55%; diagnostic yield for individuals with dysmorphic or congenital anomalies was 21%. Based on the results, the National Health Service implemented GS as the first-tier test for 25+ different clinical conditions. Use of GS/ES also reveals dual molecular diagnoses that contribute to complex phenotypes (i.e., two significant findings associated with non-overlapping clinical presentations).[10]

Evidence for the clinical utility of ES/GS in individuals suspected of having rare genetic disease includes numerous retrospective and prospective case series, and randomized controlled trials. Relevant outcomes include improved clinical decision-making (e.g., initiation of specific treatments, withholding of contraindicated treatments, changes to surveillance, changes in reproductive decision making, and resource utilization.[22,41,42] An impact on medical management has been clearly demonstrated in both rapid ES/GS and non-rapid ES/GS cohorts.

A meta-analysis of relevant articles published between 2011 and 2021 compared the diagnostic rate and clinical utility of ES and GS across pediatric and adult populations, as well as the number of variants of uncertain significance (VUS) and health economic outcomes associated with these technologies.[43] Based on nine studies that compared ES and GS within the cohorts, the odds of a diagnosis by GS was 1.2 times greater than that of ES. Pooled clinical utility of GS (61%) was higher than that of ES (48%) and the rate of VUS by ES and GS did not differ significantly.

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ES/GS has been shown to positively impact healthcare utilization through cost-savings compared to serial genetic testing strategies.[7,29,39] Several health economic studies have been published that demonstrate that GS is the most efficient approach to the diagnosis of children with rare and undiagnosed genetic conditions compared to previous standard of care.[7,43,44] If GS is unavailable, ES represents the next most efficient option compared with standard of care. Other strategies provided the same or fewer diagnoses at a higher incremental cost per diagnosis.

Genetic counselors play a critical role in guiding testing strategy and assessing the utility of genetic testing in individuals with rare disease, as well as supporting informed consent. Practice guidelines outline the role of genetic counselors in consent and result disclosure/interpretation for ES/GS.[33] Genetic counselors are trained to assess appropriate testing strategies and prevent order errors.[45,46] Genetic counselors can bridge access gap between medical geneticists and other specialists, ensuring appropriate utilization of genomic sequencing in individuals with rare disease.[45,46]

Congenital Anomalies

Many congenital anomalies have an underlying genetic etiology, and may occur in isolation, or in conjunction with other features. ES/GS have demonstrated diagnostic utility in individuals with multiple congenital anomalies, particularly when ordered early in the diagnostic evaluation.[39,41] The ACMG evidence-based clinical practice guideline supports the use of ES/GS as a first- or second-tier test for individuals with one or more congenital anomalies with onset prior to age 1 year.[9] Clinical utility includes short-term active clinical management changes (modifications to medications, procedures, or treatment) and long-term clinical management (referral to specialists and surveillance for disease-related conditions, or lifestyle changes).

Neurodevelopmental Disorders

Neurodevelopmental disorders, including global developmental delay, intellectual disability, and/or autism spectrum disorder, are a heterogeneous group of conditions that impact brain development and affect various aspects of daily functioning. A meta-analysis investigating the diagnostic yield of ES in neurodevelopmental disorders (NDD) showed that ES outperformed chromosomal microarray, with an overall diagnostic yield of 36% (31% for isolated NDD, and 53% for NDD plus associated conditions).[47] In another study of 100 individuals with intellectual disability, use of GS as a first-line genetic test yielded a diagnostic rate of 27%, more than doubled compared to clinical microarray (12%), including identification of structural variants, single nucleotide variants, uniparental disomy, and short tandem repeats.[48] The ACMG evidence-based clinical practice guideline supports the use of ES/GS as a first- or second-tier test for individuals with developmental delay (DD) or intellectual disability (ID) with onset prior to age 18 years.[9] Isolated autism without ID or congenital malformation was formally out of scope for the practice guideline, but evaluation of ES/GS in this population is ongoing.[49]

Cerebral Palsy

Another neurodevelopmental disorder, cerebral palsy (CP), is a group of disorders impacting the ability to move and maintain balance.[50,51] Historically cerebral palsy has been attributed to birth related issues, such as asphyxia and birth trauma, however, more recently a substantial portion of individuals with CP have been identified to have an underlying genetic condition in one of the ~300 genes currently associated with CP.[50,52,53] Genomic sequencing studies have demonstrated a diagnostic yield of about 20-35% in individuals with known or suspected CP. [50-54] This yield is similar to other neurodevelopmental disorders in which guidelines or consensus statements recommend genomic sequencing.[9,47] Additionally, for individuals with CP and an identified genetic diagnosis 37-93% have a clinical impact including medication intervention, medical surveillance, and reproductive management.[50,51]

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Epilepsy

Epilepsy is a neurological disorder that causes recurrent, unprovoked seizures. While the cause of epilepsy is unknown in approximately 50% of cases, it can be caused by genetic factors, head trauma, structural brain abnormalities, stroke, infections, autoimmune conditions, metabolic conditions, tumors, or prenatal injury.[55] It is estimated that 30% of all epilepsies have a genetic cause.[56] A genetic diagnosis changed treatment in 12-80% of epilepsy patients including optimal anti-seizure medication, dietary treatment, and epilepsy surgical decisions.[57] A genetic diagnosis also informs recurrence risk estimations used in family planning. A practice guideline on genetic testing for epilepsy was published in 2022, adopted by the National Society of Genetic Counselors (NSGC), and endorsed by the American Epilepsy Society (AES).[58] The guideline recommends genetic testing for individuals of any age with unexplained epilepsy to include exome/genome sequencing and/or a multi-gene panel (>25 genes) as first-tier testing followed by chromosomal microarray, with exome/genome sequencing conditionally recommended over multi-gene panel. More information can be found in the Epilepsy Genetic Testing policy.

Hearing Loss

The ACMG Professional Practice Guidelines Committee presented updated recommendations for the evaluation and etiological diagnosis of hearing loss.[59] Hearing loss is genetically heterogeneous, supporting the value of panels and ES/GS in the diagnostic evaluation. Identifying the etiology of hearing loss may affect clinical management, particularly for syndromic hearing loss, improve prognostic accuracy, and guide recurrence risk counseling. The guideline includes an updated algorithm (Figure 1) that integrates pre-test genetic counseling and initial testing using single-gene tests and comprehensive hearing loss gene panels, as well as congenital CMV testing using newborn bloodspots. If the initial testing is unrevealing, ES/GS can be considered.

Inherited Metabolic Disorders

Inherited metabolic disorders (IMDs) are rare genetic or inherited disorders resulting from an enzyme defect in biochemical and metabolic pathways affecting metabolism of proteins, fats, or carbohydrates or impaired organelle function.[60] IMDs can have complex clinical presentations and often impact multiple organ systems. Diagnosis typically involves a complex combination of biochemical and molecular analyses. Age of presentation can vary, with more severe forms appearing in early childhood accompanied by significant morbidity and mortality. Appropriate acute illness protocols and specific supportive therapies are necessary for individuals diagnosed with an IMD. Mitochondrial diseases are a subset of IDMs, with clinical and genetic heterogeneity that present diagnostic, clinical management, and therapeutic challenges. [60] Pathogenic variants in nuclear-encoded genes account for most pediatric mitochondrial disease (70-80%) with 20-25% of cases due to pathogenic variants in the mitochondrial genome. Mitochondrial genome variants are more frequently responsible for mitochondrial disease in adults (75%).[61] GS is advantageous in the diagnostic work-up of mitochondrial disease because of coverage of both the nuclear and mitochondrial genomes in a single test, and ability to detect heteroplasmy levels as low as 1%. GS identified both mitochondrial and non-mitochondrial diagnoses in individuals with suspected mitochondrial disorders, preventing the need for invasive tests such as a muscle biopsy.[61,62]

Inborn errors of immunity

Inborn errors of immunity (IEI), which include Primary Immunodeficiencies (PIDs) and Primary Immune Regulatory Disorders (PIRDs), are a diverse group of disorders caused by defects in the immune system resulting in increased susceptibility to infections, autoimmunity, autoinflammatory diseases, allergies, and malignancies.[63,64] Over 500 different disorders have been described due to defects in >500 different genes.[65] The

clinical variability and symptom overlap of IEIs makes diagnosis based on phenotype challenging as illustrated by data demonstrating in up to 75% of patients, their clinical characteristics alone do not allow for identification of the correct diagnosis.[66-68] If not properly diagnosed, individuals with IEIs are subject to serious, prolonged, sometimes life-threatening infections or autoimmunity.[69,70] The Clinical Immunology Society recommends genetic testing for diagnosis and precision treatment.[70] Exome sequencing studies have demonstrated a diagnostic yield of about 40%, which varies based on different factors including disease subtypes.[71,72] While an accurate diagnosis is essential for appropriate management, identifying the underlying genetic cause is also important to inform prognosis and treatment decisions such as consideration and/or performance of bone marrow or thymus transplantation, enzyme replacement therapy, biologic supportive therapy, and IgG replacement.[70,73,74]

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CPT Codes:

Procedure(s) addressed by this policy:	Procedure Code(s)
Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis	81415
Sequence analysis, each comparator exome (e.g., parent(s), sibling(s))	81416
Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis	81425
Sequence analysis, each comparator genome (e.g., parent(s), sibling(s))	81426
Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis (e.g., RCIGM Rapid Whole Genome Sequencing; Rady Children's Institute for Genomic Medicine)	0094U
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	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, each comparator genome (e.g., parent, sibling)	0213U
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	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, each comparator exome (e.g., parent, sibling)	0215U

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Update details:

2024-25: Expanded inclusion criteria to include cerebral palsy and inborn errors of immunity (IEI). Revised policy title from “Genomic Sequencing for Rare Disease” to “Exome and Genome Sequencing for Rare Disease”. Revised points within the Other Considerations section related to the use of ES/GS as a first-tier test and guidance regarding provider-type restrictions. Reformatted policy to move criteria and other considerations section. Reviewed and updated references.