Clinical Policy: Genetic Testing: Exome and Genome Sequencing

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See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Exome sequencing (ES) (also known as 'whole exome sequencing (WES)') involves sequencing and often copy number variant (CNV) analysis of the portion of the genome that contains protein-coding DNA, which are termed exons. Together, all the exons in a genome are known as the exome, which constitutes approximately 1% of the genome and is currently estimated to contain about 85% of heritable disease-causing variants.

Genome sequencing (GS) (also known as 'whole genome sequencing (WGS)') is a comprehensive method that sequences both coding and noncoding regions of the genome. GS has typically been limited to use in the research setting but is emerging in the clinical setting and has a greater ability to detect large deletions or duplications in protein-coding regions compared with ES. GS requires greater data analysis but less DNA preparation prior to sequencing.

ES and GS have been proposed for use in patients presenting with disorders and anomalies not immediately explained by standard clinical workup. Potential candidates for ES and GS include patients who present with a broad spectrum of suspected genetic conditions.

Rapid exome sequencing (rES) and rapid genome (rGS) sequencing involves sequencing of the exome or genome, respectively, in an accelerated time frame. Preliminary results can typically be returned in less than 7 days, and a final report in less than two weeks. Studies suggest that the use of rES or rGS in acutely ill infants presenting with complex phenotypes that are likely rare genetic conditions, can identify a genetic diagnosis more quickly, allowing clinicians and family members to change acute medical or surgical management options and end the diagnostic odyssey. Ultra-rapid GS involves sequencing of the genome typically in less than 72 hours and is currently considered investigational.

Trio testing is preferred whenever possible. Testing of one available parent is a valid alternative if both are not immediately available and one or both parents can be done later if needed. While trio sequencing is preferred and recommended, an alternative method referred to as "Patient Plus" by PreventionGenetics may be considered. "Patient Plus" involves sequencing and copy number variant (CNV) analysis of the patient, and then targeted testing for the key variants found in the patient is performed on parental specimens. This approach permits detection of de novo variants and phasing of variants in recessive genes to increase diagnostic yield from a singleton sample in situations where full trio sequencing may not be feasible or preferable.

Exome sequencing or genome sequencing can reveal incidental findings or secondary findings. These findings are defined as results that are not related to the indication for undergoing the sequencing but may be of medical value or utility. Disclosure of these findings has been a topic

of intense debate within the medical genetics' community. In 2013, ACMG published recommendations for reporting secondary findings that included a list of conditions to be included. The list currently includes 59 genes that confer highly-penetrant and medically actionable conditions.

Pre-test and post-test genetic counseling that facilitates informed decision-making, the possibility to identify secondary finding with the option to 'opt out' of receiving these results, elicits patient preferences regarding secondary and/or incidental findings if possible, and formulates a plan for returning such results before testing occurs is strongly advised.

If a genetic diagnosis is not found by ES or GS, periodic reanalysis of the previously obtained genomic sequence is recommended. Reevaluation can occur on the variant-level or case-level. When appropriate, retesting may be considered (see above). Any variants identified and reported prior to the current ACMG variant classification standards should be reevaluated using the current ACMG standards.

Variant-level reanalysis should be considered in the following circumstances:

- Availability of a new community resource (e.g., gnomAD)
- Publication and/or adoption of a novel/updated methodology for variant assessment
- Publication of evidence supporting new gene–disease relationships and/or mechanisms of disease

Case-level reanalysis should be considered in the following circumstances:

- Significant changes in clinical and family history occur
- Significant improvements have been made to the bioinformatics handling of the data

Policy/Criteria

Standard Exome Sequencing

I. It is the policy of Coordinated Care of Washington, Inc., in accordance with the Health Care Authority's Health Technology Assessment, that whole exome sequencing (WES) (81415, 81416, 81417, 0214U, 0215U), with trio testing, when possible, is considered **medically necessary** for the evaluation of unexplained congenital or neurodevelopmental disorders in a phenotypically affected individual when ALL of the following are met:

A. A board-certified or board-eligible Medical Geneticist or an Advanced Practice Nurse in Genetics (APGN) credentialed by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC), who is not employed by a commercial genetic testing laboratory, has evaluated the patient and family history and recommends and/or orders the test.

B. A genetic etiology is considered the most likely explanation for the phenotype, based on either:

   i. Multiple abnormalities affecting unrelated organ systems (e.g., multiple congenital anomalies), or

   ii. TWO of the following

      1. Significant abnormality affecting at minimum, a single organ system,
      2. Profound global developmental delay or intellectual disability as defined below,
      3. Family history strongly suggestive of a genetic etiology, including consanguinity,

4. Period of unexplained developmental regression (unrelated to autism or epilepsy),
5. Biochemical findings suggestive of an inborn error of metabolism where targeted testing is not available.

C. Other circumstances (e.g., environmental exposures, injury, infection) do not reasonably explain the constellation of symptoms.
D. Clinical presentation does not fit a well-described syndrome for which single-gene or target panel testing (e.g., comparative genomic hybridization [CGH]/chromosomal microarray analysis [CMA]) is available.
E. The differential diagnosis list and/or phenotype warrant testing of multiple genes and one of the following:
   i. WES is more efficient and economical than the separate single-gene tests or panels that would be recommended based on the differential diagnosis (e.g., genetic conditions that demonstrate a high degree of genetic heterogeneity),
   ii. WES results may preclude the need for multiple invasive procedures or screening that would be recommended in the absence of testing (e.g., muscle biopsy).
F. A standard clinical work-up has been conducted and did not lead to a diagnosis.
G. Results will impact clinical decision-making for the individual being tested.
H. Pre- and post-test counseling is performed by an American Board of Medical Genetics or American Board of Genetic Counseling certified genetic counselor.

II. It is the policy of Coordinated Care of Washington, Inc., that *repeat* standard exome sequencing for the above indications may be considered **medically necessary** when meeting all the following:
A. Significant new symptoms develop in the member/enrollee or the member/enrollee's family history
B. The member/enrollee has been re-evaluated by a Board-Certified or Board-Eligible Medical Geneticist, a Certified Genetic Counselor, an advanced practice practitioner (e.g., APRN or Physician's Assistant) in genetics, who is not employed by a commercial genetic testing laboratory that recommends repeat exome sequencing
C. There have been improvements in technology/chemistry (e.g., new methods for DNA capture and/or sequencing), bioinformatics advancements, or new information regarding the genetic etiology of a condition that could explain the patient's clinical features and would not have been able to be detected by the previous exome sequencing the patient underwent.

III. It is the policy of Coordinated Care of Washington, Inc., that current evidence does not support *repeat* standard exome sequencing (81415, 81416, 0214U, 0215U) for all other indications.

IV. It is the policy of Coordinated Care of Washington, Inc., in accordance with the Health Care Authority's Health Technology Assessment, that current evidence does not support standard exome sequencing for all other indications, including:
A. Screening asymptomatic/healthy individuals for genetic disorders,
B. Uncomplicated autism spectrum disorder, developmental delay, mild to moderate global developmental delay,
C. Other circumstances (e.g., environmental exposures, injury, infection) that reasonably explain the constellation of symptoms,

D. Carrier testing for "at risk" relatives,
E. Prenatal or pre-implantation testing.

Rapid Exome Sequencing

I. It is the policy of Coordinated Care of Washington, Inc., that rapid exome sequencing (81415, 81416, 81417) may be considered medically necessary when meeting all the following:
   A. The member/enrollee is an acutely ill infant (≤2 months)
   B. The patient and patient's family history have been evaluated by a Board Certified or Board-Eligible Medical Geneticist, or an Advanced Practice Nurse in Genetics (APGN)
   C. 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:
      i. Multiple congenital abnormalities affecting unrelated organ systems
      ii. Two of the following criteria are met:
         a) Abnormality significantly affecting (at minimum) a single organ system
         b) Dysmorphic features
         c) Encephalopathy
         d) Symptoms of a complex neurodevelopmental disorder (e.g., dystonia, hemiplegia, spasticity/hypertonia, epilepsy, hypotonia)
         e) Family history strongly suggestive of a genetic etiology, including consanguinity
         f) Clinical or laboratory findings suggestive of an inborn error of metabolism
   D. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity)
   E. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available
   F. A diagnosis cannot be made in a timely manner by standard clinical evaluation, excluding invasive procedures such as muscle biopsy
   G. There is a predicted impact on the health outcome, including impact on medical management during the hospitalization based on the results
   H. Pre- and post-test counseling by an appropriate provider, such as a Board-Certified Medical Geneticist, a Certified Genetic Counselor, or an Advanced Practice Nurse in Genetics
   I. The acutely ill infant does not have any of the following diagnoses:
      i. Isolated Transient Neonatal Tachypnea
      ii. Isolated unconjugated hyperbilirubinemia
      iii. Isolated Hypoxic Ischemic Encephalopathy with clear precipitating event
      iv. Isolated meconium aspiration

II. It is the policy of Coordinated Care of Washington, Inc., that current evidence does not support rapid exome sequencing (81415, 81416, 81417) for all other indications.

Standard Genome Sequencing

I. It is the policy of Coordinated Care of Washington, Inc., that current evidence does not support standard genome sequencing (81425, 81426, 81427, 0012U, 0209U, 0212U, 0213U, 0265U, 0267U) for any indication.

Rapid Genome Sequencing

I. It is the policy of Coordinated Care of Washington, Inc., that current evidence does not support rapid genome sequencing or ultra rapid genome sequencing (81425, 81426, 81427, 0094U) for any indication.

Definitions

Exome Sequencing (ES) is a genomic technique for sequencing all the protein-coding regions of genes in the genome (also known as the exome).

Genome Sequencing (GS) is a genomic technique for sequencing the complete DNA sequence, which includes protein coding as well as non-coding DNA elements.

Trio Testing includes testing of the child and both parents and increases the chances of finding a definitive diagnosis, while reducing false-positive findings.

Comparator Exome Sequencing is used only for comparison with the proband (individual undergoing exome sequencing) and is used to inform the pathogenicity of variants. A comparator exome is typically one or both parents to the proband.

Global developmental delay (GDD) is used to categorize children who are younger than five years of age. It defines a significant delay (performance two standard deviations or more below the mean on age-appropriate, standardized, normal-referenced testing) in two or more developmental domains, including gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living and is thought to predict a future diagnosis of ID. Such delays require accurate documentation by using norm-referenced and age-appropriate standardized measures of development administered by experienced developmental specialists, or documentation of profound delays based on age-appropriate developmental milestones are present.

Intellectual disability (ID) is a life-long disability diagnosed at or after age five when intelligence quotient (IQ) testing is considered valid and reliable. The Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-V) defines patients with ID as having an IQ less than 70, onset during childhood, and dysfunction or impairment in more than two areas of adaptive behavior or systems of support.

Background

The portion of this policy describing Whole Exome Sequencing is based entirely on Washington State Health Care Authority (HCA) Health Technology Assessment (HTA) and Health Care Authority Billing Guidelines.

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG) (2012) published a position statement on clinical application of exome and genome testing. ACMG recommends considering ES/GS sequencing 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 is available."
- "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."

In 2013, ACMG published the following recommendations for reporting of incidental findings in clinical exome and genome sequencing:

1. "Constitutional mutations found in the genes on the minimum list (Table 1) should be reported by the laboratory to the ordering clinician, regardless of the indication for which the clinical sequencing was ordered.
    - Additional genes may be analyzed for incidental variants, as deemed appropriate by the laboratory.
    - Incidental variants should be reported regardless of the age of the patient.
    - Incidental variants should be reported for any clinical sequencing conducted on a constitutional (but not tumor) tissue. This includes the normal sample of a tumor-normal sequenced dyad and unaffected members of a family trio."
2. "The Working Group recommends that laboratories seek and report only the types of variants within these genes that we have delineated (Table 1).
    - For most genes, only variants that have been previously reported and are a recognized cause of the disorder or variants that are previously unreported but are of the type that is expected to cause the disorder, as defined by prior ACMG guidelines,20 should be reported.
    - For some genes, predicted loss-of-function variants are not relevant (e.g., COL3A1 and most hypertrophic cardiomyopathy genes).
    - For some genes (e.g., APOB), laboratories should only report variants for certain associated conditions."
3. "It is the responsibility of the ordering clinician/team to provide comprehensive pre and posttest counseling to the patient.
    - Clinicians should be familiar with the basic attributes and limitations of clinical sequencing.
    - Clinicians should alert patients to the possibility that clinical sequencing may generate incidental findings that could require further evaluation.
    - Given the complexity of genomic information, the clinical geneticist should be consulted at the appropriate time, which may include ordering, interpreting, and communicating genomic testing. "
4. "These recommendations reflect limitations of current technology and are therefore focused on disorders that are caused by point mutations and small insertions and deletions, not those primarily caused by structural variants, repeat expansions, or copy-number variations."
5. "The Working Group recommends that the ACMG, together with content experts and other professional organizations, refine and update this list at least annually."

In 2016, ACMG updated its recommendations on reporting secondary findings in WGS and WES testing. ACMG determined that reporting some secondary findings would likely have medical benefit for the patients and families of patients undergoing clinical sequencing, recommending that, when a report is issued for clinically indicated exome and genome sequencing, a minimum list of conditions, genes, and variants should be routinely evaluated and reported to the ordering clinician. The 2016 update added 4 genes and removed 1 gene resulting in an updated secondary findings minimum list including 59 medically actionable genes recommended for return in clinical genomic sequencing.
In 2018, ACMG published points to consider encouraging engagement of older children and adolescents being considered for exome and/or genome sequencing, and that:

- "The purpose of the engagement process is to ensure that the mature older child is actively involved in conversation to understand the goals and implications of genomic testing and potential findings and to consider its personal benefits and limitations while having the opportunity to express their feelings and opinions".
- "It is critical to engage the child as much as possible in this process, which includes the assent of the child whenever reasonable."
- "Children as young as 8 years of age should be part of an active engagement process to the extent that they are considered by the clinician and parent to be psychologically and cognitively capable."

In 2019, ACMG published points to consider around exome or genome reanalysis and retesting (discussed in Clinical Considerations). These considerations include points to consider for variant-level reanalysis, case-level reanalysis, and retesting for laboratories and clinicians.
In 2021, ACMG published ACMG SF v3.0, an updated list of genes included in the secondary findings, which added an additional 14 genes bringing the total up to 73 genes. ACMG also published a policy statement regarding updated recommendations for reporting of secondary findings in clinical exome and genome sequencing which clarified that ACMG supports the continued research and discussion around population screening for the genes included in the secondary findings list, however "ACMG has made it clear that the ACMG SF is not validated for general population screening".
Additionally, the following policy recommendations were made regarding consenting and reporting practices:

- "The SF list is intended as a "minimum list" of actionable secondary findings."
- "Providing the opportunity for an informed decision and opt out, if desired, at the time of consent should continue to be the standard for secondary findings."
- "The option to receive SFs should be offered regardless of the age of the patient. The best interest of the child should still be prioritized when disclosing risk for adult-onset conditions in minors."
- "The option to opt out of SFs should also be presented to the individual in the context of prenatal ES/GS."
- "The consent process should include discussion of the categories of reportable gene–phenotype pairs related to the ACMG SF list."
- "Thoughtful consideration of the context of a positive SF result during results disclosure, and when making related medical management recommendations, is necessary."
- "If laboratories report apparent somatic mosaicism, the consent process should address this."

- "Pre-test and post-test genetic counseling should be provided to any person receiving SF results in order to discuss the types of possible results, limitations of testing, and medical implications of any results."

In 2021, The American College of Medical Genetics and Genomics (ACMG) published an evidence-based clinical practice guideline on exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability. ACMG recommends using exome or genome sequencing be used as a first or second tier test for patients diagnosed with one or more congenital anomalies before the age of 1, or with intellectual disability/developmental delay before the age of 18. In previous guidelines, ACMG has recommended the use of such testing for clinical management of the proband. In this 2021 guideline, ACMG recommends exome or genome sequencing for active and long-term clinical management of the program, as well as for implications on family-focused and reproductive outcomes.

National Society for Genetic Counselors

The National Society for Genetic Counselors (NSGC) released a position statement (2013, updated 2020) stating the following in regard to secondary and incidental findings in genetic testing:

> "The National Society of Genetic Counselors strongly advises pre-test counseling that facilitates informed decision-making, elicits patient preferences regarding secondary and/or incidental findings if possible, and formulates a plan for returning such results before testing occurs.
>
> Germline and somatic genetic testing, in both clinical and research contexts, may identify secondary findings and incidental findings as a part of the test performed. Secondary findings are purposely analyzed as part of the test, but unrelated to the primary testing indication. Incidental findings are detected unexpectedly during the analysis, and unrelated to the primary testing indication. Both types of variants may be disclosed as a part of the return-of-results process.

The pre-test counseling process should establish clear expectations for what categories of results will and will not be returned. Healthcare practitioners conducting the informed consent and return-of-results processes for broad genomic testing and screening should ensure that their patients have access to practitioners with genetic expertise, such as genetic counselors."

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2019, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

CPT® Codes	Description
0012U	Gemline disorder, gene rearrangement detection by whole genome next-generation sequencing, DNA, whole blood, report of specific gene rearrangement(s)

CPT® Codes	Description
0036U	Exome (i.e., somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses
0094U	Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis
0209U	Cytogenomic constitutional (genome-wide) analysis, interrogation or genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities
0212U	Rare diseases (constitutional/heritable disorder), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband
0213U	Rare diseases (constitutional/heritable disorder), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator genome (e.g., parent, sibling)
0214U	Rare diseases (constitutional/heritable disorder), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband
0215U	Rare diseases (constitutional/heritable disorder), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator exome (e.g., parent, sibling)
0265U	Rare constitutional and other heritable disorders, whole genome and mitochondrial DNA sequence analysis, blood, frozen and formalin-fixed paraffin-embedded (FFPE) tissue, saliva, buccal swabs or cell lines, identification of single nucleotide and copy number variants
0267U	Rare constitutional and other heritable disorders, identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping and whole genome sequencing
81415	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (e.g., parents, siblings)
81417	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (e.g., updated knowledge or unrelated condition/syndrome)
81425	Genome (unexplained constitutional or heritable disorder or syndrome); sequence analysis

CPT® Codes	Description
81426	Genome (unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (e.g., parents, siblings)
81427	Genome (unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (e.g., updated knowledge or unrelated condition/syndrome)

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	11/20	03/21
Annual review. Expanded Description. Added Effective Date. Added 0036U, 0214U, 0215U, 81417. Replaced Not Covered with Not Medically Necessary.	01/22	02/22
Policy renumbered and renamed from WA.CP.MP.524 Whole Exome Sequencing to WA.CP.MP.219 Genetic Testing: Exome and Genome Sequencing. Added sections on repeat exome sequencing, rapid exome sequencing, standard genome sequencing and rapid genome sequencing. Added Definitions. Revised Background. Expanded code list. Updated References.	03/22	03/22

References

1. 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
2. ACMG Board of Directors. Points to consider in the clinical application of genomic sequencing. Genet Med. 2012;14(8):759-761. doi:10.1038/gim.2012.74
3. Kingsmore SF, Cakici JA, Clark MM, 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. doi:10.1016/j.ajhg.2019.08.009
4. Petrikin JE, Cakici JA, Clark MM, et al. The NSIGHT1-randomized controlled trial: rapid whole-genome sequencing for accelerated etiologic diagnosis in critically ill infants. NPJ Genom Med. 2018;3:6. Published 2018 Feb 9. doi:10.1038/s41525-018-0045-8
5. "Rapid Genome Sequencing". Seattle Children's Hospital Patient-centered Laboratory Utilization Guidance Services. http://www.schplugs.org/wp-content/uploads/Rapid-Genome-Sequencing-Policy_FINAL_Oct-2019.pdf. October 2019.
6. Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing [published correction appears in Genet Med. 2017 May;19(5):606]. Genet Med. 2013;15(7):565-574. doi:10.1038/gim.2013.73
7. "Secondary and Incidental Findings in Genetic Testing". Position Statement from National Society of Genetic Counselors. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/secondary-and-incidental-findings-in-genetic-testing-1. Released September 27, 2013. Updated March 23, 2020
8. Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement

of the American College of Medical Genetics and Genomics [published correction appears in Genet Med. 2017 Apr;19(4):484]. Genet Med. 2017;19(2):249-255. doi:10.1038/gim.2016.190
9. Bush LW, Bartoshesky LE, David KL, et al. Pediatric clinical exome/genome sequencing and the engagement process: encouraging active conversation with the older child and adolescent: points to consider-a statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2018;20(7):692-694. doi:10.1038/gim.2018.36
10. Deignan JL, Chung WK, Kearney HM, et al. 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
11. 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(3):275-284. doi:10.1111/cge.12654
12. Wenger AM, Guturu H, Bernstein JA, Bejerano G. Systematic reanalysis of clinical exome data yields additional diagnoses: implications for providers. Genet Med. 2017;19(2):209-214. doi:10.1038/gim.2016.88
13. ACMG Board of Directors. Points to consider for informed consent for genome/exome sequencing. Genet Med. 2013;15(9):748-749. doi:10.1038/gim.2013.94
14. 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) [published online ahead of print, 2021 May 20]. Genet Med. 2021;10.1038/s41436-021-01171-4. doi:10.1038/s41436-021-01171-4
15. 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) [published online ahead of print, 2021 May 20]. Genet Med. 2021;10.1038/s41436-021-01172-3. doi:10.1038/s41436-021-01172-3
16. 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) [published online ahead of print, 2021 Jul 1]. Genet Med. 2021;10.1038/s41436-021-01242-6. doi:10.1038/s41436-021-01242-6
17. Pivalizza P, Lalani SR. In: Armsby C, ed. *Intellectual disability in children: Evaluation for a cause*. UpToDate, 2018. Accessed December 14, 2021. https://www.uptodate.com/contents/intellectual-disability-in-children-evaluation-for-a-cause
18. Dimmock D, Caylor S, Waldman B, et al. Project Baby Bear: Rapid precision care incorporating rWGS in 5 California children's hospitals demonstrates improved clinical outcomes and reduced costs of care. Am J Hum Genet. 2021;108(7):1231-1238. doi:10.1016/j.ajhg.2021.05.008
19. Whitehead, N., Kahwati, L., Moore, A., et al. RTI International. *Whole Exome Sequencing*. Washington Health Technology Assessment. October 12, 2019.
20. Washington State Health Care Authority. Physician-related Services/Health Care Billing Guide. https://www.hca.wa.gov/assets/billers-and-providers/Physician-related-serv-bg-20220101.pdf Revision effective January 1, 2022.

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/Enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

Note: For Medicaid members/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.