

Approval and implementation dates for specific health plans may vary. Please consult the applicable health plan for more details.

Clinical Appropriateness Guidelines

Genetic Testing

Appropriate Use Criteria: Chromosomal Microarray Analysis

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. The Guidelines establish objective and evidence-based criteria for medical necessity determinations, where possible, that can be used in support of the following:

- To establish criteria for when services are medically necessary
- 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 address 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 and legal 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. Resources reviewed include widely used treatment guidelines, randomized controlled trials or prospective cohort studies, and large systematic reviews or meta-analyses. Carelon reviews all of its Guidelines at least annually.

Carelon makes its Guidelines publicly available on its website. Copies of the Guidelines are also available upon oral or written request. Additional details, such as summaries of evidence, a list of the sources of evidence, and an explanation of the rationale that supports the adoption of the Guidelines, are included in each guideline document.

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. Use of the Guidelines by any external AI entity without the express written permission of Carelon is prohibited.

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, and in the case of reviews for Medicare Advantage Plans, the Guidelines are only applied where there are not fully established CMS criteria. If requested by a health plan, Carelon will review requests based on health plan medical policy/guidelines in lieu of the Carelon Guidelines. 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 is likely to outweigh any potential harms, including from delay or decreased access to services that may result (net benefit).
- Widely used treatment guidelines and/or current clinical literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.
- There exists a reasonable likelihood that the intervention will change management and/or lead to an improved outcome for the patient.

Providers may be required to submit clinical documentation in support of a request for services. Such documentation must a) accurately reflect the clinical situation at the time of the requested service, and b) sufficiently document the ordering provider's clinical intent.

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 justify a finding of clinical appropriateness. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account to the extent permitted by law.

Genetic tests not specifically mentioned in the guidelines are considered not medically necessary.

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. Requests for ongoing services may depend on completion of previously authorized services in situations where a patient's response to authorized services is relevant to a determination of clinical appropriateness.

Chromosomal Microarray Analysis

General Recommendations

Genetic Counseling

Counseling is encouraged prior to chromosomal microarray analysis (CMA) and should include **ALL** of the following components:

- Interpretation of personal and family medical histories to provide a risk assessment for disease occurrence or recurrence
- Education about inheritance patterns, genetic testing, disease management, prevention, risk reduction, 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
- Counseling should include the following details:
 - Limitations of the testing used
 - A negative result does not indicate heritable risk is zero or low
 - Identification of incidental and inconclusive results called variants of uncertain significance is possible
 - Modifications to genetic variants' pathogenicity interpretations can occur, and patients may be recontacted with reclassified results in the future

Note: Post-test counseling should be performed for any genetic test result.

Rationale

Genetic testing is a procedure that involves risk that accompanies its potential benefits. The clinical team and the patient should consider the balance of risks and potential benefits before testing is pursued through informed consent. As with any procedure, the clinical utility of the genetic test must be considered along with its psychological and sociologic implications.¹ Counseling by a genetic counselor and/or a team clinician provides a patient-centered approach to the care of individuals who are undergoing a diagnostic genetic test.²

It is also recognized that accessibility to genetic counselors is limited by available resources as well as other social determinants of health. Therefore, as it relates to microarray, the importance should be placed on counseling in a general sense, such as informed consent, as noted above.³

Genomic technologies generate large amounts of data, and this increases the potential for uncertainty in managing and adapting to this information.⁴ Clinicians are tasked with accurately interpreting and communicating information about test validity and the reliability of test results, as well as the probability for individual patient benefit.^{4, 5} Uncovering incidental findings and being overwhelmed with information are important barriers to genetic testing, particularly among vulnerable patient subgroups.⁴ Genetic counseling is an invaluable resource for patients undergoing genetic testing, but there are practical limitations because of the scarcity of genetic counselors relative to the current need, as noted above.

Clinical Indications

General Requirements

Testing should be performed in a laboratory with established experience in this clinical domain that has met quality standards set by the Clinical Laboratory Improvement Amendments (CLIA) program overseen by the Centers for Medicare & Medicaid Services (CMS). Prior to using any test result findings for medical management, it is important to ensure that findings were obtained from not only a CLIA-certified lab but also one accredited by the College of American Pathologists (CAP) to issue a report of findings directly to ordering health care providers. Some states (e.g., New York) may have additional reporting requirements.

Diagnostic testing using chromosomal microarray analysis (CMA) should occur **only once per lifetime** per individual or per fetus per pregnancy.

Condition-Specific Requirements for Use of CMA

Prenatal evaluation

Fetal chromosomal microarray analysis is considered **medically necessary** for **ANY** of the following:

- Fetal demise (stillbirth)
- History of two (2) or more miscarriages
- Individuals undergoing invasive diagnostic testing (amniocentesis or chorionic villus sampling) for any indication

Postnatal/Pediatric evaluation

Chromosomal microarray analysis is considered **medically necessary** in the initial postnatal evaluation of individuals with **ANY** of the following:

- Multiple congenital anomalies without an established diagnosis
- Congenital or early onset epilepsy (before age 3 years) without suspected environmental causes
- Autism spectrum disorder with no identifiable cause (idiopathic)
- Developmental delay or intellectual disability with no identifiable cause (idiopathic)
- Neonatal death

Not Medically Necessary

Chromosomal microarray analysis is considered **not medically necessary** when whole genome sequencing is or has been performed.

If chromosomal microarray has been performed prenatally, it is **not medically necessary** to repeat it postnatally.

Rationale

Cytogenetic microarray (CMA) platforms are designed for the detection of DNA copy number gains and losses associated with unbalanced chromosomal aberrations, known as copy number variations (CNVs). The benefits of this technique include the ability to analyze DNA from nearly any tissue, better definition and characterization of abnormalities detected by standard chromosomal study, and the ability to detect copy neutral absence of heterozygosity with platforms incorporating [single nucleotide polymorphisms](#) (SNP) probes. Chromosomal microarray continues to be widely used for prenatal and pediatric

genetic testing.⁶ The utility of this technology for detection of gains and losses in patients with intellectual disabilities, autism, and/or congenital anomalies, as well as applicability in prenatal specimens, has been well documented.⁷ In addition to other professional organizations, the Canadian College of Medical Geneticists recently reinforced the recommendation of using CMA as a first-tier test for patients with neurodevelopmental disorders, such as global developmental delay, intellectual disability, and/or autism spectrum disorder—thus reserving exome sequencing and comprehensive gene panels for second-tier testing.⁸ American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine jointly recommend ‘prenatal chromosomal microarray analysis...for a patient with a fetus with one or more major structural abnormalities identified on ultrasonographic examination. They also state that microarray can be considered ‘for all women, regardless of age, who undergo prenatal diagnostic testing’ as an alternative to karyotype.⁹ In prenatal samples with a normal karyotype, microarray analysis has been shown to identify clinically relevant deletions or duplications in 6.0% with a structural anomaly, 3.6%-4.2% with intrauterine growth restriction, 1% with isolated polyhydramnios and in 1.7% of those whose indications were advanced maternal age or positive screening for Down’s syndrome.¹⁰⁻¹³ ⁸ Use of CMA testing in cases of intrauterine fetal death analyzing amniotic fluid, placenta or products of conception is recommended by ACOG committee opinion and in the evaluation of perinatal death Centre of Research Excellence in Stillbirth & Perinatal Society of Australia and New Zealand (2024) Care Around Stillbirth and Neonatal Death Clinical Practice Guideline.^{14, 15}

There are limitations with CMA: it will not detect all pathogenic variants associated with a given syndrome or detect genetic events that do not affect relative copy number. For example, it is unable to detect molecularly balanced chromosomal rearrangements. Also, CMA does not always elucidate the chromosomal mechanism of genetic imbalance.⁷

Optical Genome Mapping

Not Medically Necessary

Optical Genome Mapping is considered **not medically necessary** in prenatal and postnatal evaluation.

Rationale

Optical genome mapping (OGM) is an emerging next generation cytogenomic technique that can detect not only copy number variants (CNVs), triploidy and absence of heterozygosity (AOH) like CMA, but can also define the location of duplications and detect other structural variants (SV), including balanced rearrangements and repeat expansions/contractions.¹⁶ A study by Barseghyan, Pang, and Clifford et al., showed comparative performance of OGM with CMA and demonstrated additional variants found in balanced translocations with OGM; however, the possibility of conflict of interest bias with authorship limits full assessment. Similarly, a study by Goumy, Guy, and Soler et al., found that OGM performed well in detecting genomic alterations in cell cultures from prenatal samples, but the utility of OGM in relation to CMA or exome sequencing remains to be defined.¹⁷ OGM may be considered an alternative methodology for structural variant analysis, but more studies are required to show clinical utility.

References

1. Burke W. Genetic tests: clinical validity and clinical utility. *Curr Protoc Hum Genet*. 2014;81:9.15.1–9..8.
2. Resta R, Biesecker BB, Bennett RL, et al. A new definition of Genetic Counseling: National Society of Genetic Counselors’ Task Force report. *J Genet Couns*. 2006;15(2):77–83.
3. CDC. How Accessible are Genetics Providers and How Can Access be Increased? 2020.
4. Borno HT, Rider JR, Gunn CM. The Ethics of Delivering Precision Medicine-Pretest Counseling and Somatic Genomic Testing. *JAMA Oncol*. 2020;6(6):815–6.
5. Patch C, Middleton A. Genetic counselling in the era of genomic medicine. *Br Med Bull*. 2018;126(1):27–36.
6. Wen T, Rudd MK, Manning MA. Addendum: Yield of additional genetic testing after chromosomal microarray for diagnosis of neurodevelopmental disability and congenital anomalies: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genetics in Medicine*. 2025;27(3):101335.
7. Shao L, Akkari Y, Cooley LD, et al. Chromosomal microarray analysis, including constitutional and neoplastic disease applications, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(10):1818–29.

8. Carter MT, Srour M, Au PB, et al. Genetic and metabolic investigations for neurodevelopmental disorders: position statement of the Canadian College of Medical Geneticists (CCMG). *J Med Genet.* 2023;60(6):523–32.
9. AGOC Committee on Genetics. Committee Opinion No. 682 Summary: Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology. *Obstetrics & Gynecology.* 2016;128(6):1462–3.
10. Wapner RJ, Martin CL, Levy B, et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. *N Engl J Med.* 2012;367(23):2175–84.
11. Monier I, Receveur A, Houfflin-Debarge V, et al. Should prenatal chromosomal microarray analysis be offered for isolated fetal growth restriction? A French multicenter study. *Am J Obstet Gynecol.* 2021;225(6):676.e1–.e15.
12. Tsakmaki E, Ververi A, Chatzakis C, et al. Genomic abnormalities in apparently isolated polyhydramnios and the role of confirmed fetal phenotype: a systematic review and meta-analysis. *Am J Obstet Gynecol MFM.* 2024;6(10):101469.
13. Wu X, He S, Li Y, et al. Fetal genetic findings by chromosomal microarray analysis and karyotyping for fetal growth restriction without structural malformations at a territory referral center: 10-year experience. *BMC Pregnancy Childbirth.* 2023;23(1):73.
14. Centre of Research Excellence in Stillbirth & Perinatal Society of Australia and New Zealand. *Care Around Stillbirth and Neonatal Death Clinical Practice Guideline.* 2024.
15. ACOG. Management of Stillbirth: Obstetric Care Consensus No. 10. *Obstet Gynecol.* 2020;135(3):e110–e32.
16. Li H, Hu J, Wu Q, et al. Chromosomal abnormalities detected by chromosomal microarray analysis and pregnancy outcomes of 4211 fetuses with high-risk prenatal indications. *Sci Rep.* 2024;14(1):15920.
17. Mazzonetto PC, Villela D, da Costa SS, et al. Low-pass whole genome sequencing is a reliable and cost-effective approach for copy number variant analysis in the clinical setting. *Ann Hum Genet.* 2024;88(2):113–25.

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

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May Be Medically Necessary When Criteria are Met

| Code | May Be Medically Necessary When Criteria are Met |
|-------|---|
| 81228 | Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization (CGH) microarray analysis |
| 81229 | Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis |
| 81349 | Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis |
| 81405 | Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) |
| 0209U | Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities |
| 0252U | Fetal aneuploidy short tandem-repeat comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy |
| 0318U | Pediatrics (congenital epigenetic disorders), whole genome methylation analysis by microarray for 50 or more genes, blood |
| 0469U | Rare diseases (constitutional/heritable disorders), whole genome sequence analysis for chromosomal abnormalities, copy number variants, duplications/deletions, inversions, unbalanced translocations, regions of homozygosity (ROH), inheritance pattern that indicate uniparental disomy (UPD), and aneuploidy, fetal sample (amniotic fluid, chorionic villus sample, or products of conception), identification and categorization of genetic variants, diagnostic report of fetal results based on phenotype with maternal sample and paternal sample, if performed, as comparators and/or maternal cell contamination |
| S3870 | Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability |

Not Medically Necessary

| Code | Not Medically Necessary |
|-------|---|
| 81354 | Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of structural and copy number variants, optical genome mapping (OGM) |
| 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 |
| 0454U | Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping |

ICD-10 Diagnosis

Refer to the ICD-10 CM manual

History

| Status | Review Date | Effective Date | Action |
|-----------------------------|-------------|----------------|--|
| Updated codes 07/01/2026 | n/a | Unchanged | Removed CPT codes 81195, 0299U, and 0331U, as they should be only present in the Somatic Tumor Testing guidelines. |
| Revised | 10/09/2025 | 06/14/2026 | Independent Multispecialty Physician Panel (IMPP) review. Added statement to General Requirements to ensure that testing is performed in a CLIA-certified lab and accredited by the College of American Pathologists. Clarified that diagnostic testing using CMA should occur only once per lifetime per individual. For prenatal evaluation, restrictive criteria removed for those undergoing invasive diagnostic testing. Revised rationale for CMA. Added references. |
| Updated codes 01/01/2026 | n/a | Unchanged | CPT code update: added 81354 (NMN). |
| Revised | 10/28/2024 | 07/26/2025 | IMPP review. Added neonatal death to the list of indications considered medically necessary for chromosomal microarray analysis. New section for Optical Genome Mapping clarifies current position as not medically necessary. Added references. |
| Updated codes 01/01/2025 | n/a | Unchanged | CPT code update: added 81195 (NMN). |
| Revised | 01/23/2024 | 10/20/2024 | IMPP review. Clarified recommendations for genetic counseling. Clarified requirements for postnatal evaluation: individuals with congenital or early onset epilepsy (before age 3) without suspected environmental causes and those with autism spectrum disorder, developmental delay, or intellectual disability with no identifiable cause (idiopathic). Added references. |
| Updated codes 10/01/2024 | n/a | Unchanged | Added/Moved CPT codes from WGS/WES guideline: 0260U, 0264U, 0299U, 0331U (NMN), and 0469U (now MNWCM). |
| Updated codes 07/01/2024 | n/a | Unchanged | Added CPT code 0454U (NMN). |
| Updated codes 03/17/2024 | n/a | Unchanged | Added CPT code 0252U. Added required language to General Clinical Guideline per new Medicare regulations. |
| Created | 09/21/2022 | 02/12/2023 | IMPP review. Original effective date. |