

# Exome Sequencing (ES)

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
Re-evaluation of previously obtained exome sequence (e.g., updated knowledge or unrelated condition/syndrome)	81417

## What Is Exome Sequencing?

- Exome sequencing (ES) utilizes DNA-enrichment methods and massively parallel nucleotide sequencing to identify disease-associated variants throughout the human genome.
- ES has been proposed for diagnostic use in individuals who present with complex genetic phenotypes suspected of having a rare genetic condition, who cannot be diagnosed by standard clinical workup, or when features suggest a broad differential diagnosis that would require evaluation by multiple genetic tests.
- The standard approach to the diagnostic evaluation of an individual suspected of having a rare genetic condition may include combinations of radiographic, biochemical, electrophysiologic, and targeted genetic testing such as a chromosomal microarray, single-gene analysis, and/or a targeted gene panel.<sup>1</sup>
- ES is typically not an appropriate first-tier test, but can be appropriate if initial testing is unrevealing, or if there is no single-gene or panel test available for the particular condition, or if a rapid diagnosis for a critically-ill child is indicated.<sup>2,3,4,5</sup>
- Identifying a molecularly confirmed diagnosis in a timely manner for an individual with a rare genetic condition can have a variety of health outcomes<sup>2-14</sup>, including:
  - guiding prognosis and improving clinical decision-making, which can improve clinical outcome by
    - application of specific treatments as well as withholding of contraindicated treatments for certain rare genetic conditions
    - surveillance for later-onset comorbidities
    - initiation of palliative care
    - withdrawal of care
  - reducing the financial & psychological 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 related to recurrence risk and prenatal diagnosis options

- allowing for more rapid molecular diagnosis than a sequential genetic testing approach

## Test Information

- ES is limited to the DNA sequence of coding regions (exons) and flanking intronic regions of the genome, which is estimated to contain 85% of heritable disease-causing variants.
- Pathogenic variants that can be identified by ES include missense, nonsense, splice-site, and small deletions or insertions.
- At the present time, ES will typically miss certain classes of disease-causing variants, such as structural variants (e.g., translocations, inversions), abnormal chromosome imprinting or methylation, some mid-size insertions and deletions (ca. 10-500 bp), trinucleotide repeat expansion mutations, deeper intronic mutations, and low-level mosaicism.
- ES has the advantage of decreased turnaround time and increased efficiency relative to Sanger sequencing of multiple genes.
- ES is associated with technical and analytical variability, including uneven sequencing coverage, gaps in exon capture before sequencing, as well as variability in variant classification based on proprietary filtering algorithms and potential lack of critical clinical history or family samples.<sup>15</sup>

## Guidelines and Evidence

- The American College of Medical Genetics and Genomics, Association for Molecular Pathology, and College of American Pathologists convened a workgroup that developed standard terminology for describing sequence variants. The guidelines describe criteria for classifying sequence variants into five categories (pathogenic, likely pathogenic, uncertain significance, likely benign, and benign) based on criteria using typical types of variant evidence (e.g., population data, computational data, functional data, segregation data).<sup>16</sup>
- The American College of Medical Genetics has three relevant policy statements that offer guidance on: 1) the clinical application of exome and genome testing,<sup>17</sup> 2) informed consent for genome/exome sequencing,<sup>18</sup> and 3) reporting of incidental findings in clinical exome and genome sequencing.<sup>19,20</sup>
- Evidence for the clinical utility of ES in individuals with multiple congenital anomalies and/or a neurodevelopmental phenotype includes numerous large case series. Relevant outcomes include improved clinical decision-making (e.g., application of specific treatments, withholding of contraindicated treatments, changes to surveillance), changes in reproductive decision making, and resource utilization. ES serves as a powerful diagnostic tool for individuals with rare genetic conditions in which the specific genetic etiology is unclear or unidentified by standard clinical workup.<sup>10,13,21,22,23</sup>



- The average diagnostic yield of ES is 20-40% depending on the individual's age, phenotype, previous workup, and number of comparator samples analyzed.<sup>8,21,24</sup> Among individuals with a pathogenic or likely pathogenic findings by ES, 5-7% received a dual molecular diagnosis (i.e., two significant findings associated with non-overlapping clinical presentations).<sup>21,24</sup>
- The use of family trio ES reduces the rate of uncertain findings, adds to the clinical sensitivity with regard to the interpretation of clinically novel genes, and increases the diagnostic utility of ES. For example, in three publications the positive rate ranges from 31-37% in patients undergoing trio analysis compared to 20-23% positive rate among proband-only ES.<sup>5,21,25,26</sup>
- Re-evaluation of previously obtained exome sequence has the potential for additional diagnostic yield because of constant expansions of existing variant databases, as well as periodic novel gene discovery and publication.<sup>27,28,29</sup>

## Criteria

- Exome sequencing (ES) is considered medically necessary for the evaluation of unexplained congenital or neurodevelopmental disorder in children <21 years of age when ALL of the following criteria are met:
  - The patient and family history have been evaluated by a Board-Certified or Board-Eligible Medical Geneticist, or an Advanced Practice Nurse in Genetics (APGN) credentialed by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC), AND
  - A genetic etiology is considered the most likely explanation for the phenotype, based on EITHER of the following, AND
    - multiple congenital abnormalities affecting unrelated organ systems
    - TWO of the following criteria are met:
      - abnormality affecting at minimum a single organ system
      - significant neurodevelopmental disorder (e.g., global developmental delay, intellectual disability, and/or period of unexplained developmental regression)
      - symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, epilepsy, myopathy, muscular dystrophy)
      - severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles)
      - family history strongly suggestive of a genetic etiology, including consanguinity
      - laboratory findings suggestive of an inborn error of metabolism
  - Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection), AND



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

### Exclusions and Other Considerations:

- ES is considered experimental/investigational for the diagnosis of genetic disorders in individuals <21 years of age who do not meet the above criteria.
- ES is considered experimental/investigational for screening for genetic disorders in asymptomatic or pre-symptomatic individuals.
- Ideal sample type should be considered based on the clinical presentation (e.g., suspect mosaicism 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 infants. Criteria for rGS testing can be found in the [Rapid Genome Sequencing policy](#).

### References

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