

# Genome Sequencing

MOL.TS.306.C  
v1.0.2025

## Introduction

Genome sequencing is addressed by this guideline.

## Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis	81425
Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (eg, parents, siblings) (list separately in addition to code for primary procedure)	81426
Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)	81427
Genomic Unity Whole Genome Analysis - Comparator	0213U
Genomic Unity Whole Genome Analysis - Proband	0212U
Praxis Combined Whole Genome Sequencing and Optical Genome Mapping	0267U
Praxis Whole Genome	0265U
RCIGM Rapid Whole Genome Sequencing	0094U
RCIGM Rapid Whole Genome Sequencing, Comparator Genome	0425U

Procedures addressed by this guideline	Procedure codes
RCIGM Ultra-Rapid Whole Genome Sequencing	0426U

## Criteria

### Introduction

Requests for genome sequencing (GS) are reviewed using the following criteria.

### Genome Sequencing

Genome sequencing (GS) is considered medically necessary when ALL of the following criteria are met:

- The member has not had previous exome sequencing performed, AND
- The member has not had previous genome sequencing performed, AND
- The member has had appropriate genetic and family history evaluation, and a clinical letter detailing the evaluation is provided which includes ALL of the following information:
  - Differential diagnoses, and
  - Testing algorithm, and
  - Previous tests performed and results, and
  - A genetic etiology is the most likely explanation, and
  - Recommendation that genome sequencing is the most appropriate test, and
  - Predicted impact on member's plan of care, AND
- Member is <21 years of age, AND
- A genetic etiology is considered the most likely explanation for the phenotype, based on ONE of the following:
  - Unexplained epileptic encephalopathy (onset before three years of age) and no prior epilepsy multigene panel testing performed, OR
  - Global developmental delay (significant delay in younger children, under age 5 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) following formal assessment by a developmental pediatrician or neurologist, OR

- Moderate/severe/profound intellectual disability (defined by Diagnostic and Statistical Manual of Mental Disorders [DSM-5] criteria, diagnosed by 18 years of age) following formal assessment by a developmental pediatrician or neurologist, OR
- Multiple congenital abnormalities defined by ONE of the following:
  - Two or more major anomalies affecting different organ systems\*, or
  - One major and two or more minor anomalies affecting different organ systems\*, OR
- TWO of the following criteria are met:
  - major abnormality affecting at minimum a single organ system\*, and/or
  - formal diagnosis of autism, and/or
  - symptoms of a complex neurodevelopmental disorder (e.g., epilepsy, self-injurious behavior, reverse sleep-wake cycles, dystonia, ataxia, alternating hemiplegia, neuromuscular disorder), and/or
  - severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome), and/or
  - period of unexplained developmental regression, and/or
  - laboratory findings suggestive of an inborn error of metabolism, AND
- 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 first tier testing (e.g., single gene testing, comparative genomic hybridization [CGH]/chromosomal microarray analysis [CMA]) is available, AND
- Multiple targeted panels are appropriate based on the member's clinical presentation, AND
- There is a predicted impact on health outcomes including:
  - Application of specific treatments, or
  - Withholding of contraindicated treatments, or
  - Surveillance for later-onset comorbidities, or
  - Initiation of palliative care, or
  - Withdrawal of care, AND
- A diagnosis cannot be made by standard clinical work-up, excluding invasive procedures such as muscle biopsy, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

\*Major structural abnormalities are generally serious enough as to require medical treatment on their own (such as surgery) and are not minor developmental variations that may or may not suggest an underlying disorder.

**CPT: 0212U, 0213U, 0265U**

- The member meets the above criteria for genome sequencing, AND
- The member meets criteria for whole mitochondrial DNA (mtDNA) sequencing based on current eviCore guideline, *Mitochondrial Disorders Genetic Testing*, AND
- The member has not had previous whole mtDNA sequencing analysis performed, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**Rapid Whole Genome Sequencing (rWGS)**

The following criteria apply for individuals who are **inpatient** at the time of testing. rWGS is considered medically necessary for the evaluation of acutely-ill infants 12 months of age or younger when ALL of the following criteria are met:

- The member has not had previous exome sequencing performed, AND
- The member has not had previous genome sequencing performed, AND
- The member has had appropriate genetic and family history evaluation, AND
- The etiology of the infant's features is not known and a genetic etiology is considered a likely explanation for the phenotype, based on EITHER of the following:
  - Multiple congenital abnormalities affecting unrelated organ systems, or
  - TWO of the following criteria are met:
    - abnormality affecting at minimum a single organ system
    - encephalopathy
    - symptoms of a complex neurodevelopmental disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia)
    - family history strongly suggestive of a genetic etiology, including consanguinity
    - laboratory findings suggestive of an inborn error of metabolism
    - abnormal response to therapy, AND
- Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), AND
- Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted panel testing is available, AND

- A diagnosis cannot be made in a timely manner by standard clinical evaluation or laboratory testing, excluding invasive procedures such as muscle biopsy, AND
- Predicted impact on health outcomes, including immediate impact on medical management based on the molecular results, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**Exclusions and Other Considerations:**

- Trio samples are preferred.
- rWGS is considered not medically necessary in individuals with the following diagnoses:
  - Isolated transient neonatal tachypnea
  - Isolated unconjugated hyperbilirubinemia
  - Isolated hypoxic ischemic encephalopathy with clear precipitating event
  - Isolated meconium aspiration
  - Isolated prematurity
  - Infection/sepsis with normal response to therapy
- GS or rWGS used for prenatal diagnosis is considered not medically necessary.
- GS and rWGS are considered E/I/U for screening for genetic disorders in asymptomatic or pre-symptomatic individuals.
- GS combined with Optical Genome Mapping (e.g. 0267U) is considered experimental, investigational, or unproven (E/I/U).

**Billing and Reimbursement****Introduction**

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Prenatal diagnosis by genome sequencing (GS) is not reimbursable.
- GS is not reimbursable for screening for genetic disorders in asymptomatic or pre-symptomatic individuals.

- Genome deletion/duplication analysis (typically billed with 81228 or 81229) is not separately reimbursable.
- GS will be considered for reimbursement only when billed with an appropriate CPT code:
  - 81425 should be billed for the proband. 81425 should only be billed when analyzing the entire genome sequence, rather than a targeted set of genes.
  - 81426 should be billed when a comparator genome is performed. A trio of the proband and both parents is generally preferred, although other family members may be more informative based on the clinical presentation. A maximum of two units of 81426 will be considered for reimbursement.
  - 81427 should be billed for re-evaluation of a previously obtained genome due to updated clinical information or expanded scientific knowledge or for the purpose of evaluating a patient for an unrelated condition/syndrome on a different date of service. 81427 is not reimbursable for reflex from targeted to full genome.
- 81425 is not reimbursable for a targeted genome analysis. If targeted analysis is performed, the appropriate GSP panel code, unlisted code (e.g. 81479), or Tier 1 or Tier 2 code(s) must be billed instead.
- 81425 will be reimbursable once per lifetime.

## What is genome sequencing?

### Definition

Genome sequencing (WGS or GS) utilizes DNA-enrichment methods and massively parallel nucleotide sequencing to identify disease-associated variants throughout the human genome.

- GS 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>
- Broad genomic testing is typically not the most 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.<sup>2</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>2-9</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 and 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 or preconceptional (utilizing in-vitro fertilization with preimplantation genetic diagnosis) diagnosis options
- allowing for more rapid molecular diagnosis than a sequential genetic testing approach

## Test information

### Introduction

Both coding (exons) and noncoding (introns) regions are analyzed by GS.<sup>10</sup> Often, coding regions are first analyzed by GS. If no pathogenic mutations are found, the noncoding regions are then analyzed.<sup>10</sup>

Pathogenic variants that can be identified by GS include missense, nonsense, splice-site, and small deletions or insertions. "Data can also be examined for copy-number variant (CNVs) or structural variants that may either be outside of the coding regions or more easily detected using GS due to increased quantitative accuracy."<sup>10</sup>

### Guidelines and evidence

#### American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2021) published a guideline on the use of exome and genome sequencing in the pediatric population that stated:<sup>11</sup>

- "We strongly recommend ES [exome sequencing] and GS [genome sequencing] as a first-tier or second-tier test (guided by clinical judgment and often clinician–patient/family shared decision making after CMA or focused testing) for patients with one or more CAs prior to one year of age or for patients with DD/ID with onset prior to 18 years of age."

- “Consistent with existing guidelines/recommendations/position statements, patients with clinical presentations highly suggestive of a specific genetic diagnosis should undergo targeted testing first.”
- “Isolated autism without ID or congenital malformation is formally out of scope for this recommendation but evaluation of exome/genome studies is ongoing.”
- Diagnostic yield of genome-wide sequencing was determined to be outside the scope of the systematic evidence review.

ACMG (2013) stated the following regarding informed consent for exome and genome testing:<sup>12</sup>

- “Before initiating GS/ES, counseling should be performed by a medical geneticist or an affiliated genetic counselor and should include written documentation of consent from the patient.”
- “Incidental/secondary findings revealed in either children or adults may have high clinical significance for which interventions exist to prevent or ameliorate disease severity. Patients should be informed of this possibility as a part of the informed consent process.”
- “Pretest counseling should include a discussion of the expected outcomes of testing, the likelihood and type of incidental results that may be generated, and the types of results that will or will not be returned. Patients should know if and what type of incidental findings may be returned to their referring physician by the laboratory performing the test.”
- “GS/ES is not recommended before the legal age of majority except for:
  - Phenotype-driven clinical diagnostic uses
  - Circumstances in which early monitoring or interventions are available and effective; or
  - Institutional review board–approved research.”
- “As part of the pretest counseling, a clear distinction should be made between clinical and research-based testing.”
- “Patients should be informed as to whether individually identifiable results may be provided to databases, and they should be permitted to opt out of such disclosure.”
- “Patients should be informed of policies regarding re-contact of referring physicians as new knowledge is gained about the significance of particular results.”

ACMG (2021) published guidelines for the reporting of incidental findings in clinical exome and genome sequencing that stated:<sup>13,14</sup>

- “Variants classified as likely pathogenic and pathogenic variants should be reported. Variants of uncertain significance, likely benign, and benign variants should not be reported as a secondary finding.”



- This guideline includes a table of “ACMG SF v3.0 genes and associated phenotypes recommended for return from clinical exome and genome sequencing.” ACMG has published updates to this list to expand upon the recommended genes.<sup>15,16</sup>

### **American College of Obstetricians and Gynecologists**

The American College of Obstetricians and Gynecologists (ACOG, 2018; reaffirmed 2023) stated the following in a technology assessment for modern genetics in obstetrics and gynecology:<sup>17</sup>

- "The American College of Medical Genetics and Genomics recommends considering whole-exome sequencing when specific genetic tests available for a phenotype, including targeted sequencing tests, have failed to arrive at a diagnosis in a fetus with multiple congenital anomalies suggestive of a genetic disorder."

The 2020 guidelines for management of stillbirth stated:<sup>18</sup>

- "Microarray is the preferred method of evaluation for these reasons but, due to cost and logistic concerns, karyotype may be the only method readily available for some patients. In the future, whole exome sequencing or whole genome sequencing may be part of the stillbirth workup, but it is not currently part of the standard evaluation."

### **American College Obstetricians and Gynecologists and Society for Maternal Fetal Medicine**

A joint statement, the American College of Obstetricians and Gynecologists and the Society for Maternal Fetal Medicine (ACOG/SMFM, 2016; reaffirmed 2023) stated the following regarding prenatal ES.<sup>19</sup>

- "The routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published."

### **International Society for Prenatal Diagnosis**

The International Society for Prenatal Diagnosis (2022) updated position statement on the use of prenatal genome-wide sequencing stated:<sup>20</sup>

- "Although wider integration of genome-wide sequencing into prenatal care is now considered appropriate for specific indications, it remains a complex test, particularly when used clinically for prenatal diagnosis of fetuses with suspected genetic disorders."
- "There is still limited genotype-phenotype correlation for the genetic disorders identified in the fetal period. Since ultrasound and/or MRI imaging is frequently limited, the fetal phenotypes of many conditions have not been well described and new fetal phenotypes for conditions recognized postnatally are now being identified."

- “There is no universal consensus on the management of IF [incidental findings] and SF [secondary findings] and each center should convey their policy detailing whether they are or are not reported, and if reported what is included for parents and fetus.”
- Data support benefit of prenatal genomic analysis for clinical indications such as multiple congenital anomalies with a negative microarray and previous undiagnosed fetus with major or multiple anomalies. Routine prenatal genomic testing (by parental request) is not supported by the current body of evidence.

### **International Society for Prenatal Diagnosis, Society for Maternal Fetal Medicine, and Perinatal Quality Foundation**

A joint statement from the International Society for Prenatal Diagnosis (ISPD, 2018), the Society for Maternal Fetal Medicine (SMFM, 2018), and the Perinatal Quality Foundation (PQF, 2018) on prenatal ES stated:<sup>21</sup>

- “The routine use of prenatal [genome wide] sequencing as a diagnostic test cannot currently be supported due to insufficient validation data and knowledge about its benefits and pitfalls. Prospective studies with adequate population numbers for validation are needed.... Currently, it is ideally done in the setting of a research protocol. Alternatively, sequencing may be performed outside a research setting on a case-by-case basis when a genetic disorder is suspected for which a confirmatory genetic diagnosis can be obtained more quickly and accurately by sequencing. Such cases should be managed after consultation with and under the expert guidance of genetic professionals working in multidisciplinary teams with expertise in the clinical diagnostic application of sequencing, including interpretation of genomic sequencing results and how they translate to the prenatal setting, as well as expertise in prenatal imaging and counseling.”
- “There is currently limited genotype-phenotype correlation for the genetic disorders identified in the fetal period because ultrasound imaging is frequently limited, and the fetal phenotypes of many conditions have not been well described.”

### **Selected Relevant Publications**

The clinical utility of prenatal genomic sequencing is currently lacking. Multiple recent reviews cite a need for further research to better understand the impact of testing in the clinical setting.<sup>22-25</sup> Future studies are needed to “better understand which pregnancies benefit most and how to prioritise cases in a way that maximizes benefit” and to “determine the extent to which prenatal genomic sequencing results actually alter perinatal care.”<sup>25,26</sup>

Prenatal genomic sequencing aims to improve reproductive decision-making, allow for more informed pregnancy and perinatal management options, and reduce morbidity and mortality.<sup>24,25</sup> However, there is a paucity of well-designed studies examining the use of prenatal WGS, and routine usage cannot be recommended due to insufficient data and a need to address several complex clinical scenarios that may arise during clinical use.<sup>23,25,26</sup>

---

**Note** This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for genome sequencing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

---

## References

1. Shashi V, McConkie-Rosell A, Rosell B, et al. The utility of the traditional medical genetics diagnostic evaluation in the context of next-generation sequencing for undiagnosed genetic disorders. *Genet Med*. 2014; 16: 176–182.
2. Sawyer SL, Hartley T, Dymont DA et al. Utility of whole-exome sequencing for those near the end of the diagnostic odyssey: time to address gaps in care. *Clin Genet*. 2016; 89: 275–284.
3. Dixon-Salazar TJ, Silhavy JL, Udpa N, et al. Exome sequencing can improve diagnosis and alter patient management. *Sci Transl Med*. 2012;4(138):138ra178.
4. Halverson CM, Cliff KE, & JB McCormick. Was it worth it? Patients' perspectives on the perceived value of genomic-based individualized medicine. *J Community Genet*. 2016;7(2):145–152.
5. Iglesias A, Anyane-Yeboah K, Wynn J, et al. The usefulness of whole-exome sequencing in routine clinical practice. *Genet Med*. 2014;16(12):922-931.
6. Nolan D, Carlson M. Whole exome sequencing in pediatric neurology patients: clinical implications and estimated cost analysis. *J Child Neurol*. 2016;31(7):887-894.
7. Stark Z, Tan TY, Chong B, et al. A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders. *Genet Med*. 2016;18(11):1090-1096.
8. Thevenon J, Duffourd Y, Masurel-Paulet A, et al. Diagnostic odyssey in severe neurodevelopmental disorders: toward clinical whole-exome sequencing as a first-line diagnostic test. *Clin Genet*. 2016; 89: 700–707.
9. Valencia CA, Husami A, Holle J, et al. Clinical impact and cost-effectiveness of whole exome sequencing as a diagnostic tool: a pediatric center's experience. *Front Pediatr*. 2015;3:67.
10. Rehm HL, Bale SJ, Bayrak-Toydemir P, et al. ACMG clinical laboratory standards for next-generation sequencing. *Genet Med*. 2013;15(9):733-747.

11. 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). *Genet Med.* 2021;23(11):2029-2037. doi: 10.1038/s41436-021-01242-6
12. ACMG Board of Directors. Points to consider for informed consent for genome/exome sequencing. *Genet Med.* 2013;15(9):748–749.
13. Miller DT, Lee K, Gordon AS, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2021; doi:10.1038/s41436-021-01171-4 [Epub ahead of print]
14. Miller DT, Lee K, Chung WK, et al. ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2021;doi: 10.1038/s41436-021-01172-3 [Epub ahead of print]
15. Miller DT, Lee K, Abul-Husn NS, et al. ACMG SF v3.1 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2022;24(7):1407-1414. doi:10.1016/j.gim.2022.04.006
16. Miller DT, Lee K, Abul-Husn NS, et al. ACMG SF v3.2 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2023;25(8):100866. doi:10.1016/j.gim.2023.100866
17. American College of Obstetricians and Gynecologists' Committee on Genetics. ACOG technology assessment in obstetrics and gynecology no. 14 summary. *Obstet Gynecol.* 2018;132(3):807-808. doi: 10.1097/aog.0000000000002832. Reaffirmed 2023.
18. American College of Obstetricians and Gynecologists, Society for Maternal and Fetal Medicine. Obstetric care consensus number 10: Management of stillbirth. *Obstet Gynecol.* 2020;135(3):e110-e128.
19. Committee on Genetics and the Society for Maternal-Fetal Medicine. Committee opinion no.682: Microarrays and next-generation sequencing technology: The use of advanced genetic diagnostic tools in obstetrics and gynecology. *Obstet Gynecol.* 2016;128(6):e262-e268.
20. Ven den Veyver IB, Chandler N, Wilkins-Haug LE, Wapner RJ, Chitty LS, ISPD Board of Directors. International Society for Prenatal Diagnosis Updated Position Statement on the use of genome-wide sequencing for prenatal diagnosis. *Prenat Diagn.* 2022;42(6):796-803. doi: 10.1002/pd.6157.

21. International Society for Prenatal Diagnosis; Society for Maternal and Fetal Medicine; Perinatal Quality Foundation. Joint position statement from the International Society for Prenatal Diagnosis (ISPD), the Society for Maternal Fetal Medicine (SMFM), and the Perinatal Quality Foundation (PQF) on the use of genome-wide sequencing for fetal diagnosis. *Prenat Diagn.* 2018;38(1):6-9.
22. Klapwijk JE, Srebniak MI, Go ATJI, et al. How to deal with uncertainty in prenatal genomics: A systematic review of guidelines and policies. *Clin Genet.* 2021;100(6):647-658. doi:10.1111/cge.14010
23. Pauta M, Martinez-Portilla RJ, Borrell A. Diagnostic yield of exome sequencing in fetuses with multisystem malformations: systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2022;59(6):715-722. doi:10.1002/uog.24862
24. Best S, Wou K, Vora N, Van der Veyver IB, Wapner R, Chitty LS. Promises, pitfalls and practicalities of prenatal whole exome sequencing. *Prenat Diagn.* 2018;38(1):10-19. doi:10.1002/pd.5102
25. Mellis R, Oprych K, Scotchman E, Hill M, Chitty LS. Diagnostic yield of exome sequencing for prenatal diagnosis of fetal structural anomalies: A systematic review and meta-analysis. *Prenat Diagn.* 2022;42(6):662-685. doi:10.1002/pd.6115
26. Abou Tayoun AN, Spinner NB, Rehm HL, Green RC, Bianchi DW. Prenatal DNA sequencing: clinical, counseling, and diagnostic laboratory considerations. *Prenat Diagn.* 2018;38(1):26-32. doi:10.1002/pd.5038