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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**

# Table of Contents

# 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.

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. 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 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.

## 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 on-going 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

Genetic counseling is strongly recommended prior to chromosomal microarray analysis (CMA) and should include **ALL** of the following components:

- Interpretation of personal and family medical history, as well as any prior tests, to assess the probability of disease occurrence or recurrence
- Discussion of the risks/benefits and alternatives to CMA
- Discussion of the range of possible test results including variants of uncertain significance
- Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition
- Counseling for the psychological aspects of genetic testing
- Post-test counseling for any finding detected on CMA

#### Rationale

Genetic testing is a procedure that involves risk that accompanies its potential benefits. The clinician 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] Genetic counselors provide a patient-centered contribution to the care of individuals who are undergoing genetic testing. Genetic counseling is a communication process aimed at helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease.[2] Genetic counselors have advanced training in medical genetics and counseling which helps guide and support patients seeking more information about how inherited diseases and conditions might affect them or their families. This expertise is also applied to interpret genetic test results based on an individual's personal and family history. Genetic counselors are often specialized in prenatal or pediatric domains.

The current literature demonstrates the clinical value of genetic counselor involvement in service delivery, including improvements in clinical management and positive psychological impact along with increased patient engagement. Physicians have varying levels of knowledge on how to interpret genetic and genomic information, and often express low confidence and high uncertainty in counseling about genetic testing findings.[3] Professional genetic counselors add unique value to the existing care team. For example, a study of the accuracy of routine prenatal genetic screening in patients referred for genetic counseling found that genetic history obtained by the referring provider was missing detail in over half, and of these approximately 40% had their clinical care changed by discovery of this information by a genetic counselor.[4] In the pediatric setting, even when a medical geneticist is involved in the care, the addition of a genetics counselor significantly improves adherence to medical management.[5] These are only a small sample of the literature that exists clearly demonstrating the value of genetic counseling.

In the past decade, there has been explosive growth in the number of genetic tests available, the number and types of companies involved in providing these tests, diversity of the business models involved, and the diverse settings where genetic tests are accessed by consumers. There is access to some kinds of testing through direct-to-consumer channels, but most of the healthcare-associated testing is from full-service commercial laboratories, for-profit specialized laboratories, or not-for-profit laboratories, such as those associated with academic medical centers.[6] While laboratory business models vary widely, there is increasing interest in use of de-identified data from genetic testing for use in research and discovery and other business purposes beyond the application to individual patient care. These other uses of genetic information have partly fueled a trend for broader indications for testing and testing of larger panels of genes. Furthermore, while genetic counselors have traditionally been trained to counsel patients in healthcare settings prior to germline testing for diseases with a Mendelian inheritance pattern, their education and skills can also be readily adapted to other settings. Genetic testing services are now delivered both in person and via telehealth, and counselors may be employed not only by healthcare institutions but also by laboratories working under various distinct business models.

Genomic technologies generate large amounts of data, and this increases the potential for uncertainty in managing and adapting to this information. 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.[7] Uncovering incidental findings and being overwhelmed with information are important barriers to genetic testing, particularly among vulnerable patient subgroups.[8] 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. Clinicians are often required to stretch their skillsets and play a role in providing basic counseling about genetic testing and will need more training and skills to do so effectively. Further research is needed regarding the use of clinical practice tools to enhance patient care and uphold the clinical and ethical ideals of medical care in this complicated realm of care delivery.

The use of genetic counseling by professionals not employed by testing laboratories is strongly recommended for a wide variety of common clinical scenarios across all realms of medicine. Genetic counseling is considered mandatory for a subset of clinical scenarios, such as those involved with CMA testing, where the stakes are predictably high in terms of the potential medical and psychological consequences of the testing process. The specific scenarios for which genetic counseling is mandatory and the minimum expected qualifications for genetic counseling providers may vary by health plan.

# Clinical Indications

## General Requirements

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

## Condition-Specific Requirements

### Postnatal evaluation

Chromosomal microarray analysis (CMA) is considered **medically necessary** as a first-line test in the initial postnatal evaluation of individuals with **ANY** of the following:

- Multiple congenital anomalies not specific to a well-delineated genetic syndrome
- Congenital or early onset epilepsy (before age 3 years) without suspected non-genetic etiology
- Non-syndromic autism spectrum disorders
- Non-syndromic developmental delay or intellectual disability

### Prenatal evaluation

Chromosomal microarray analysis is considered **medically necessary** for the prenatal evaluation of a fetus for **ANY** of the following:

- Structural anomaly noted on ultrasound
- Fetal demise or history of 2 or more miscarriages
- Individuals undergoing invasive diagnostic testing based on advanced maternal age or positive findings on other screening tests

#### Rationale

Cytogenetic microarray (CMA) platforms are designed for the detection of DNA copy number gains and losses associated with unbalanced chromosomal aberrations. 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 SNP probes. 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.[9] In samples with a normal karyotype, microarray analysis has been shown to identify clinically relevant deletions or duplications in 6.0% with a structural anomaly and in 1.7% of those whose indications were advanced maternal age or positive screening for Down's syndrome.[10] There are also limitations with CMA. It will not detect all mutations 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.[9]

# References


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# 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



### 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 |

| Code | May Be Medically Necessary When Criteria are Met |
|---|---|
| 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 |
|---|---|
| 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 |
| 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 |
| 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 |
| 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 10/01/2024 | n/a | Unchanged | Added CPT codes (moved 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 (MNWCM). Added required language to General Clinical Guideline per new Medicare regulations. |
| Created | 09/21/2022 | 02/12/2023 | Independent Multispecialty Physician Panel (IMPP) review. Original effective date. |