



Whole Exome Sequencing LAB-006

Iowa Medicaid Program	Prior Authorization	Effective Date	01/01/2021
Revision Number	6	Last Reviewed	01/16/2026
Reviewed By	Medicaid Medical Director	Next Review	01/15/2027
Approved By	Medicaid Clinical Advisory Committee	Approved Date	01/15/2021

Descriptive Narrative

Whole exome sequencing (WES) involves the analysis of protein-coding regions of the human genome. This comprises less than 1 percent of the genome and includes areas most likely to contain mutations that result in clinical phenotypes and disease. Such large-scale genomic sequencing is useful in scenarios suggestive of a single genetic etiology but lacking a clear diagnostic testing path and in which stepwise testing can result in a costly and prolonged diagnostic evaluation. WES is a reasonable approach in such clinical situations as over 85 percent of known disease-causing mutations are located in the exons.

One indication for the use of WES is for the diagnosis of complex phenotypes. These individuals may be left without a clinical diagnosis of their disorder, despite a lengthy diagnostic work-up that may include combinations of radiographic and electrophysiologic, biochemical, and targeted genetic evaluations. For some of these members, performing WES after initial conventional testing has failed to make the diagnosis may return a likely pathogenic variant.

Determining genetic causality for disease and establishing a molecular diagnosis in clinical practice can help to:

1. Confirm a suspected or established clinical diagnosis;
2. Inform prognosis;
3. Aid in selecting treatment, surveillance, or preventive options;
4. Reveal mode of inheritance;
5. Identify carrier/risk status of family members; and
6. Guide decisions for the use of new therapies or member management.

WES in Children

One of the most common medical indications for WES is evaluation of severe intellectual disability (ID) or developmental delay believed to have a genetic etiology in a child with a negative initial evaluation. In some cases, evaluation of an affected child and both parents (trio testing) is performed – especially when the inheritance pattern is dominant and a de novo mutation is suspected. According to studies, the likelihood of reaching a molecular diagnosis is about 25 percent. Testing may be appropriate when an extensive evaluation including chromosomal microarray analysis is negative for developmental delay with a suspected genetic etiology.

Definitions

Exons are protein-making (coding) sections. About 1 percent of a person's DNA makes protein. Collectively, all exons together are referred to as the exome.

Genotype is the genetic constitution of a person.

Global developmental delay (GDD) is the preferred term to describe intellectual and adaptive impairment in infants and children younger than 5 years of age who fail to meet expected developmental milestones in multiple areas of functioning. Not all children with GDD meet criteria for ID as they grow older. The prevalence of GDD is estimated to be 1 to 3 percent. GDD does not necessarily predict later ID, although there is a strong correlation.

ID (Intellectual Disability) is a neurodevelopmental disorder characterized by deficits in intellectual and adaptive skills, affecting at least one of three adaptive domains (conceptual, social, and practical) with varying severity. The older term "mental retardation" is no longer used in clinical practice. Standardized intelligence quotient testing is no longer used to classify ID severity. The prevalence of ID in the general population is approximately 1 percent. ID is mild in approximately 85 percent of affected persons.

Mendelian disorders are genetic conditions mainly caused by the changes or alterations in a single gene or due to the abnormalities in the genome.

Next generation sequencing (NGS) is a type of DNA sequencing technology that uses parallel sequencing of multiple small fragments of DNA to determine sequence. This "high-throughput" technology has allowed a dramatic increase in the speed and a decrease in the cost at which a person's genome can be sequenced.

Phenotype is the set of observable characteristics of a person resulting from the interaction of its genotype with the environment.

Trio testing involves the genotyping for both the affected child and his or her parents. Trio testing can reduce the number of variants that have to be considered as causative, thereby facilitating better interpretation of testing results and minimizing reporting of costly false-positive results.

Whole exome sequencing (WES) is a DNA analysis technique that looks at all of the exons in a person at one time, rather than gene by gene.

Whole genome sequencing (WGS) determines the sequence of all of the DNA in a person, which includes the protein making (coding) exons as well as non-coding DNA elements. The remaining (non-exomic) DNA consists of introns and regulatory regions that control other aspects of gene function such as splicing and gene expression levels.

Criteria

Prior authorization is required.

WES (including trio testing) is considered medically necessary for the evaluation of neurodevelopmental disorders, multiple congenital anomalies, or epilepsy/seizure disorders when **ALL** the following are met:

1. Member is 17 years of age or younger; **AND**
2. Pretest genetic counseling has been completed by a qualified health provider such as a board-certified genetic counselor or physician with expertise in clinical genetics; **AND**
3. A letter supporting medical necessity of requested testing has been submitted, which contains **ALL** the following:
 - a. Differential diagnosis; **AND**
 - b. Results of previous testing; **AND**
 - c. Statement that a genetic etiology is the most likely explanation of the members symptoms; **AND**
 - d. Predicted impact on the member's plan of care; **AND**
4. A genetic etiology is the most likely explanation for the phenotype as demonstrated by **TWO** or more of the following:
 - a. Presence of multiple congenital abnormalities; **OR**
 - b. Presence of developmental delay or intellectual disability for which first tier testing has not established a diagnosis (single gene testing or chromosomal microarray analysis); **OR**
 - c. Presence of a severe neuropsychiatric condition (schizophrenia, bipolar disorder, Tourette syndrome); **OR**
 - d. Periods of unexplained developmental regression in which the member loses an acquired function or fails to progress beyond a plateau following a period of normal development; **OR**

- e. Presence of epilepsy or a seizure disorder for which a genetic etiology is suspected and standard medical evaluation has not been diagnostic; **AND**
5. No other causative circumstance such as environmental exposure, injury, or infection can account for the clinical presentation; **AND**
6. The testing would result in an impact on the member's health outcomes.

WES reanalysis of previously obtained standard WES for one of the above medically necessary indications (i.e., unexplained neurodevelopmental disorders, multiple congenital anomalies, or epilepsy/seizure disorder in children) is considered medically necessary when **ONE** of the following criteria is met:

1. Additional symptoms have presented in the member that broaden the phenotype assessed during the original exome evaluation; **OR**
2. The birth or diagnosis of a similarly affected first-degree relative that has expanded the clinical picture.

Due to insufficient evidence of efficacy, WES is considered investigational for all other indications, including but not limited to the following:

1. Evaluation of fetal demise.
2. Molecular profiling of tumors for the diagnosis, prognosis, or management of cancer.
3. Preimplantation genetic testing in embryos.
4. Screening asymptomatic individuals for genetic disorders.
5. When used for any of the following diagnoses: cardiovascular disease, neurologic disorders (other than those noted above), or immunodeficiency disorders.

The role of WES and WGS in these circumstances remains uncertain. Based on review of existing evidence, there are currently no clinical indications for this technology in these conditions. Alternatives include individual gene or syndrome-specific gene panel testing based on established risk assessment and management guidelines.

Coding

The following list of codes is provided for reference purposes only and may not be all inclusive. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment, nor does the exclusion of a code imply that its association to the HCPCS/CPT code is inappropriate.

CPT	Description
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).

Compliance

1. Should conflict exist between this policy and applicable statute, the applicable statute shall supersede.
2. Federal and State law, as well as contract language, including definitions and specific contract provisions or exclusions, take precedence over medical policy and must be considered first in determining eligibility for coverage.
3. Medical technology is constantly evolving, and Iowa Medicaid reserves the right to review and update medical policy on an annual and as-needed basis.

Medical necessity guidelines have been developed for determining coverage for member benefits and are published to provide a better understanding of the basis upon which coverage decisions are made. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in the service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national accreditation organizations. Criteria are revised and updated annually, or more frequently if new evidence becomes available that suggests needed revisions.

References

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Carelon. Clinical Appropriateness Guidelines. Genetic Testing. Whole Exome Sequencing and Whole Genome Sequencing. Effective Date: 06/15/2025.
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Briek P. Bulic L. Bracic M. et al. Implementing Whole Genome Sequencing in Clinical Practice: Advantages, Challenges, and Future Perspectives. Cells. 2024 March 13.

Xu J. Yishan W. Luo Y. et al. Genetic analysis of 280 children with unexplained developmental delay or intellectual disability using whole exome sequencing. BMC Pediatrics 24, article number: 766 (2024).

Genetic Testing for Epilepsy. American Academy of Pediatrics. Last Updated. 07/14/2025.

Manickam K. McClain MR. Demmer LA. et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine. 2021;23(11):2029-37.

MCG Ambulatory Care Guidelines. 29th Ed. Whole Genome Sequencing/Whole Exome Sequencing. . Last Update: 6/13/2025. Accessed 11/16/2025.

Development of utilization management criteria may also involve research into other state Medicaid programs, other payer policies, consultation with experts and review by the Medicaid Clinical Advisory Committee (CAC). These sources may not be referenced individually unless they are specifically published and are otherwise applicable to the criteria at issue.

Criteria Change History

Change Date	Changed By	Description of Change	Version
[mm/dd/yyyy]			[#]
Signature			
Change Date	Changed By	Description of Change	Version
01/16/2026	CAC	Annual review. References updated.	6
Signature			
William (Bill) Jagiello, DO 			
Change Date	Changed By	Description of Change	Version
01/17/2025	CAC	Annual review. References updated.	5
Signature			
William (Bill) Jagiello, DO 			
Change Date	Changed By	Description of Change	Version
01/19/2024	CAC	Annual review.	4
Signature			
William (Bill) Jagiello, DO 			
Change Date	Changed By	Description of Change	Version
01/20/2023	CAC	Annual review.	3
Signature			
William (Bill) Jagiello, DO 			
Change Date	Changed By	Description of Change	Version
01/21/2022	CAC	Annual review.	2
Signature			
William (Bill) Jagiello, DO 			
Change Date	Changed By	Description of Change	Version
01/15/2021	CAC	Criteria implementation.	1
Signature			
William (Bill) Jagiello, DO 			

CAC = Medicaid Clinical Advisory Committee