

MN.011.E Whole Genome and Whole Exome Sequencing

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Thank you for being a valued provider for members in one or more of our health plans: Jefferson Health Plans Medicare Advantage, Jefferson Health Plans Individual and Family Plans, Jefferson Health Plans CHIP, and/or Jefferson Health Plans EverWell (our Medicaid plan).

PRODUCT VARIATIONS

This policy applies to all Jefferson Health Plans lines of business.

POLICY STATEMENT

Whole Exome Sequencing (WES) or Whole Genome Sequencing (WGS) are considered medically necessary for evaluation of unexplained neurodevelopmental disorder or multiple genetic anomalies, or epilepsy/ seizure disorder in children ≤ 21 years of age when *all* the following criteria are met:

1. The test is ordered by a board-certified genetic counselor or board-certified medical geneticist or other board-certified physician with expertise in clinical genetics.
2. Family history strongly suggestive of a genetic etiology, including consanguinity; and the member and family history have been evaluated by a Board-Certified or Board-Eligible Medical Geneticist.
3. Member receives pre- and post-test counseling by an appropriate independent provider (not an employee of the genetic testing laboratory), such as board-certified genetic counselor or board-certified medical geneticist or other board-certified physician with expertise in clinical genetics.
4. There is a predicted impact on health outcomes including:

- a. Reducing diagnostic uncertainty (e.g., eliminating lower yield testing and additional screening testing that may later be proven unnecessary once a diagnosis is achieved).
 - b. Guiding prognosis and improving clinical decision-making.
 - c. Application of specific treatments; or
 - d. Withholding of contraindicated treatments; or
 - e. Surveillance for later-onset comorbidities; Initiation of palliative care; or withdrawal of care.
 - f. For people planning a pregnancy, informing genetic counseling related to recurrence risk and prenatal diagnosis options.
5. Clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing is available.
6. A diagnosis cannot be made by standard clinical work-up, excluding invasive procedures such as muscle biopsy.
7. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposures, injury, infection).
8. The previous genetic testing (e.g., comparative genomic hybridization (CGH) chromosomal microarray analysis (CMA); karyotyping analysis; FISH (fluorescence in-situ hybridization) analysis and single-gene or targeted panel testing failed to yield a diagnosis.
9. A genetic etiology is considered the most likely explanation for the phenotype:
 - significant developmental delay, intellectual disability (e.g., characterized by significant limitations in both intellectual functioning and in adaptive behavior).
 - symptoms of a complex neurodevelopmental disorder (e.g., self-injurious behavior, reverse sleep-wake cycles, dystonia, hemiplegia, spasticity, epilepsy, muscular dystrophy).
 - severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome).
10. WES or WGS is more efficient 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).
11. A clinical letter detailing the evaluation by a board-certified genetic counselor or board-certified medical geneticist or other board-certified physician with expertise in clinical genetics which includes **All** of the following information:
 - a. Differential diagnosis; and
 - b. Testing algorithm; and
 - c. Previous tests performed and results; and
 - d. A genetic etiology is the most likely explanation; and
 - e. Recommendation that whole exome sequencing or whole genome sequencing is the most appropriate test.

Rapid whole genome sequencing (rWGS) is medically necessary for critically ill newborns in neonatal and pediatric intensive care units when an underlying genetic etiology is suspected. It has been shown to improve clinical outcomes and to be cost effective in these clinical settings.

Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS) is considered investigational for the diagnosis of genetic disorders in all other situations.

Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS) is considered investigational for screening for genetic disorders.

WGS is a more costly screening tool that has its own limitations. All requests for this testing will be reviewed on case-by-case basis for medical necessity for the evaluation of children with severe intellectual disability who did not have a diagnosis after extensive genetic testing that in some cases included exome sequencing.

POLICY GUIDELINES

Family trio testing (whole exome sequencing or whole genome sequencing of the biologic parents or sibling of the affected child) is considered medically necessary when criteria for whole exome sequencing or whole genome sequencing of the child are met.

CODING

Note: The Current Procedural Terminology (CPT®), Healthcare Common Procedure Coding System (HCPCS), and the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes that may be listed in this policy are for reference purposes only. Listing a code in this policy does not imply that the service is covered and is not a guarantee of payment. Other policies and coverage guidelines may apply. When reporting services, providers/facilities should code to the highest level of specificity using the code that was in effect on the date the service was rendered. This list may not be all inclusive.

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CPT Code	Description
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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)
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)
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)
0094U	Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis.
0212U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband.
0213U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent, sibling).

HCPCS Code	Description
N/A	

ICD-10 Codes	Description
N/A	

BENEFIT APPLICATION

Medical policies do not constitute a description of benefits. This medical necessity policy assists in the administration of the member's benefits which may vary by line of business. Applicable benefit documents govern which services/items are eligible for coverage, subject to benefit limits, or excluded completely from coverage. This policy is invoked only when the requested service is an eligible benefit as defined in the Member's applicable benefit contract on the date the service was rendered. Services determined by the Plan to be investigational or experimental, cosmetic, or not medically necessary are excluded from coverage for all lines of business.

DESCRIPTION OF SERVICES

WES and WGS have been proposed for use in patients presenting with disorders and anomalies that have not been explained by standard clinical workup. About 1% of a person's DNA makes protein. These protein making sections are called exons. All the exons together are called the exome. 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 the DNA in a person, which includes the protein making (coding) as well as non-coding DNA elements.

Next generation sequencing (NGS) is not always the most appropriate clinical genetic test. It is expensive, time-consuming, and often unnecessary for diagnosing genetic conditions for which the clinical evaluation has limited potential. However, it is appropriate to consider exome sequencing or targeted NGS gene panels when many pathogenic genes need to be screened. Exome sequencing should be considered when a condition demonstrates high heritability in a family or is suspected to have a genetic basis, but the number of potential candidate genes is large, or responsible gene(s) are unknown.

One of the most common medical indications for whole genome sequencing or whole exome sequencing is evaluation of severe intellectual disability 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 sequencing") is performed - especially when the inheritance pattern is dominant, and a de novo mutation is suspected. The value of NGS in this setting has been illustrated in several studies, in which the likelihood of reaching a molecular diagnosis is on the order of 25 percent. NGS may thus be appropriate

when an extensive evaluation including chromosomal microarray is negative for developmental delay with a suspected genetic etiology.

Although WGS has the potential to identify causal variants for a wide variety of conditions that may be missed with other technologies, as well as to identify predictive biomarkers, the information derived from WGS has not yet been translated into improved outcomes and changed medical management. Further studies are needed to establish the clinical utility of WGS.

CLINICAL EVIDENCE

Currently, the diagnostic yield of exome sequencing appears to be no greater than 50% and possibly less for patients with suspected genetic disorder accompanied by multiple anomalies. Medical management options may be available for only a subset of those diagnosed. Reproductive decisions for parents considering an additional pregnancy may be informed by determining the mode of inheritance. Appropriate use of exome sequencing requires considerable genetic, clinical, and genetic counseling expertise.

As cited in a 2013 Blue Cross Blue Shield Association (BCBSA) Technology Evaluation Center (TEC) Special Report on exome sequencing for patients with suspected genetic disorders. Currently there are no published studies that systematically examine potential outcomes of interest such as changes in medical management (including revision of initial diagnoses), and changes in reproductive decision making after a diagnosis of a Mendelian disorder by WES.

A small number of studies of patient series, and a larger number of very small series or family studies report anecdotal examples of medical management and reproductive decision-making outcomes of exome sequencing in patients who were not diagnosed by traditional methods. These studies show that over and above traditional molecular and conventional diagnostic testing, exome sequencing can lead to a diagnosis that influences patient care and/or reproductive decisions but gave no indication of the proportion of patients for which this is true.

The publication of many small diagnostic studies with positive results but few with negative results; raise the possibility of publication bias—the impact of which is unknown. ⁴ Since the publication of the 2013 TEC Special Report, studies continue to demonstrate that WES can be used to identify novel genetic mutations in a range of clinical conditions.

DISCLAIMER

Approval or denial of payment does not constitute medical advice and is neither intended to guide nor influence medical decision making. Policy Bulletins are developed to assist in administering plan benefits and constitute neither offers of coverage nor medical advice. This Policy Bulletin may be updated and therefore is subject to change.

For Jefferson Health Plans EverWell and Jefferson Health Plans CHIP products: Any requests for services that do not meet criteria set in PARP will be evaluated on a case-by-case basis.

POLICY HISTORY

This section provides a high-level summary of changes to the policy since the previous version.

Summary	Version	Version Date
2025 Annual review. Code list expanded per DHS. References updated.	E	09/18/2025
2024 Annual review. No revisions. References updated.	D	12/01/2023
2023 Ad-hoc review. Policy criteria updated to include coverage for Whole Genome Sequencing (WGS)	D	12/01/2023
2023 Annual review. No revisions. References updated accordingly.	C	12/01/2019
2022 Annual Policy Review. No revisions to this version.	C	12/1/2019
2021 Annual Policy Review. No revisions to this version.	C	12/1/2019
2020 Annual Policy Review. No revisions to this version.	C	12/1/2019
Policy statement and coverage criteria updated. Language was added to the description and clinical evidence sections. CPT codes 81417 and 81427 were added to the coding table. Reference section was updated.	C	12/1/2019
Annual policy review. No revisions to this version.	B	12/1/2018
New policy bulletin.	A	3/2/2017

REFERENCES

1. BCBSA Technology Assessment Program, August 2013 Volume 28, No. 5 “Special Report: Exome Sequencing for Clinical Diagnosis of Patients with Suspected Genetic Disorders”.
2. Medicare Managed Care Manual, Section 90.4. Electronically available at the <https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/mc86c04.pdf>
3. Novitas Solutions Inc. Local Coverage Determination LCD L35062 Biomarkers Overview Effective 12/12/2021. <https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?LCDId=35062>
4. Up To Date-Next generation DNA sequencing (NGS): Principles and clinical implications-Peter J Hulick, MD; Literature review current through current through: Jul 2024. | This topic last updated: 05/02/25
5. Clinical exome sequencing for genetic identification of rare Mendelian disorders: Lee H, Deignan JL, Dorrani N, and el.-JAMA 2014.
6. Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data: Wright CF, Fitzgerald TW, end el. Lancet. 2015.
7. Clinical whole-exome sequencing for the diagnosis of mendelian disorders: Yang Y, Muzny DM, Reid JG, end el.- N Engl J Med. 2013.

Molecular findings among patients referred for clinical whole-exome sequencing: Yang Y, Muzny DM, end el.- JAMA. 2014.
8. Making new genetic diagnoses with old data: iterative reanalysis and reporting from genome-wide data in 1,133 families with developmental disorders: Wright CF, McRae JF, end el. Genet Med. 2018
9. Exome Sequencing and the Management of Neurometabolic Disorders: Tarailo-Graovac M, Shyr C, end el. N Engl J Med. 2016.
10. Genome sequencing identifies major causes of severe intellectual disability. Gilissen C, Hehir-Kwa JY, Nature. 2014.
11. NIH's Undiagnosed Diseases Program expands: 6 new sites offer potential answers to more patients: Kuehn BM, JAMA. 2014.

12. Effect of Genetic Diagnosis on Patients with Previously Undiagnosed Disease:
Splinter K, Adams DR, end el. N Engl J Med. 2018.