Exome Sequencing

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Introduction

Exome 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
Exome sequencing (e.g., unexplained constitutional or heritable disorder or syndrome)	81415
Exome sequencing, comparator (e.g., parent(s), sibling(s))	81416
Exome sequencing re-evaluation (e.g., updated knowledge or unrelated condition/ syndrome)	81417
Genomic Unity Exome Plus Analysis - Comparator	0215U
Genomic Unity Exome Plus Analysis - Proband	0214U

Criteria

Introduction

Requests for exome sequencing are reviewed using the following criteria.

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Exome Sequencing

- Exome sequencing (ES) 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 exome 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, cerebral palsy), 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 inherited metabolic disorder, 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 more appropriate targeted testing (e.g., single gene testing, comparative genomic hybridization [CGH]/chromosomal microarray analysis [CMA]) is available, 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 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.

Prenatal Exome

Testing of a fetus using exome sequencing is considered medically necessary when ALL of the following criteria are met:

- Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested
- Standard diagnostic genetic testing (CMA and/or karyotype) of the fetus has been performed and is uninformative
- Testing is performed on direct amniotic fluid/chorionic villi, cultured cells from amniotic fluid/chorionic villi or DNA extracted from fetal blood or tissue
- At least one of the following is present:
  - Multiple fetal structural anomalies affecting unrelated organ systems
  - Fetal hydrops of unknown etiology
  - A fetal structural anomaly affecting a single organ system and family history strongly suggests a genetic etiology

Genomic Unity Exome Plus Analysis (CPT: 0214U and 0215U)

The member meets the above criteria for exome 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

Other considerations

- ES on tissue from a pregnancy loss is considered not medically necessary.
- Exome deletion/duplication analysis (typically billed with 81228 or 81229) is considered experimental, investigational, or unproven (E/I/U).
- ES is considered E/I/U for screening for genetic disorders in asymptomatic or pre-symptomatic individuals.

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.

- ES on tissue from a pregnancy loss is not reimbursable.
- ES is not reimbursable for screening for genetic disorders in asymptomatic or pre-symptomatic individuals.
- Exome deletion/duplication analysis (typically billed with 81228 or 81229) is not reimbursable.
- ES will be considered for reimbursement only when billed with an appropriate CPT code:
  - 81415 should be billed for the proband. 81415 should only be billed when analyzing the entire exome sequence, rather than a targeted set of genes.
  - 81416 should be billed when a comparator exome 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 81416 will be considered for reimbursement.

  - Re-evaluation of a previously obtained exome due to updated clinical information or expanded scientific knowledge or for the purpose of evaluating an individual for an unrelated condition/syndrome on a different date of service will be considered for reimbursement only when billed using 81417. 81417 is not reimbursable for reflex from targeted to full exome.
- 81415 is not reimbursable for a targeted exome analysis (e.g. XomeDxSlice custom gene panel completed on a single exome platform). The appropriate GSP panel code, unlisted code (e.g. 81479), or Tier 1 or Tier 2 code(s) must be billed.
- 81415 will be reimbursable once per lifetime.

What is exome sequencing?

Exome sequencing (ES/WES) 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 diagnostic evaluation of an individual suspected of having a rare genetic condition may include combinations of radiographic, biochemical, electrophysiological, and genetic testing such as a chromosomal microarray, single-gene analysis, targeted gene panel, and/or broad genomic sequencing, including exome/genome sequencing.[1]
- ES may be appropriate if any prior testing is unrevealing, there is no single-gene or panel test available for the particular condition, or a rapid diagnosis for a critically ill child is indicated.[2-5]
- Identifying a molecularly confirmed diagnosis in a timely manner for an individual with a rare genetic condition can have a variety of health outcomes,[2-12] 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 preconception (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

Exome sequencing 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. Results of testing with ES include known pathogenic variants definitely associated with disease or a variant of uncertain significance (VUS).[13,14]

- Pathogenic variants that can be identified by ES include missense, nonsense, splice-site, and small deletions or insertions.
- At the present time, ES can fail to detect 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. The current evidence base evaluating ES to specifically identify deletions/duplications is limited but suggests improved detection in recent years.[15]
- 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.[16]

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics (ACMG, 2012) stated the following regarding the clinical application of exome and genome testing:[17]

- "WGS [whole genome sequencing]/WES should be considered in the clinical diagnostic assessment of a phenotypically affected individual when:"
  - "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."

  - "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."
  - "A patient presents with a likely genetic disorder, but specific genetic tests available for that phenotype have failed to arrive at a diagnosis."
  - "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."
  - "Prenatal diagnosis by genomic (i.e., next-generation whole-exome or whole-genome) sequencing has significant limitations. The current technology does not support short turnaround times, which are often expected in the prenatal setting. There are high rates of false positives, false negatives, and variants of unknown clinical significance. These can be expected to be significantly higher than seen when array CGH is used in prenatal diagnosis."
- The following were recommended pretest considerations:
  - "Pretest counseling should be done by a medical geneticist or an affiliated genetic counselor and should include a formal consent process."
  - "Before initiating WGS/WES, participants should be counseled regarding the expected outcomes of testing, the likelihood and type of incidental results that could be generated, and what results will or will not be disclosed."
  - "As part of the pretest counseling, a clear distinction should be made between clinical and research-based testing. In many cases, findings will include variants of unknown significance that might be the subject for research; in such instances a protocol approved by an institutional review board must be in place and appropriate prior informed consent obtained from the participant."

The American College of Medical Genetics (ACMG, 2013) stated the following regarding informed consent for exome and genome testing:[18]

- "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."

- "Patients should be counseled regarding the potential benefits and risks of GS/ES, the limitations of such testing, potential implications for family members, and alternatives to such testing."
- "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."

The American College of Medical Genetics (ACMG, 2021) published an updated guideline for the reporting of secondary findings (SF) in clinical exome and genome sequencing. They stated:[19]

- "The overall goal of the SFWG [Secondary Findings Working Group] is to recommend a minimum list of genes that places limited excess burden on patients and clinical laboratories while maximizing the potential to reduce morbidity and mortality when ES/GS is being performed."
- "Variants of uncertain significance should not be reported in any gene."
- “It is important to reiterate here that use of the SF results should not be a replacement for indication-based diagnostic clinical genetic testing.”
- A table of “ACMG SF v3.0 gene and associated phenotypes recommended for return as secondary findings from clinical exome and genome sequencing” was provided. ACMG has published updates to this list to expand upon the recommended genes.[20,21,22]

The American College of Medical Genetics and Genomics (ACMG, 2020) issued an educational Points to Consider Statement addressing good process, benefits, and limitations of using exome sequencing in the prenatal setting.[23]

A 2020 systematic evidence-based review by the ACMG on genome-wide sequencing for pediatric patients with congenital anomalies (CA), developmental delay (DD), or intellectual disability (ID) stated:[24]

- "There is evidence that ES/GS for patients with CA/DD/ID informs clinical and reproductive decision-making, which could lead to improved outcomes for patients and their family members. Further research is needed to generate evidence regarding health outcomes to inform robust guidelines regarding ES/GS in the care of patients with CA/DD/ID."

ACMG (2021) published a clinical guideline on the use of exome and genome sequencing in the pediatric population that stated:[25]

- "We strongly recommend ES and GS 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.

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:[26]

- “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:[27]

- “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

In 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.[28]

- "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:[29]

- "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 currently 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 described."
- "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:[30]

- "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

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.[10,15,31-33]

- The average diagnostic yield of ES is 20-40% depending on the individual's age, phenotype, previous workup, and number of comparator samples analyzed.[8,11,31,34,35] 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).[31,34]
- 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 individuals undergoing trio analysis compared to 20-23% positive rate among proband-only ES.[5,31,36,37]
- 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.[38-40]

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, Dyment 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. Dillon O, et al. Exome sequencing has higher diagnostic yield compared to simulated disease-specific panels in children with suspected monogenic disorders. *EJHG*. 2018;26(5):644–651.
4. Soden S, Saunders C, Willig L, et al. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. *Sci Transl Med*. 2014;6(265):265ra168.
5. Kingsmore S, Cakici J, Clark M, et al. A randomized, controlled trial of the analytic and diagnostic performance of singleton and trio, rapid genome and exome sequencing in ill infants. *Am J Hum Genet*. 2019;105(4):719-733.
6. 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.
7. Halverson CM, Clift 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.
8. Iglesias A, Anyane-Yeboa K, Wynn J, et al. The usefulness of whole-exome sequencing in routine clinical practice. *Genet Med.* 2014;16(12):922-931.
9. 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.
10. 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.
11. Vissers LELM, Van Nimwegen KJM, Schieving JH, et al. A clinical utility study of exome sequencing versus conventional genetic testing in pediatric neurology. *Genet Med*. 2017;19(9):1055-1063.
12. Smith HS, Swint JM, Lalani SR, et al. Clinical application of genome and exome sequencing as a diagnostic tool for pediatric patients: a scoping review of the literature. *Genet Med*. 2019;21(1):3-16.

13. Seleman M, Hoyos-Bachiloglu R, Geha RS, et al. Uses of next-generation sequencing technologies for the diagnosis of primary immunodeficiencies. *Front Immunol*. 2017;8:847-847. doi: 10.3389/fimmu.2017.00847.
14. Wallace SE, Bean LJH. Educational Materials — Genetic Testing: Current Approaches. 2017 Mar 14 [Updated 2020 Jun 18]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available at: **https://www.ncbi.nlm.nih.gov/books/NBK279899**
15. Shickh S, Mighton C, Uleryk E, Pechlivanoglou P, Bombard Y. The clinical utility of exome and genome sequencing across clinical indications: a systematic review. *Hum Genet*. 2021;140(10):1403-1416. doi:10.1007/s00439-021-02331-x
16. Rehder C, Bean LJH, Bick D, et al. Next-generation sequencing for constitutional variants in the clinical laboratory, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(8):1399-1415. doi: 10.1038/s41436-021-01139-4
17. ACMG Board of Directors. Points to consider in the clinical application of whole-genome sequencing. *Genet Med.* 2012; 14:759–761.
18. ACMG Board of Directors. Points to consider for informed consent for genome/exome sequencing. *Genet Med.* 2013;15(9):748–749.
19. 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 Aug;23(8):1391-1398.
20. 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. *Genet Med.* 2021. doi: 10.1038/s41436-021-01172-3
21. 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
22. 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
23. Monaghan KG, Leach NT, Pekarek D, Prasad P, Rose NC. The use of fetal exome sequencing in prenatal diagnosis: a points to consider document of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2020;22(4):675–680. doi: 10.1038/s41436- 019-0731-7.
24. Malinowski J, Miller DT, Demmer L, et al. Systematic evidence-based review: outcomes from exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability. *Genet Med.* 2020;22(6):986-1004. doi: 10.1038/s41436-020-0771-z.
25. 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
26. 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.
27. 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. Reaffirmed 2025.
28. 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. Reaffirmed 2023.
29. Van 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
30. 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.

31. Farwell KD, Shahmirzadi L, El-Khechen D, et al. Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families with undiagnosed genetic conditions. *Genet Med*. 2015;17(7):578-586.
32. Chung CCY, Hue SPY, Ng NYT, et al. Meta-analysis of the diagnostic and clinical utility of exome and genome sequencing in pediatric and adult patients with rare diseases across diverse populations. *Genet Med*. 2023;25(9):100896. doi:10.1016/j.gim.2023.100896
33. Ontario Health (Quality). Genome-wide sequencing for unexplained developmental disabilities or multiple congenital anomalies: a health technology assessment. *Ont Health Technol Assess Ser*. 2020;20(11):1-178.
34. Trujillano D, Bertoli-Avella AM, Kumar Kandaswamy K, et al. Clinical exome sequencing: results from 2819 samples reflecting 1000 families. *Eur J Hum Genet*. 2017;25(2):176-182.
35. Lewis SA, Chopra M, Cohen JS, et al. Clinical actionability of genetic findings in cerebral palsy: a systematic review and meta-analysis. *JAMA Pediatr*. 2025 Feb 1;179(2):137–44. doi: 10.1001/jamapediatrics.2024.5059.
36. Lee H, Deignan JL, Dorrani N, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. *JAMA*. 2014;312(18):1880-1887.
37. Retterer K, Juusola J, Cho MT, et al. Clinical application of whole-exome sequencing across clinical indications. *Genet Med*. 2016;18:696–704.
38. Wenger AM, Guturu H, Bernstein JA, et al. Systematic reanalysis of clinical exome data yields additional diagnoses: Implications for providers. *Genet Med*. 2017;19(2):209-214.
39. Wright CF, McRae JF, Clayton S, et al. Making new genetic diagnoses with old data: Iterative reanalysis and reporting from genome-wide data in 1,133 families with developmental disorders. *Genet Med*. 2018;20(10):1216-1223.
40. Nambot S, Thevenon J, Kuentz P, et al. Clinical whole-exome sequencing for the diagnosis of rare disorders with congenital anomalies and/or intellectual disability: Substantial interest of prospective annual reanalysis. *Genet Med*. 2018;20(6):645-654.