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Clinical Appropriateness Guidelines

Genetic Testing

Appropriate Use Criteria: Whole Exome Sequencing and Whole Genome Sequencing

Proprietary

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Description and Application of the Guidelines

The Carelon Clinical Appropriateness Guidelines (hereinafter “the Carelon Clinical Appropriateness Guidelines” or the “Guidelines”) are designed to assist providers in making the most appropriate treatment decision for a specific clinical condition for an individual. As used by Carelon, the Guidelines establish objective and evidence-based criteria for medical necessity determinations where possible. In the process, multiple functions are accomplished:

- To establish criteria for when services are medically necessary (i.e., in general, shown to be effective in improving health outcomes and considered the most appropriate level of service)
- To assist the practitioner as an educational tool
- To encourage standardization of medical practice patterns
- To curtail the performance of inappropriate and/or duplicate services
- To advocate for patient safety concerns
- To enhance the quality of health care
- To promote the most efficient and cost-effective use of services

The Carelon guideline development process complies with applicable accreditation standards, including the requirement that the Guidelines be developed with involvement from appropriate providers with current clinical expertise relevant to the Guidelines under review and be based on the most up-to-date clinical principles and best practices. Relevant citations are included in the References section attached to each Guideline. Carelon reviews all of its Guidelines at least annually.

Carelon makes its Guidelines publicly available on its website twenty-four hours a day, seven days a week. Copies of the Carelon Clinical Appropriateness Guidelines are also available upon oral or written request. Although the Guidelines are publicly-available, Carelon considers the Guidelines to be important, proprietary information of Carelon, which cannot be sold, assigned, leased, licensed, reproduced or distributed without the written consent of Carelon.

Carelon applies objective and evidence-based criteria, and takes individual circumstances and the local delivery system into account when determining the medical appropriateness of health care services. The Carelon Guidelines are just guidelines for the provision of specialty health services. These criteria are designed to guide both providers and reviewers to the most appropriate services based on a patient’s unique circumstances. In all cases, clinical judgment consistent with the standards of good medical practice should be used when applying the Guidelines. Guideline determinations are made based on the information provided at the time of the request. It is expected that medical necessity decisions may change as new information is provided or based on unique aspects of the patient’s condition. The treating clinician has final authority and responsibility for treatment decisions regarding the care of the patient and for justifying and demonstrating the existence of medical necessity for the requested service. The Guidelines are not a substitute for the experience and judgment of a physician or other health care professionals. Any clinician seeking to apply or consult the Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment.

The Guidelines do not address coverage, benefit or other plan specific issues. Applicable federal and state coverage mandates take precedence over these clinical guidelines. If requested by a health plan, Carelon will review requests based on health plan medical policy/guidelines in lieu of the Carelon Guidelines. Pharmaceuticals, radiotracers, or medical devices used in any of the diagnostic or therapeutic interventions listed in the Guidelines must be FDA approved or conditionally approved for the intended use. However, use of an FDA approved or conditionally approved product does not constitute medical necessity or guarantee reimbursement by the respective health plan.

The Guidelines may also be used by the health plan or by Carelon for purposes of provider education, or to review the medical necessity of services by any provider who has been notified of the need for medical necessity review, due to billing practices or claims that are not consistent with other providers in terms of frequency or some other manner.

General Clinical Guideline

Clinical Appropriateness Framework

Critical to any finding of clinical appropriateness under the guidelines for a specific diagnostic or therapeutic intervention are the following elements:

- Prior to any intervention, it is essential that the clinician confirm the diagnosis or establish its pretest likelihood based on a complete evaluation of the patient. This includes a history and physical examination and, where applicable, a review of relevant laboratory studies, diagnostic testing, and response to prior therapeutic intervention.
- The anticipated benefit of the recommended intervention should outweigh any potential harms that may result (net benefit).
- Current literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.
- Based on the clinical evaluation, current literature, and standards of medical practice, there exists a reasonable likelihood that the intervention will change management and/or lead to an improved outcome for the patient.

If these elements are not established with respect to a given request, the determination of appropriateness will most likely require a peer-to-peer conversation to understand the individual and unique facts that would supersede the requirements set forth above. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account.

Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions

Requests for multiple diagnostic or therapeutic interventions at the same time will often require a peer-to-peer conversation to understand the individual circumstances that support the medical necessity of performing all interventions simultaneously. This is based on the fact that appropriateness of additional intervention is often dependent on the outcome of the initial intervention.

Additionally, either of the following may apply:

- Current literature and/or standards of medical practice support that one of the requested diagnostic or therapeutic interventions is more appropriate in the clinical situation presented; or
- One of the diagnostic or therapeutic interventions requested is more likely to improve patient outcomes based on current literature and/or standards of medical practice.

Repeat Diagnostic Intervention

In general, repeated testing of the same anatomic location for the same indication should be limited to evaluation following an intervention, or when there is a change in clinical status such that additional testing is required to determine next steps in management. At times, it may be necessary to repeat a test using different techniques or protocols to clarify a finding or result of the original study.

Repeated testing for the same indication using the same or similar technology may be subject to additional review or require peer-to-peer conversation in the following scenarios:

- Repeated diagnostic testing at the same facility due to technical issues
- Repeated diagnostic testing requested at a different facility due to provider preference or quality concerns
- Repeated diagnostic testing of the same anatomic area based on persistent symptoms with no clinical change, treatment, or intervention since the previous study

- Repeated diagnostic testing of the same anatomic area by different providers for the same member over a short period of time

Repeat Therapeutic Intervention

In general, repeated therapeutic intervention in the same anatomic area is considered appropriate when the prior intervention proved effective or beneficial and the expected duration of relief has lapsed. A repeat intervention requested prior to the expected duration of relief is not appropriate unless it can be confirmed that the prior intervention was never administered.

Whole Exome Sequencing and Whole Genome Sequencing

Clinical Indications

Whole Exome Sequencing

Whole exome sequencing (WES) is considered **medically necessary** in the evaluation of an individual who meets **ALL** of the following criteria:

- **ONE** of the following criteria is met:
    - Multiple anomalies not specific to a well-delineated genetic syndrome apparent before 1 year of age
    - Apparently non-syndromic developmental delay or intellectual disability with onset prior to 18 years of age
    - For the evaluation of a fetus with abnormal fetal anatomic findings which are characteristic of a genetic abnormality and no diagnostic findings were found on karyotype and/or chromosomal micro array testing
- When the results of testing would confirm or establish a clinical diagnosis
- Genetic counseling, which encompasses **ALL** of the following components, has been performed:
    - Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence
    - Education about inheritance, genetic testing, disease management, prevention and resources
    - Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition
    - Counseling for the psychological aspects of genetic testing

Note: WES may include comparator WES testing of the biologic parents or sibling of the affected individual.

Whole Genome Sequencing

Whole genome sequencing (WGS) is considered **not medically necessary** in the outpatient setting for all indications.

Rationale

Whereas whole exome sequencing (WES) involves sequencing all protein coding regions of the DNA (about 1.5% of the human genome), whole genome sequencing entails sequencing all coding (exons) and noncoding (intron) nuclear DNA as well as mitochondrial DNA. The rationale for exploring the role of whole genome sequencing (WGS) rather than WES is that some rare genetic diseases involve noncoding structural rearrangements and break points in non-coding regions which are not detected in routine exome analyses.

Research related to WGS testing typically involves careful selection of severely ill patients (often neonates). Congenital anomalies are structural or functional abnormalities usually evident at birth, or shortly thereafter, and can be consequential to an individual's life expectancy, health status, and physical or social functioning.[1] In this setting, clinical geneticists and experienced multidisciplinary teams are typically involved and when a specific illness phenotype is suspected, single gene testing or multi-gene panel testing and sometimes chromosomal microarray testing is pursued with turnaround times of around 4 weeks. WGS testing typically takes 8-12 weeks and has been explored mostly in situations where all other testing is negative or when the seriously ill infant has multiple non-specific phenotypic features.[2] Importantly, pre- and post-test genetic counseling is critically important in this setting. There is research evaluating WGS in highly selected cases as an early single

pass test that includes all single nucleotide variants, copy number variations, structural variations, and mitochondrial DNA. Trio analysis is sometimes included, and this involves WGS testing not only the affected child but also both parents.

The feasibility of a rapid WGS (rWGS) testing approach was tested using a payor funded, prospective, real-world quality improvement project in the regional ICUs of five tertiary care children's hospitals—Project Baby Bear. Participation was limited to acutely ill Medi-Cal beneficiaries who were admitted November 2018 to May 2020, were < 1 year old and within one week of hospitalization, or had just developed an abnormal response to therapy. The primary outcomes evaluated were changes in medical care reported by physicians and changes in the cost of care.[3] Of 184 infants enrolled, 74 (40%) received a diagnosis by rWGS that explained their admission in a median time of 3 days. In 58 (32%) affected individuals, rWGS led to changes in medical care. Testing and precision medicine cost $1.7 million but modeled data suggested cost savings associated with this approach when commercial costs were considered. The savings were not attributable to the diagnostic capability of the rWGS testing as much as acceleration of the diagnostic journey and reduced length of stay in the newborn intensive care unit. The applicability of this ultra-rapid testing to the real world is limited by the limited availability of this testing and the necessity of trio testing (meaning both parents submit specimens along with the child), which enables the rapid 3-day turnaround time.

In 2020, the Pediatric Exome Sequencing/Genome Sequencing Guideline Work Group (Peds ES/GS GWG) was convened to develop an evidence-based guideline for the clinical use of ES/GS in patients with congenital anomalies, developmental delay, or intellectual disability. This working group addressed the question “Should exome sequencing or genome sequencing be used in the evaluation of patients with more than one congenital anomaly apparent before one year of age OR in patients with developmental disability/intellectual disability diagnosed prior to 18 years of age compared to standard testing without exome or genome sequencing?” The evidence review involved 36 studies where the patient population was greater than twenty. The authors concluded that WES or WGS testing has a higher diagnostic yield and may be more cost effective when ordered early in the diagnostic evaluation.[1]

A more recent systematic review examining the role of genomic medicine with WES or WGS testing in critically ill infants was conducted with data from 21 included studies reflecting results from 1654 patients. A mean of 46% (range, 15%-72%) of patients had a positive genetic test result, and a mean of 37% (range, 13%-61%) met the criteria for experiencing utility.[4] This review found that studies disproportionally highlighted patient cases that resulted in treatment change, and larger studies reported substantially lower utility. The authors concluded that a more complete definition of utility that is used consistently may improve understanding of potential benefits and harms of this testing of critically ill infants. An editorial related to this systematic review emphasized that strengthening the rigor with which utility is measured is critically important and may serve as the foundation for evaluation of genomic medicine in other clinical contexts outside of neonatal intensive care.[5]

References

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2. Dunn P, Albury CL, Maksemous N, et al. Next Generation Sequencing Methods for Diagnosis of Epilepsy Syndromes. Front Genet. 2018;9:20. Epub 2018/02/23. PMID: 29467791
3. 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):1231-8. Epub 2021/06/06. PMID: 34089648
4. Callahan KP, Mueller R, Flibotte J, et al. Measures of Utility Among Studies of Genomic Medicine for Critically Ill Infants: A Systematic Review. JAMA Netw Open. 2022;5(8):e2225980. Epub 2022/08/11. PMID: 35947384
5. Smith HS. Genomic Medicine's Critical Outcome Measure-Utility. JAMA Netw Open. 2022;5(8):e2225988. Epub 2022/08/11. PMID: 35947388

Codes

The following code list is not meant to be all-inclusive. Authorization requirements will vary by health plan. Please consult the applicable health plan for guidance on specific procedure codes.

Specific CPT codes for services should be used when available. Nonspecific or not otherwise classified codes may be subject to additional documentation requirements and review.

CPT/HCPCS

81415	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (eg, parents, siblings)
81417	Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)
81425	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81426	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (eg, parents, siblings)
81427	Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)
81440	**Nuclear encoded** mitochondrial genes (eg, neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including *BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP*
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
81460	Whole mitochondrial genome (eg, Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection
81465	Whole mitochondrial genome large deletion analysis panel (eg, Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection if performed
0036U	Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses
0094U	Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis
0212U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband (Do not report 0212U in conjunction with 81425)
0213U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent, sibling)
0214U	Rare diseases (constitutional/heritable disorders), 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 disorders), 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 (eg, parent, sibling)
0260U	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping
0264U	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping
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
0266U	Unexplained constitutional or other heritable disorders or syndromes, tissue specific gene expression by whole transcriptome and next-generation sequencing, blood, formalin-fixed paraffin embedded (FFPE) tissue or fresh frozen tissue, reported as presence or absence of splicing or expression changes
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
0299U	Oncology (pan tumor), whole genome optical genome mapping of paired malignant and normal DNA specimens, fresh frozen tissue, blood, or bone marrow, comparative structural variant identification
0300U	Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification

0331U	Oncology (hematolymphoid neoplasia), optical genome mapping for copy number alterations and gene rearrangements utilizing DNA from blood or bone marrow, report of clinically significant alterations
0335U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, fetal sample, identification and categorization of genetic variants (Do not report 0335U in conjunction with 81425, 0212U)
0336U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent) (Do not report 0336U in conjunction with 81426, 0213U)
0410U	Oncology (pancreatic), DNA, whole genome sequencing with 5-hydroxymethylcytosine enrichment, whole blood or plasma, algorithm reported as cancer detected or not detected
0417U	Rare diseases (constitutional/heritable disorders), whole mitochondrial genome sequence with heteroplasmy detection and deletion analysis, nuclear-encoded mitochondrial gene analysis of 335 nuclear genes, including sequence changes, deletions, insertions, and copy number variants analysis, blood or saliva, identification and categorization of mitochondrial disorder-associated genetic variants
0425U	Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis, each comparator genome (eg, parents, siblings)
0426U	Genome (eg, unexplained constitutional or heritable disorder or syndrome), ultra-rapid sequence analysis

ICD-10 Diagnosis

Refer to the ICD-10 CM manual

History

Status	Review Date	Effective Date	Action
Updated	n/a	01/01/2024	Added CPT codes 81440, 81455, 0299U, 0300U, 0331U, 0410U, 0417U, 0425U, and 0426U. Removed 0012U.
Created	09/21/2022	02/12/2023	Independent Multispecialty Physician Panel (IMPP) review. Original effective date.