FirstChoice VIP CARE
by Select Health of South Carolina

Whole genome, mitochondrial genome, and exome sequencing

Clinical Policy ID: CCP.1449

Recent review date: 7/2024

Next review date: 11/2025

Policy contains: Exome; genetic test; genome; high-throughput nucleotide sequencing; next-generation sequencing

FirstChoice VIP Care has developed clinical policies to assist with making coverage determinations. FirstChoice VIP Care's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered, on a case by case basis, by FirstChoice VIP Care when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. FirstChoice VIP Care's clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. FirstChoice VIP Care's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, FirstChoice VIP Care will update its clinical policies as necessary. FirstChoice VIP Care's clinical policies are not guarantees of payment.

Coverage policy

Whole mitochondrial genome sequencing is clinically proven and, therefore, may be medically necessary to confirm the diagnosis of a mitochondrial disorder, when genetic counseling is provided before and after testing (United Kingdom expert working group [Mavraki, 2023]; Mitochondrial Medicine Society [Parikh, 2015]).

Repeat whole mitochondrial genome sequencing using a different tissue sample may be medically necessary when there is a strong likelihood of mitochondrial disease and the initial sample is nondiagnostic, or to assess the risk of other organ involvement and heterogeneity in family members (Mavraki, 2023; Parikh, 2015).

Whole exome sequencing is clinically proven and, therefore, may be medically necessary to establish a diagnosis for an unexplained disorder when all of the following clinical and testing criteria are met:

One of the following clinical criteria:

- A suspected genetic disorder where a specific single-gene or targeted panel test is not available (American College of Medical Genetics and Genomics, 2012).
- A suspected genetic disorder where corresponding genetic tests have been nondiagnostic (American College of Medical Genetics and Genomics, 2012).

- A complex, unspecific genetic disorder with multiple differential diagnoses when whole exome sequencing would be a more efficient and practical diagnostic approach (American College of Medical Genetics and Genomics, 2012).
- A genetically heterogeneous disorder that requires multiple panel testing or clinical testing when whole exome sequencing may preclude the need for multiple and/or invasive procedures, follow-up, or screening that would be recommended in the absence of testing (American College of Medical Genetics and Genomics, 2012).
- The fetus presents with one or more significant sonographic anomalies suggestive of genetic etiology, and routine prenatal diagnostic methods are nondiagnostic (Monaghan, 2020).

All of the following testing criteria (American College of Medical Genetics and Genomics, 2013, 2015; Miller, 2023):

- The test is ordered by a genetic specialist.
- The test is analytically and clinically valid (i.e., supported by peer-reviewed published research).
- The test results will directly impact diagnosis, treatment, management, or prevention of disease of the member.
- Genetic counseling is provided before and after testing by a primary care provider and a geneticist (who is a physician or a licensed genetic counselor). If access to a genetic counselor or medical geneticist is not possible, genetic counseling may be initiated by a physician with relevant genetic expertise.
- Informed consent is obtained prior to testing and includes disclosure of the limitations of the testing method, incidental or secondary findings (and the option of not receiving these findings), the risks and benefits of the test information on the member's care and/or family, and current professional guidelines.
- The test results will be discussed with the member or guardian and documented in the clinical record.
- Member or guardian's desire for engagement with the integrated multidisciplinary team is documented in the clinical record.

Reanalysis of a whole exome sequencing test is clinically proven and, therefore, may be medically necessary after the initial variant classification has occurred and the new results will impact clinical management when either (Deignan, 2019):

- Member experiences additional symptoms that cannot be explained by the results of the initial test.
- New data (e.g., new gene-disease relationships and/or mechanisms of disease) or family history emerges suggesting a link between the member's symptoms and specific genetic variants.

Limitations

Whole exome sequencing and whole genome sequencing are not medically necessary for a member's symptoms that can be explained by other genetic or clinical testing.

All other uses of whole exome sequencing and whole genome sequencing are investigational/not clinically proven and, therefore, not medically necessary, including, but not limited to, pre-implantation testing, prenatal screening, general population screening, or as a first-tier test for newborn screening (American College of Medical Genetics and Genomics, 2012; American College of Obstetricians and Gynecologists, 2022).

Alternative covered services

- Chromosomal microarray analysis.

- Fluorescent in situ hybridization.
- Standard cytogenetic testing (e.g., karyotyping).
- Targeted mutation analysis consistent with personal and family histories.
- Clinical evaluation by an appropriately trained in-network provider.
- Genetic counseling.

Background

Whole genome sequencing and whole exome sequencing are molecular testing methods used to examine genetic variations within an individual's genetic code at the nucleotide level. Both methods, classified as next-generation sequencing, rely on rapid simultaneous sequencing of large amounts of deoxyribonucleic acid (DNA) to test for genetic disorders (National Library of Medicine, 2021).

Most known mutations that cause disease occur in exons. Whole exome sequencing can determine variations in the protein-coding region of any gene to be identified, rather than in only a select few genes, and can be an efficient method of detecting possible disease-causing mutations. Whole genome sequencing determines the order of all the nucleotides in an individual's DNA. It can determine variations in any part of the human genome, including those that whole exome sequencing or single gene sequencing would miss. It provides uniform analysis of whole regions of the human genome and an intrinsically richer data depth for understanding gene polymorphisms of clinical significance (National Library of Medicine, 2021).

Many genetic and non-genetic disorders involve mitochondrial dysfunction as a primary or secondary feature. Genetic variants that affect mitochondrial function may originate in the nuclear DNA, mitochondrial DNA, or both. Nuclear DNA pathogenic variants may be inherited in Mendelian autosomal recessive, autosomal dominant, or X-linked patterns. Mitochondrial DNA and any of its genetic variants are inherited maternally or occur *de novo* in the oocyte or embryo. Identical mitochondrial DNA variants may exist in all mitochondrial genomes within a mitochondrion or cell (homoplasmy) or only in a portion of the mitochondrial genomes (heteroplasmy). Heteroplasmy levels and quantification of mitochondrial DNA content have implications for further molecular testing (McCormick, 2018).

Such disease and genetic heterogeneity and a lack of reliable biomarkers for primary mitochondrial disease pose a diagnostic challenge, often resulting in misdiagnosis. When family history and clinical presentation is nonspecific but highly suggestive of a mitochondrial disorder, a battery of tests may be required to achieve a diagnosis, including genetic testing (Chinnery, 2021).

As the costs of next-generation sequencing have reportedly fallen and efficiency has improved, the demand to map the individual genome has increased. While many more genetic changes can be identified with whole exome and whole genome sequencing than with select gene sequencing, the significance of much of this information is unknown (Meynert, 2014).

The U.S. Food and Drug Administration and the Centers for Medicare & Medicaid Services have primary authority to evaluate and regulate genomic testing available for clinical care according to three criteria (National Human Genome Research Institute, 2022):

- Analytical validity refers to how consistently and accurately the test predicts the presence or absence of a particular gene or genetic change. Federal standards called Clinical Laboratory Improvement Amendments or even stricter state requirements for laboratory quality exist to ensure analytical validity.

- Clinical validity refers to how well the genetic variants being analyzed correlate to the presence, absence, or risk of a specific disease. The U.S. Food and Drug Administration and some states require information about clinical validity for some genetic tests.
- Clinical utility refers to the impact of test results on diagnosis, treatment, management, or prevention of a disease.

The regulatory pathway for next-generation sequencing continues to evolve. The U.S. Food and Drug Administration (2018) has cleared a limited number of single-gene, disease-specific, targeted, and next-generation sequencing-based in vitro diagnostic tests to diagnose pre-specified clinical conditions. It has not approved or cleared testing intended for more general use to aid in the diagnosis of suspected medical conditions arising from inherited or de novo germline variants (i.e., "germline diseases"). No legally marketed predicate device exists, and as a result, next-generation sequencing tests are automatically classified as class III devices subject to premarket approval application requirements.

To ensure safety and efficacy, the U.S. Food and Drug Administration (2018) issued guidance for providing recommendations for designing, developing, and validating next-generation sequencing-based tests intended to aid clinicians in the diagnosis of symptomatic individuals with suspected germline diseases. In time, a combination of general and special controls through the de novo classification process may be sufficient to mitigate the risks associated with these tests, at which point the test could receive a class II designation and serve as a predicate for future 510(k) submissions.

Findings

Whole exome sequencing and whole genome sequencing represent significant methodological advancements in clinical research but are applied cautiously in clinical practice. Such caution is warranted in light of the limited evidence supporting clinical validity and clinical utility for commercially available sequencing tests and associated clinical applications. The power of sequencing methods lies in their ability to match a patient's specific phenotype to the genes associated with that phenotype (Bean, 2019). Targeted sequencing approaches apply a discrete panel of genes or targets known to have strong associations with pathogenesis of disease or clinical relevance Targeted sequencing offers the ability to identify low-frequency variants in targeted regions with high confidence, making it suitable for profiling low-quality and fragmented clinical DNA samples (Bewicke-Copley, 2019; Zhao, 2019).

Guidelines

Professional organizations have dedicated substantial resources to developing clinical standards and guidelines to address clinical application. The American College of Medical Genetics and Genomics (Miller, 2023) and the National Institutes of Health Clinical Genome Resources (Hunter, 2016; Webber, 2018) developed a curated list of clinically actionable genomic variants to assist in standardizing the reporting and managing of secondary findings.

The American College of Medical Genetics and Genomics further recommends:

- Whole exome sequencing only after consultation with a clinical genetics physician (Miller, 2023).
- Against next-generation sequencing outside of research before the legal age of majority except for phenotype-driven, clinical diagnostic uses and circumstances in which early monitoring or interventions are available and effective (American College of Medical Genetics and Genomics, 2013).
- Fetal exome sequencing when a diagnosis cannot be obtained using routine prenatal methods in a fetus with one or more significant sonographic anomalies. Whole exome sequencing may be recommended

for trio analysis of the index child and both biological parents or siblings to improve the diagnostic rate (Monaghan, 2020).

- Against the clinical use of polygenic risk scores, which apply genome-wide association studies to estimate the probability of genetic susceptibility to a condition of interest, to guide medical management, understanding the limitations of the testing and applicability to the specific patient (Abu-El-Haija, 2023).
- Periodic reevaluation and reanalysis of previously classified variants when either the phenotypes of impacted individuals change over time or information regarding the phenotypic spectrum of a condition and relevant related variants expands, after the initial variant classification has occurred (Deignan, 2019).

Choice of sequencing method should balance the need to maximize diagnostic yield and minimize secondary findings, as the results may have high clinical significance for which interventions exist to prevent or ameliorate disease severity. While routine use of whole exome sequencing and whole genome sequencing is not considered the standard of care, select pediatric and adult patients may benefit from tests for diagnostic confirmation (American College of Medical Genetics and Genomics, 2012; American College of Obstetricians and Gynecologists, 2022; Bean, 2019; Mavraki, 2023; Parikh, 2015; Zhao, 2019):

- 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 clinically or prior genetic testing has been nondiagnostic.
- When clinically complex disorders with known extreme genetic heterogeneity require multiple panel testing or clinical testing, and next-generation sequencing would be a more efficient and practical approach.

While the cost effectiveness of prenatal exome sequencing is not known and is difficult to assess accurately, it may eliminate the need for single-gene and gene panel tests when a specific diagnosis cannot be determined by a prenatal phenotype that would direct specific gene testing (Monaghan, 2020). Exome sequencing may avoid delay in possible in utero or neonatal treatment and guide palliative care for a fatal prognosis. At the present time, there are no data supporting the clinical use for exome sequencing for other reproductive indications (American College of Obstetricians and Gynecologists, 2022).

Mitochondrial disorders

For diagnosis of suspected mitochondrial disorders, the Mitochondrial Medicine Society (Parikh, 2015) and a best practices consensus guideline from the United Kingdom that was ratified by the Association for Clinical Genomic Science (Mavraki, 2023) provide recommendations for diagnostic testing that are broadly applicable to an international audience. Expert consensus panels have addressed mitochondrial DNA variant interpretation (McCormick, 2020; Richards, 2015).

Next-generation sequencing in extended gene panels, whole exome sequencing, and whole genome sequencing of the mitochondrial genome may be considered first-line diagnostics. As a single test, comprehensive sequencing of the mitochondrial genome has significantly improved testing reliability and sensitivity to accurately diagnose mitochondrial disorders and provides information regarding point mutations, heteroplasmy levels, and deletions and duplications that are important diagnostic considerations. Comprehensive next-generation sequencing is particularly beneficial for more complex phenotypes or urgent referrals. When considering nuclear genome testing, single-gene testing has limited value, because mutations in different genes can produce the same phenotype. Blood is generally the preferred sample, but testing of other tissue samples may be necessary for diagnostic confirmation depending on symptom presentation and sample availability (Mavraki, 2023; Parikh, 2015).

Evidence reviews

A number of limitations needs to be resolved before whole exome and whole genome sequencing can replace targeted sequencing or other genetic analyses as the standard of care. The evidence of the clinical utility is limited to single cases or small patient cohorts from which economic studies were derived (Schwarze, 2018; Smith, 2019).

A systematic review of 36 economic and outcome studies refuted widely held claims that the cost of whole exome sequencing was falling over time, and only limited evidence that the cost of whole genome sequencing was decreasing. The most commonly used outcome measure was diagnostic yield, rather than survival or quality of life. The evidence of impact on clinical management, which is the major driver of cost effectiveness, was rarely reported. Study investigators called for examining clinical utility in large cohorts and including comparisons to other screening and diagnostic approaches with clearly defined clinical end points and associated health care costs (Schwarze, 2018). Interpretation of variants and variants of unknown significance, unanticipated but potentially valuable findings not related to the ordering indication (incidental or secondary findings), and the cost and reimbursement of testing are main challenges to the clinical utility of these testing methods (Mackley, 2017).

In 2021, we updated the references with no policy changes warranted.

In 2022, we added the following systematic reviews with no policy changes warranted. Systematic reviews highlight the variability in diagnostic yield of targeted sequencing, whole genome sequencing, and whole exome sequencing across study populations, with many dependent factors that precluded a meaningful meta-analysis or greater certainty in findings (Guadagnolo, 2021; Sheidley, 2022; Shickh, 2021; Stefanski, 2021).

In 2023, we updated references and defined the subject matter. No policy changes are warranted.

In 2024, we added a new guideline on the clinical use of polygenic risk scores from the American College of Medical Genetics and Genomics (Abu-El-Haija, 2023) and several systematic reviews/meta-analyses to the policy. Guideline recommendations were consolidated and presented at the beginning of the findings section. We included new medical necessity criteria for reanalysis of initial exome sequencing results based on Deignan (2019).

Multiple systematic reviews and meta-analyses have attempted to estimate the diagnostic yield and clinical utility of whole genome sequencing, whole exome sequencing, and targeted sequencing across a range of suspected genetic disorders or phenotypic presentations (Chung, 2023; Ferreira, 2023; Gonzalez-Mantilla, 2023; Nurchis, 2023; Shreeve, 2024). Few high-quality studies have addressed clinical utility in terms of changes to clinical management. Although technically feasible, limitations in the evidence base, particularly with respect to cost effectiveness, prevent wide acceptance of these sequencing methods as a first tier diagnostic test (Nurchis, 2022).

Later in 2024, to address a field request, we changed coverage statement to address mitochondrial genome sequencing as medically necessary for diagnostic confirmation of suspected mitochondrial disorders based on guideline recommendations (Mavraki, 2023; Parikh, 2015).

References

On May 6, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "exome (MeSH)," "genome wide association study (MeSH)," “high-throughput nucleotide sequencing,” (MeSH), and "genetic tests (MeSH)." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

Abu-El-Haija A, Reddi HV, Wand H, et al. The clinical application of polygenic risk scores: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2023;25(5):100803. Doi: 10.1016/j.gim.2023.100803.

American College of Medical Genetics and Genomics Board of Directors. Clinical utility of genetic and genomic services: A position statement of the American College of Medical Genetics and Genomics. *Gen Med*. 2015;17(6):505-507. Doi: 10.1038/gim.2015.41.

American College of Medical Genetics and Genomics Board of Directors. Policy statement. Points to consider in the clinical application of genomic sequencing. https://www.acmg.net/PDFLibrary/Genomic-Sequencing-Clinical-Application.pdf. Published May 15, 2012.

American College of Medical Genetics and Genomics Board of Directors. Points to consider for informed consent for genome/exome sequencing. *Gen Med.* 2013;15(9):748-749. Doi: 10.1038/gim.2013.94.

American College of Obstetricians and Gynecologists. Committee on Gynecologic Practice. Committee opinion number 727. Cascade testing: Testing women for known hereditary genetic mutations associated with cancer. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2018/01/cascade-testing-testing-women-for-known-hereditary-genetic-mutations-associated-with-cancer. Published January 2018. Reaffirmed 2022.

Bean LJH, Funke B, Carlston CM, et al. Diagnostic gene sequencing panels: From design to report – a technical standard of the American College of Medical Genetics and Genomics (ACMG). *Gen Med.* 2019:10.1038/s41436-41019-40666-z. Doi: 10.1038/s41436-019-0666-z.

Bewicke-Copley F, Arjun Kumar E, Palladino G, Korfi K, Wang J. Applications and analysis of targeted genomic sequencing in cancer studies. *Comput Struct Biotechnol J.* 2019;17:1348-1359. Doi: 10.1016/j.csbj.2019.10.004.

Chinnery PF. Primary Mitochondrial Disorders Overview. 2000 Jun 8. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. https://www.ncbi.nlm.nih.gov/books/NBK1224/. Last updated July 29, 2021.

Chung CCY, Hue SPY, Ng NYT, Doong PHL, Chu ATW, Chung BHY. 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.

Deignan JL, Chung WK, Kearney HM, Monaghan KG, Rehder CW, Chao EC. Points to consider in the reevaluation and reanalysis of genomic test results: A statement of the American College Of Medical Genetics and Genomics (ACMG). *Genet Med*. 2019;21(6):1267-1270. Doi: 10.1038/s41436-019-0478-1.

Ferreira EA, Buijs MJN, Wijngaard R, et al. Inherited metabolic disorders in adults: Systematic review on patient characteristics and diagnostic yield of broad sequencing techniques (exome and genome sequencing). *Front Neurol*. 2023;14:1206106. Doi: 10.3389/fneur.2023.1206106.

Gonzalez-Mantilla PJ, Hu Y, Myers SM, et al. Diagnostic yield of exome sequencing in cerebral palsy and implications for genetic testing guidelines: A systematic review and meta-analysis. *JAMA Pediatr*. 2023;177(5):472-478. Doi: 10.1001/jamapediatrics.2023.0008.

Guadagnolo D, Mastromoro G, De Palma F, Pizzuti A, Marchionni E. Prenatal exome sequencing: Background, current practice and future perspectives – A systematic review. *Diagnostics (Basel)*. 2021;11(2):224. Doi: 10.3390/diagnostics11020224.

Hunter JE, Irving SA, Biesecker LG, et al. A standardized, evidence-based protocol to assess clinical actionability of genetic disorders associated with genomic variation. *Gen Med.* 2016;18(12):1258-1268. Doi: 10.1038/gim.2016.40.

Mackley MP, Fletcher B, Parker M, Watkins H, Ormondroyd E. Stakeholder views on secondary findings in whole-genome and whole-exome sequencing: A systematic review of quantitative and qualitative studies. *Gen Med*. 2017;19(3):283-293. Doi: 10.1038/gim.2016.109.

Mavraki E, Labrum R, Sergeant K, et al. Genetic testing for mitochondrial disease: The United Kingdom best practice guidelines. *Eur J Hum Genet*. 2023;31(2):148-163. Doi: 10.1038/s41431-022-01249-w.

McCormick EM, Lott MT, Dulik MC, et al. Specifications of the ACMG/AMP standards and guidelines for mitochondrial DNA variant interpretation. *Hum Mutat*. 2020;41(12):2028-2057. Doi: 10.1002/humu.24107.

McCormick EM, Zolkipli-Cunningham Z, Falk MJ. Mitochondrial disease genetics update: Recent insights into the molecular diagnosis and expanding phenotype of primary mitochondrial disease. *Curr Opin Pediatr*. 2018;30(6):714-724. Doi: 10.1097/mop.0000000000000686.

Meynert AM, Ansari M, FitzPatrick DR, Taylor MS. Variant detection sensitivity and biases in whole genome and exome sequencing. *BMC bioinformatics.* 2014;15(1):247. Doi: 10.1186/1471-2105-15-247.

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 ff Medical Genetics and Genomics (ACMG). *Genet Med*. 2023;25(8):100866. Doi: 10.1016/j.gim.2023.100866.

Monaghan KG, Leach NT, Pekarek D, et al. The use of fetal exome sequencing in prenatal diagnosis: A points to consider document of the American College of Medical Genetics and Genomics (ACMG). *Gen Med.* 2020;22(4):675-680. Doi: 10.1038/s41436-019-0731-7.

National Human Genome Research Institute. Regulation of genetic tests. https://www.genome.gov/10002335/. Last updated February 2, 2022.

National Library of Medicine: Medline plus. What are whole exome sequencing and whole genome sequencing? https://medlineplus.gov/genetics/understanding/testing/sequencing/. Updated July 28, 2021.

Nurchis MC, Altamura G, Riccardi MT, et al. Whole genome sequencing diagnostic yield for paediatric patients with suspected genetic disorders: Systematic review, meta-analysis, and grade assessment. *Arch Public Health*. 2023;81(1):93. Doi: 10.1186/s13690-023-01112-4.

Nurchis MC, Riccardi MT, Radio FC, et al. Incremental net benefit of whole genome sequencing for newborns and children with suspected genetic disorders: Systematic review and meta-analysis of cost-effectiveness evidence. *Health Policy*. 2022;126(4):337-345. Doi: 10.1016/j.healthpol.2022.03.001.

Parikh S, Goldstein A, Koenig MK, et al. Diagnosis and management of mitochondrial disease: A consensus statement from the Mitochondrial Medicine Society. *Genet Med*. 2015;17(9):689-701. Doi: 10.1038/gim.2014.177.

Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-24. Doi: 10.1038/gim.2015.30.

Schwarze K, Buchanan J, Taylor JC, Wordsworth S. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. *Gen Med.* 2018;20(10):1122-1130. Doi: 10.1038/gim.2017.247.

Sheidley BR, Malinowski J, Bergner AL, et al. Genetic testing for the epilepsies: A systematic review. *Epilepsia*. 2022;63(2):375-387. Doi: 10.1111/epi.17141.

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.

Shreeve N, Sproule C, Choy KW, et al. Incremental yield of whole genome sequencing over chromosome microarray and exome sequencing for congenital anomalies in prenatal period and infancy: Systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2024;63(1):15-23. Doi: 10.1002/uog.27491.

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. *Gen Med.* 2019;21(1):3-16. Doi: 10.1038/s41436-018-0024-6.

Stefanski A, Calle-Lopez Y, Leu C, Perez-Palma E, Pestana-Knight E, Lal D. Clinical sequencing yield in epilepsy, autism spectrum disorder, and intellectual disability: A systematic review and meta-analysis. *Epilepsia*. 2021;62(1):143-151. Doi: 10.1111/epi.16755.

U.S. Food and Drug Administration. Considerations for design, development, and analytical validation of next generation sequencing (NGS) – based in vitro diagnostics (IVDS) intended to aid in the diagnosis of suspected germline diseases. Guidance for stakeholders and Food and Drug Administration staff. https://www.fda.gov/media/99208/download. Published April 13, 2018.

Webber EM, Hunter JE, Biesecker LG, et al. Evidence-based assessments of clinical actionability in the context of secondary findings: Updates from ClinGen's Actionability Working Group. *Hum mutat.* 2018;39(11):1677-1685. Doi: 10.1002/humu.23631.

Zhao EY, Jones M, Jones SJM. Whole-genome sequencing in cancer. *Cold Spring Harb Perspect Med.* 2019;9(3):a034579. Doi: 10.1101/cshperspect.a034579.

Policy updates

3/2020: initial review date and clinical policy effective date: 4/2020

3/2021: Policy references updated.

3/2022: Policy references updated.

3/2023: Policy references updated.

3/2024: Policy references updated. Coverage modified.

7/2024: Policy references updated. Coverage modified.