carelon

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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: Prenatal Screening using Cell-free DNA

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. 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.

Prenatal Screening using Cell-free DNA

Description and Scope

Cell-free DNA (cfDNA) screening for aneuploidy, sometimes called noninvasive prenatal screening (NIPS) or noninvasive prenatal testing (NIPT), evaluates DNA from the placenta in the maternal circulation to screen for specific chromosomal abnormalities, known as aneuploidies, in the pregnancy.

These tests can identify pregnancies at increased risk for these conditions but cannot definitively diagnose, confirm, or exclude them. Screening tests that show increased risk should be confirmed by diagnostic testing prior to any intervention.

For testing associated with reproduction, see the Carelon Guidelines Carrier Screening in the Reproductive Setting.

General Recommendations

Genetic counseling

The approach chosen for any prenatal screening technique should involve shared decision-making between the patient and the clinician. Counseling is encouraged prior to any prenatal screening that involves cell-free DNA and should include **ALL** of the following components:

- Clearly defined differences between screening and diagnostic prenatal genetic testing
- Risk assessment for and education about aneuploidies
- 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: Post-test counseling should be performed for any positive or non-reportable cfDNA screen result.

Rationale

As stated above, it should be stressed that this specific type of testing is a screening modality, as opposed to a diagnostic one. Additionally, the approach chosen for any prenatal screening technique should involve shared decision-making between the patient and the clinical team. Like any other genetic screening test, cell-free DNA testing is a process that involves risk that accompanies its potential benefits and, therefore, the clinical team and the patient should consider the balance of risks and potential benefits before testing is pursued through informed consent. Furthermore, the clinical utility of a genetic screening test must be considered along with its psychological and sociological implications.[1] Counseling, either by a genetic counselor and/or team clinician, provides a patient-centered approach to the care of individuals who are undergoing a genetic screening test, such as prenatal testing.

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

As with any genetic test, whether for screening or diagnosis, genomic technologies generate large amounts of data, and this increases the potential for uncertainty in managing and adapting to this information. The clinical team is 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.[2] Uncovering incidental findings and being overwhelmed with information are important possible consequences to genetic testing, particularly among vulnerable patient subgroups.[3] Counseling is an invaluable resource for patients undergoing genetic screening testing, but there are practical limitations because of the scarcity of resources relative to the current need, as noted above.

Clinical Indications

General Requirements

Prenatal screening using cell-free DNA (cfDNA) should occur only once per fetus per pregnancy.

Condition-Specific Requirements

Viable singleton or twin pregnancy

Prenatal screening using cell-free DNA (cfDNA) is considered **medically necessary** in viable singleton or twin pregnancies at 9 weeks gestation or later for aneuploidies of the following chromosomes:

- 13
- 18
- 21
- X
- Y

This includes the following indications:

- As follow-up to abnormal maternal serum screen results when diagnostic testing is declined
- Pregnancies with multiple anomalies **AND** diagnostic testing is not possible

Not Medically Necessary:

The use of cfDNA screening is considered **not medically necessary** for clinical scenarios including, but not limited to, the following:

- Higher order gestations (≥ 3 fetuses)
- Fetal demise
- Co-twin demise (vanishing twin)
- Multiple fetal anomalies
- Concurrent screening with other maternal serum biomarkers
- Prior to 9 weeks gestation

The use of cfDNA screening is considered **not medically necessary** when screening for the following:

- Sex only (without family history of an X-linked disorder)
- Single genes (e.g., CFTR, HBB, SMN1, RhD)
- Microdeletions (e.g., DiGeorge syndrome, Cri-du-chat syndrome)
- Twin zygosity (monozygotic versus dizygotic)
- Genome-wide copy number variants
- Aneuploidies of other autosomal chromosomes, e.g., trisomy 7, trisomy 15, trisomy 16, trisomy 22, etc.
- Polygenic risk assessment

Note: Some of the tests listed above have a role in care under certain circumstances, but they should not be routinely offered.

Rationale

Chromosomal abnormalities (aneuploidy, translocations, duplication, or deletions) are present in approximately 1 in 150 live births, with 3% to 5% of pregnancies ultimately complicated by birth defects or genetic disorders.[4] For various reasons, some patients choose to pursue screening for underlying genetic disorders with decisions about such testing and possible subsequent actions being driven heavily by patient values. Various screening techniques are available, and the field is rapidly evolving. Techniques in the first trimester include serum screening using markers (such as beta human chorionic gonadotropin, alpha-fetoprotein, inhibin A, and unconjugated estriol), and ultrasound testing to assess nuchal translucency. Integrated screening techniques produce a detection rate of about 96% with around 5% false positives.[4]

Over the past 12 years, the rapid advances in genomic medicine have brought new technology into use for prenatal screening. Cell-free DNA (cfDNA) screening refers to sequence analysis of placental cfDNA fragments that circulate in the blood of pregnant women, along with the translation of this method into screening for chromosome abnormalities. Approaches for cfDNA include shotgun whole genome and targeted sequencing.[5] The shotgun approach of whole genome sequencing generates short sequences from across the genome which are then aligned to a reference chromosome and counted. In contrast, targeted sequencing of the cfDNA is based on next-generation sequencing (NGS) and involves amplification of selected chromosomal loci on the chromosomes of interest.[6,7] Of note, while cfDNA methods can detect chromosomal abnormalities in pregnancy, they do not assess the risk of fetal structural anomalies such as neural tube defects or ventral wall defects.[6]

Cell-free DNA was initially validated as a clinical prenatal screen for pregnancies at high risk for trisomy 21, and it has since been approved to determine fetal sex and screen for fetal aneuploidy, including trisomies 13 (Patau syndrome), 18 (Edward syndrome), and 21 (Down syndrome) in high-risk and average-risk pregnancies.[6] At any given maternal age, the rate of common trisomies is similar between singleton and twin pregnancies, and cfDNA screening provides higher predictive values among twin pregnancies compared to traditional serum and nuchal translucency based techniques.[8] A systematic evidence review evaluating cfDNA for screening in a general risk population found that it is the most effective screening approach for trisomies 13, 18, and 21 in singleton and twin gestations with both high detection and low false-positive rates.[9] In addition, a systematic review and meta-analysis evaluating cfDNA screening in singleton pregnancies found that it reliably detects sex chromosome abnormalities (45,X, 47,XXY, 47,XXX and 47,XYY) with high sensitivity and specificity.[10]

Authors stress that false positives and false negatives exist with all prenatal cfDNA screens. Several professional societies and the U.S. Food and Drug Administration (FDA) endorse genetic counseling prior to and following prenatal screening to explore the conditions being screened, the patient's desire avidity for this information, follow-up logistics, decision-making options, and the significance of screening results.[11-14] Definitive diagnosis of abnormalities detected on screening requires sampling of pregnancy tissue by chorionic villous sampling or amniocentesis for chromosomal array analysis.[6] These diagnostic tests are associated with some risk of miscarriage.

The position of the American College of Obstetrics and Gynecology (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) in 2020 was that "prenatal genetic screening (serum screening with or without nuchal translucency ultrasound or cell-free DNA screening) and diagnostic testing (chorionic villus sampling [CVS] or amniocentesis) options should be discussed and offered to all pregnant women regardless of maternal age or risk of chromosomal abnormality. After review and discussion, every patient has the right to pursue or decline prenatal genetic screening and diagnostic testing."[11] The American College of Medical Genetics and Genomics (ACMG) position has been favorable toward offering women the option of cfDNA screening since 2016, ultimately recommending that patients receive accurate and balanced information to promote patient-centered, nondirective decision-making.[15] In 2020, ACMG recommended informing all pregnant women that cfDNA screening is the most sensitive screening option for common aneuploidies, did not recommend maternal age or risk of chromosomal abnormality as a basis to choose between aneuploidy testing approaches, and did not recommend having multiple screening methods performed simultaneously.[16] In a 2023 ACMG Practice Guideline published based on a systematic evidence review, ACMG strongly recommends cfDNA screening over traditional screening methods for all pregnant patients with singleton and twin gestations for fetal trisomies 21, 18, and 13. They also strongly recommend cfDNA screening be offered to individuals with a singleton gestation to screen for fetal sex chromosome abnormalities (monosomy X, XXX, XXY, and XYY) based on a high certainty of evidence.[12] This same ACMG Practice Guideline uses weaker language to *conditionally suggest* that cfDNA screening for 22q11.2 deletion syndrome be offered to all patients, based on a *moderate certainty of the evidence*; however, ACMG's systematic evidence review demonstrated that the sensitivity and specificity of copy number variant screening are below that of the common trisomies and sex chromosome abnormalities.[12] In addition, the 2023 International Society for Prenatal Diagnosis (ISPD) Position Statement affirms there is insufficient data to assess the performance and clinical utility of routine cfDNA screening for microdeletion/microduplications syndromes including 22q11.2 deletion syndrome, and cfDNA screening for microdeletion/microduplications syndromes is not recommended for the routine care of unselected populations.[13] Furthermore, while cfDNA screening is not regulated by the FDA, an FDA Safety Communication was released in 2022 regarding false positive results with cfDNA screening. Specifically, the FDA stated that the ability of a cfDNA screening test to

determine fetal risk of a genetic abnormality depends on the pregnancy's *a priori* risk. Because the prevalence of microdeletions is low in an average-risk population, the chance of receiving a false positive result is higher.[14]

ACMG and ISPD both cite lack of sufficient data to assess the performance and clinical utility of routine cfDNA for rare autosomal trisomies (RATs) as rationale for providing no recommendation or not recommending screening for RATs in the routine care of unselected populations,[13] respectively. Lastly, noninvasive prenatal screening for single-gene disorders is not widespread in clinical practice because of the low prevalence of diseases, the complexity of the testing methods, and the chance of a no-call result in a high-risk pregnancy.[17]

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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
81420	Fetal chromosomal aneuploidy (eg, trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21
81479	Unlisted molecular pathology procedure
81507	Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy
81599	Unlisted multianalyte assay with algorithmic analysis [when specified as cell-free fetal DNA-based prenatal testing involving multianalyte assays and an algorithmic analysis for fetal aneuploidy]
0327U	Fetal aneuploidy (trisomy 13, 18, and 21), DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy, includes sex reporting, if performed

Not Medically Necessary

Code	Not Medically Necessary
81422	Fetal chromosomal microdeletion(s) genomic sequence analysis (eg, DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood.
0060U	Twin zygosity, genomic targeted sequence analysis of chromosome 2, using circulating cell-free fetal DNA in maternal blood
0341U	Fetal aneuploidy DNA sequencing comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplication, mosaicism, and segmental aneuploid
0488U	Obstetrics (fetal antigen noninvasive prenatal test), cell-free DNA sequence analysis for detection of fetal presence or absence of 1 or more of the Rh, C, c, D, E, Duffy (Fya), or Kell (K) antigen in alloimmunized pregnancies, reported as selected antigen(s) detected or not detected
0489U	Obstetrics (single-gene noninvasive prenatal test), cell-free DNA sequence analysis of 1 or more targets (eg, CFTR, SMN1, HBB, HBA1, HBA2) to identify paternally inherited pathogenic variants, and relative mutation-dosage analysis based on molecular counts to determine fetal inheritance of maternal mutation, algorithm reported as a fetal risk score for the condition (eg, cystic fibrosis, spinal muscular atrophy, beta hemoglobinopathies [including sickle cell disease], alpha thalassemia)
0494U	Red blood cell antigen (fetal RhD gene analysis), next-generation sequencing of circulating cell-free DNA (cfDNA) of blood in pregnant individuals known to be RhD negative, reported as positive or negative
0536U	Red blood cell antigen (fetal RhD), PCR analysis of exon 4 of RHD gene and housekeeping control gene GAPDH from whole blood in pregnant individuals at 10+ weeks gestation known to be RhD negative, reported as fetal RhD status

ICD-10 Diagnosis

Refer to the ICD-10 CM manual

History

Status	Review Date	Effective Date	Action
Updated codes 04/01/2025	n/a	Unchanged	Added CPT code 0536U (NMN).
Revised	04/15/2024	11/17/2024	Independent Multispecialty Physician Panel (IMPP) review. Changed prenatal testing to prenatal screening throughout guideline. Expanded criteria to include follow-up screening for abnormal maternal serum screen results in viable singleton/twin pregnancies when diagnostic testing is declined and screening for pregnancies with multiple anomalies when diagnostic testing is not possible. Added references.
Updated codes 10/01/2024	n/a	Unchanged	Added CPT codes 0488U, 0489U, 0494U (NMN).
Revised	07/18/2023	03/17/2024	IMPP review. Clarified required components of genetic counseling. For viable singleton or twin pregnancy, clarified sex prediction for pregnancies at risk for an X-linked disorder. Updated references. Split codes into those considered medically necessary when criteria are met (MNWCM) and not MN. Added CPT 0341U (NMN). Added

Status	Review Date	Effective Date	Action
			required language to General Clinical Guideline per new Medicare regulations.
Updated	n/a	10/01/2023	Added CPT code 81599.
Created	09/21/2022	02/12/2023	IMPP review. Original effective date.