



## Prenatal Screening Clinical Coverage Criteria

### Overview

Approximately 3% to 5% of pregnancies are complicated by birth defects or genetic disorders. Chromosomal abnormalities are present in approximately 1 in 150 live births, and congenital malformations remain the leading cause of infant death and a leading cause of childhood death. These chromosomal abnormalities include aneuploidy (defined as having one or more extra or missing chromosomes), translocations, duplications, and deletions. The most common chromosomal disorder is trisomy 21 (Down syndrome), with an incidence of 1 per 800 live births. Trisomy 13 and 18 can also result in live births, though with a significantly lower incidence. Sex chromosome aneuploidies are less common than autosomal aneuploidies. The only known viable monosomy is monosomy X (Turner syndrome). Risk of aneuploidy increases with maternal age. Other factors also influence patients' risk in any given pregnancy, including having a previous pregnancy with a chromosomal abnormality. A past family history of aneuploidy increases current pregnancy risk of aneuploidy, especially if a parent is a balanced Robertsonian translocation carrier, though most cases are sporadic and secondary to chromosomal nondisjunction (Carlson and Bora, 2017).

All patients should be offered aneuploidy screening or diagnostic testing during pregnancy. Just as importantly, available options should be explained to patients and families in depth, most notably including the risks and benefits of each option, and how results might be reported. Patients who choose cell-free DNA screening should be counseled that the test remains a screening test for aneuploidy at this time and that microdeletion testing continues to have poor positive predictive values due to the low prevalence of these disorders. It is not recommended that patients undergo more than one screening modality but rather that women who have positive screens and wish to pursue further testing be counseled on diagnostic testing with amniocentesis and chorionic villus sampling (CVS) so as not to delay diagnosis. Amniocentesis and CVS are increasingly safe with low rates of pregnancy loss and should continue to be available to all women who desire diagnostic testing regardless of risk factors or presence or absence of anomalies (Carlson and Bora, 2017).

### Policy

This Policy applies to the following Fallon Health products:

- Fallon Medicare Plus
- MassHealth ACO
- NaviCare HMO SNP
- PACE (Summit Eldercare PACE, Fallon Health Weinberg PACE)
- Community Care

Effective for dates of service on or after November 21, 2024, screening for fetal chromosomal aneuploidy (CPT 81420) does not require prior authorization when the claim is submitted by a contracted provider.

All genetic testing including preconception and prenatal carrier screening requires prior authorization.

## Fallon Health Clinical Coverage Criteria

Screening for fetal chromosomal abnormalities should be an informed patient choice based on provision of adequate and accurate information, and the patient's clinical context, accessible health care resources, values, interests, and goals. Prenatal screening (serum screening with or without nuchal translucency ultrasound or cell-free DNA screening) and diagnostic testing (chorionic villus sampling or amniocentesis) options should be discussed and offered to all pregnant patients regardless of age or risk for chromosomal abnormality. After review and discussion, every patient has the right to pursue or decline prenatal screening and diagnostic testing. Pretest and posttest counseling is essential (ACOG Practice Bulletin, Number 226).

Single time point prenatal screening approaches include cell-free DNA screening, first-trimester screening or second-trimester screening. Combined screening approaches in which samples are obtained in the first and second trimesters include integrated, serum integrated, sequential, and contingent screening (ACOG Practice Bulletin, Number 226).

If prenatal screening is accepted, patients should choose one screening approach and should not undergo multiple screening approaches (ACOG Practice Bulletin, Number 226).

Regardless of screening approach, all patients should be offered a second-trimester ultrasound for fetal structural defects, since these may occur with or without fetal aneuploidy; ideally this procedure is performed between 18 and 22 weeks of gestation (with or without second-trimester maternal serum alpha-fetoprotein) (ACOG Practice Bulletin, Number 226).

### Cell-Free DNA Screening

Cell-free DNA screening is also referred to as noninvasive prenatal screening (NIPS) or noninvasive prenatal testing (NIPT). Effective for dates of service on or after November 21, 2024, cell-free DNA screening for the detection of aneuploidies in chromosomes 13, 18, 21, X and Y (CPT 81420) is covered when:

1. The member has a singleton or twin pregnancy, and
2. The member has not previously had cell-free DNA testing in the current pregnancy.

Cell-free DNA screening is not medically necessary in the following clinical scenarios:

- Higher order gestations ( $\geq 3$  fetuses)
- Fetal demise
- Co-twin demise (vanishing twin)
- Multiple fetal anomalies
- Concurrent screening with other prenatal screening approaches
- Prior to 9 weeks gestation
- To determine fetal sex only
- To evaluate single gene abnormalities (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

Testing in some of the scenarios listed above may have a role under certain circumstances, but not in routine prenatal screening.

### First-Trimester, Second-Trimester, or Combined First- and Second-Trimester Screening

Although cell-free DNA screening is frequently used to screen for the common fetal aneuploidies, the following screening approaches remain available and are considered medically necessary as alternatives to cell-free DNA screening. Patients should choose one screening approach and should not undergo multiple screening approaches.

1. First-trimester screening – Measurement of maternal serum analytes [pregnancy-associated plasma protein-A (PAPP-A), free beta human gonadotropin (hCG), with or without alpha-

fetoprotein (AFP)] and ultrasound measurement of nuchal translucency (NT) performed between 10 and 14 weeks.

2. Second-trimester screening – Also known as quad screen, includes measurement of maternal four serum analytes (hCG, AFP, inhibin A, and unconjugated estriol) performed between 15 and 22 weeks.
3. Combined First-Trimester and Second-Trimester Screening:
  - a. Integrated Screening - First-trimester NT ultrasound measurement and maternal serum analyte screening (PAPP-A) followed by a second-trimester quad screen (hCG, AFP, inhibin A, and unconjugated estriol) with single test result in the second trimester.
  - b. Serum Integrated Screening – First-trimester maternal serum analyte screening (PAPP-A) followed by a second-trimester quad screen (hCG, AFP, inhibin A, and unconjugated estriol) with single test result in the second trimester.
  - c. Stepwise Sequential – First-trimester screening with results provided: if first trimester screening is positive, patient is offered additional testing (diagnostic testing or cell-free DNA), if first trimester screening is negative, patient is informed that they have received a negative first-trimester screening result and quad screen is planned for the second trimester with a final combined risk assessment that incorporates first- and second-trimester results.
  - d. Contingent Screening – First-trimester screening, after which women are stratified into high-, medium-, and low-risk groups. The high-risk group is offered additional testing (diagnostic testing or cell-free DNA). The low-risk group has no further testing. The intermediate-risk group is offered second-trimester quad screening. First-trimester and second-trimester results are combined to calculate a final risk of aneuploidy in patients at intermediate risk.

### **Carrier Screening for Genetic Disorders**

Carrier screening is used to identify individuals that are at risk to have a child with an autosomal recessive or X-linked genetic disorder (Gregg et al., 2021).

All genetic testing, including preconception and prenatal carrier screening, requires prior authorization.

It is important to obtain the family history of the member, and if possible, partner as a screening tool for inherited risk. The family history should include the ethnic background of family members as well as any known consanguinity.

Carrier screening cannot completely eliminate the risk of being a carrier of a heritable condition, because:

- All genes that cause a condition may not be known.
- All genes that cause a condition may not be examined.
- Causative variants may be in a region not included in the test.
- Causative variants may be undetectable by the technology/analysis employed.
- Analysis of gene sequence and its structural variants may be technically difficult.
- Variants may be misclassified with regard to pathogenicity (e.g., laboratory's algorithm for classification of variants).

(Gregg et al., 2021)

### **Guidelines for Genetic Testing**

The following Guidelines for Genetic Testing<sup>1</sup> apply to all requests for carrier screening for genetic disorders in addition to the test-specific InterQual® Criteria:

1. The results of the test must be clinically useful to the medical management of the member.
2. Clinical documentation in the treating physician's medical records clearly supports the medical necessity of the test.
3. There is sufficient evidence in the scientific literature to support the validity and predictive accuracy of the test.
4. The test must be performed by a contracted laboratory unless none is available.

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<sup>1</sup> Refer to Fallon Health's [Genetic Testing](#) policy for additional information.

### **InterQual® Criteria**

In addition to the Guidelines for Genetic Testing that apply to all requests for genetic testing, test-specific InterQual® Criteria are used to determine medical necessity for carrier screening for genetic disorders. When InterQual® Criteria are not available, Fallon Health will determine medical necessity on an individual case-by-case basis.

### **Carrier screening for Cystic Fibrosis and Spinal Muscular Atrophy**

Carrier screening for cystic fibrosis and spinal muscular atrophy are less likely to be confined to a specific high-risk ethnic group and may be offered regardless of family history or ancestry/ethnicity (ACOG Committee Opinion Number 691, 2017. Reaffirmed 2025).

Fallon Health will use the InterQual® Criteria in effect on the date of service when making medical necessity determinations for carrier screening for cystic fibrosis (CF):

- CP: Molecular Diagnostics, Cystic Fibrosis and Cystic Fibrosis Transmembrane Regulator (CFTR) Disorders, CFTR Targeted Mutation Analysis Standard Panel (CPT 81220)
- CP: Molecular Diagnostics, Cystic Fibrosis and Cystic Fibrosis Transmembrane Regulator (CFTR) Disorders, CFTR, CFTR targeted mutation analysis expanded panel (CPT 81220)

Complete analysis of the CFTR gene by DNA sequencing is not appropriate for carrier screening.

Fallon Health will use the InterQual® Criteria in effect on the date of service when making medical necessity determinations for carrier screening spinal muscular atrophy:

- CP: Molecular Diagnostics, Spinal Muscular Atrophy (SMA), Spinal Muscular Atrophy copy number analysis of SMN1 (w/wo copy number analysis of SMN2) (CPT 81329)

Copy number analysis of SMN1 is considered sufficient for carrier screening for SMA; sequence analysis is not indicated unless an SMN1 deletion is detected (Sun et al., BMC Med Genet 2020, 21: 133). Copy number analyses of the SMN1 and SMN2 genes are generally ordered as a single test. Testing begins with SMN1 and, if a homozygous deletion is found, the laboratory performs reflex copy number analysis of SMN2. Although not causative for SMA, the SMN2 gene dosage affects the severity of disease.

### **Targeted Carrier Screening**

Targeted (risk-based) carrier screening for a specific autosomal recessive or X-linked genetic disorders other than cystic fibrosis and spinal muscular atrophy may be considered medically necessary when all of the following criteria are met:

1. The member is currently pregnant or considering pregnancy; and
2. The results of carrier screening are clinically useful to the medical management of the member; and
3. There is documented increased risk, such as positive family history or ancestry/ethnicity known to increase the likelihood of having an affected child.  
Note: If the member or member's partner to pregnancy has personal and/or family history of confirmed familial variant, targeted variant testing should be limited to testing of known familial variant.
4. Previous carrier screening or individual targeted gene testing for the gene variant(s) of interest has not been performed.

If carrier testing for a specific genetic disorder is planned, refer to the InterQual® Molecular Diagnostics Criteria for that disorder.

### **Tay Sachs disease**

"Screening for Tay-Sachs disease should be offered when considering pregnancy or during pregnancy if either member of a couple is of Ashkenazi Jewish, French-Canadian, or Cajun descent. Those with a family history consistent with Tay-Sachs disease should also be screened (ACOG Committee Opinion Number 691, 2017. Reaffirmed 2025)."

### **Fragile X syndrome**

"Fragile X premutation carrier screening is recommended for women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome and who are

considering pregnancy or are currently pregnant. If a woman has unexplained ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before age 40 years, or progressive cerebellar ataxia with or without action tremors of unknown, fragile X premutation carrier screening is recommended to determine whether she has an FMR1 premutation (ACOG Committee Opinion Number 691, 2017. Reaffirmed 2025)."

### **Expanded Carrier Screening Panels**

Carrier screening panels are sometimes referred to as expanded carrier screening panels or by their targeted ethnicity (e.g., Ashkenazi Jewish Panel). They include sequence analysis of specific genes and other testing methodologies as needed.

Fallon Health will use the InterQual® Criteria in effect on the date of service when making medical necessity determinations for expanded carrier screening panels:

- CP: Molecular Diagnostics, Carrier Screening (Genetic) for General Population, Carrier Screening Panel (CPT 81443)
- CP: Molecular Diagnostics, Carrier Screening (Genetic) for General Population, Ashkenazi Jewish Carrier Screening Panel (CPT 81412)

Note: CPT 81443 is nonpayable by MassHealth at this time.

Given the multitude of conditions that can be included in expanded carrier screening panels, ACOG recommends that the disorders selected for inclusion should meet the following consensus-determined criteria:

1. A carrier frequency of 1 in 100 or greater, and
2. A well-defined phenotype, and
3. A detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life.
4. Not primary associated with a disease of adult onset.

A list of 22 conditions deemed reasonable to include in a carrier screening panel were published by ACOG in Committee Opinion Number 690: Carrier Screening in the Age of Genomic Medicine.

ACMG (Gregg et al., 2021) recommends a tier-based system of carrier screening. ACMG recommends that all pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening for autosomal recessive and X-linked conditions. Tier 3 screening is carrier screening for conditions with a carrier frequency of 1 in 200 or greater. A total of 113 genes (corresponding to 97 autosomal recessive and 16 X-linked conditions) are included in Tier 3.

The member must not have had previous testing of any genes on the panel (exceptions may be made on a case-by-case basis if Cystic Fibrosis and/or Spinal Muscular Atrophy were previously performed individually).

### Genetic Conditions in Individuals of Eastern and Central European Jewish Descent

"When only one partner is of Ashkenazi Jewish descent, that individual should be offered screening first. If it is determined that this individual is a carrier, the other partner should be offered screening. However, the couple should be informed that the carrier frequency and the detection rate in non-Jewish individuals are unknown for most of these disorders, except for Tay-Sachs disease and Cystic Fibrosis. Therefore, it is difficult to accurately predict the couple's risk of having a child with a disorder (ACOG Committee Opinion Number 691, 2017. Reaffirmed 2025)."

"If Tay Sachs disease screening is performed as part of a pan-ethnic expanded carrier screening, it is important to recognize the limitations of the mutations screened in detecting carriers in the general population. In the presence of a family history of Tay-Sachs disease, expanded carrier screening panels are not the best approach to screening unless the familial mutation is included on the panel (ACOG Committee Opinion Number 691, 2017. Reaffirmed 2025)."

### **Limitations:**

1. Carrier screening for an inherited disorder should be performed only once in a person's lifetime, and the results should be documented in the patient's medical record. Exceptions may be considered if technical advances in testing demonstrate significant advantages that

would support a medical need to retest. The decision to rescreen a patient will only be undertaken with the guidance of a genetics professional who can best assess the incremental benefit of repeat testing for additional mutations (ACOG Committee Opinion Number 691, 2017. Reaffirmed 2025).

2. Carrier screening should not include conditions primarily associated with a disease of adult onset (such as mutations of the BRCA gene, which confers increased risk of hereditary breast cancer and ovarian cancer in adulthood).
3. Complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening because it may yield results that can be difficult to interpret. This type of testing is generally reserved for patients with Cystic Fibrosis, patients with a family history of Cystic Fibrosis, males with congenital bilateral absence of the vas deferens, or newborns with a positive newborn screening result when mutation testing, using the standard 23-mutation panel, has a negative result. Because carrier screening detects most mutations, sequence analysis should only be considered after discussion with a genetics professional to determine if it will be of value to the evaluation after standard screening has been performed (ACOG Committee Opinion Number 486, 2011).

## **Medicare Variation**

Items and services which are not reasonable and necessary for the diagnosis or treatment of illness or injury are not covered under Medicare (Medicare Benefit Policy Manual, Chapter 16, Section 20 – Services Not Reasonable and Necessary).

Medicare Part B pays for the specific preventive (screening) services listed in section 1861(w)(2) of the Social Security Act.

Prenatal screening for fetal chromosomal aneuploidy is not listed as a covered preventive (screening) service in section 1861(w)(2) of the Social Security Act.

Medicare does not have an NCD for prenatal screening for fetal chromosomal aneuploidy. National Government Services, Inc., the Part A and B Medicare Administrative Contractor (MAC) with jurisdiction in the Plan's service area has an LCD for Molecular Pathology Procedures (L35000). Per LCD L35000, many applications of the molecular pathology procedures are not covered services under Medicare given the lack of benefit category (e.g., preventive service or screening for a genetic abnormality in the absence of a suspicion of disease) and/or failure to meet the reasonable and necessary threshold for coverage (e.g., based on quality of clinical evidence and strength of recommendation or when the results would not reasonably be used in the management of a beneficiary). Per Billing and Coding : Molecular Pathology Procedures (A56199), CPT 81420, 81422 and 81507 are Group 3 Tier 1 Non-Covered Codes, unlikely to impact therapeutic decision-making in the clinical management of the beneficiary and are denied automatically as not medically necessary (Medicare Coverage Database search 01/24/2026).

Prenatal screening for fetal chromosomal aneuploidy (CPT 81420, 81422 and 81507) is not covered/not reasonable and necessary for Medicare Advantage plan members.

Carrier screening for inherited disorders is not covered/not reasonable and necessary for Medicare Advantage plan members. Per LCD L35000, molecular pathology procedures are eligible for coverage when the results of testing directly impact treatment or management of the Medicare beneficiary.

## **MassHealth Variation**

Effective for dates of service on or after November 21, 2024, noninvasive prenatal screening (cell-free DNA prenatal screening) to ascertain if a pregnancy has a risk of fetal chromosomal aneuploidy is covered for MassHealth members. The Plan will not limit availability and coverage for such screening based on the age of the pregnant patient or any other risk factor, unless the limitation is part of the generally accepted standards of professional practice as recommended by the American College of Obstetricians and Gynecologists (Massachusetts General Laws, Chapter 118E, Section 10R - Coverage for noninvasive prenatal screening).

MassHealth has Guidelines for [Medical Necessity Determination for Fragile X Carrier Screening](#), therefore the Plan's coverage criteria are not applicable.

MassHealth does not have Guidelines for carrier screening for any other genetic disorders, therefore, the Plan's coverage criteria are applicable.

## Exclusions

- Noninvasive prenatal screening (cell-free DNA) for fetal chromosomal microdeletions (CPT 81422) is considered experimental and investigational.
- Noninvasive prenatal screening to predict twin zygosity, including Twin Zygosity, Natera, Inc. (CPT 0060U) is considered experimental and investigational.
- Noninvasive prenatal screening for single-gene disorders, including Vistara, Natera, Inc. (CPT 81302, 81404, 81405, 81406, 81407, 81408, 81442) is considered experimental and investigational.
- Noninvasive prenatal screening for fetal sex determination is considered experimental and investigational. The current standard of care for fetal sex determination is ultrasound.
- Combination tests that include one or more experimental and investigational components (i.e., screening for microdeletions, twin zygosity, single-gene disorders or fetal sex determination), in addition to noninvasive prenatal screening for the detection of fetal aneuploidy in chromosomes 13, 18, 21, X and Y, are considered experimental and investigational. These tests include but are not limited to:
  - MaterniT 21 PLUS Core + ESS (LabCorp)
  - Panorama extended panel (with optional microdeletion testing) (Natera, Inc.)
  - QNatal Advanced with optional microdeletion and/or fetal sex screening (Quest Diagnostics)
  - Unity Complete (BillionToOne). Unity Complete includes aneuploidy screening, screening for zygosity in twins, screening for 22q11.2 microdeletion syndrome, fetal sex determination, and screening for up to 14 recessive and X-linked conditions.
- Noninvasive prenatal screening for other aneuploidies such as trisomy 16 and trisomy 22 is considered experimental and investigational.
- Genome-wide noninvasive prenatal screening for large deletions or duplications is considered experimental and investigational.
- Carrier screening for an inherited disorder performed more than once per lifetime. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to rescreen. The decision to rescreen a member will only be considered based on the recommendation of a genetics professional who can best assess the incremental benefit of repeat testing for additional mutations (ACOG Committee Opinion Number 691, 2017. Reaffirmed 2025).

## Summary of Evidence

### Cell-Free DNA

Cell-free DNA screening, commonly referred to as noninvasive prenatal screening (NIPS) or noninvasive prenatal testing (NIPT), screens for fetal aneuploidies by analyzing the fetal fraction, i.e., the percentage of fetal to total cell-free DNA in the maternal circulation. Fetal fraction increases with gestational age and is affected by many factors, including maternal influences and fetal influences (notably multiple gestation and fetal aneuploidy). Depending on the laboratory, cell-free DNA screening can be performed as early as 9 weeks gestation, although results are more reliable at 10 weeks and beyond. Cell-free DNA screening has the highest available detection rate of all available screening tests for trisomy 21 with a detection rate of 99% according to a recent meta-analysis (Gill et al. 2015). Detection rates for trisomy 18, 13, and sex chromosome abnormalities are significantly lower than for trisomy 21. Cell-free DNA is the most sensitive and specific screening test for the common fetal aneuploidies, nevertheless, it has the potential for false-positive and false-negative results, and furthermore, cell-free DNA testing is not equivalent to diagnostic testing. Ultrasound is recommended before testing as some ultrasound findings detectable early in pregnancy may affect the timing of cell-free DNA screening, the appropriateness of performing cell-free DNA screening, or the ability to interpret cell-free DNA

test results. These findings include an earlier than expected gestational age, confirmation of viability, number of fetuses, presence of a vanishing twin or empty gestational sac, or presence of a fetal anomaly (ACOG Practice Bulletin, Number 226).

#### First-trimester Screening

First-trimester screening includes a combination of maternal serum analytes measurement and nuchal translucency (NT) ultrasound measurement performed between 10 and 14 weeks gestation. Serum analytes include free-beta human gonadotropin (hCG) and pregnancy-associated plasma protein-A (PAPP-A), with or without alpha-fetoprotein (AFP). A risk estimate for common trisomies (generally trisomies 13, 18, and 21) is then developed that incorporates maternal age, past pregnancy history, number of fetuses in the current gestation, weight, race, serum markers, and NT measurement (ACOG Practice Bulletin, Number 226).

NT refers to the fluid-filled space on the dorsal aspect of the fetal neck. An enlarged NT (often defined as 3.0 mm or more or above the 99th percentile for the crown–rump length) is significantly associated with both fetal aneuploidy and structural malformations such as cardiac anomalies. The risk of adverse fetal outcome is proportional to the degree of NT enlargement (ACOG Practice Bulletin, Number 226).

First-trimester screening gives the potential for earlier diagnosis as well as the ability to screen for other structural, genetic, or placental disorders. The detection rate for trisomy 21 varies from 82% to 87% depending on the laboratory, using a 5% screen positive rate (ACOG Practice Bulletin, Number 226). All patients should be offered second-trimester assessment for open fetal defects (by ultrasonography, with or without second trimester serum AFP) and ultrasound screening for other fetal structural defects (ACOG Practice Bulletin, Number 226).

#### Second-Trimester Screening

Second-trimester screening is a quadruple marker screen also known as the quad screen. The quad screen can be performed between 15 and 22 weeks gestation and is a single point in time test that involves measurement of proteins secreted by the pregnancy, including hCG, AFP, inhibin A, and unconjugated estriol. These protein measurements are combined with the patients' age, race, weight, number of fetuses in the current gestation, diabetes status, and gestational age to provide a risk estimate. The detection rate for trisomy 21 is slightly lower than that of the first-trimester screen, with a reported detection rate of 81% using a 5% screen positive rate (ACOG Practice Bulletin, Number 226). Advantages of the quad screen include its ability to screen for open neural tube defects in addition to aneuploidy. Serum AFP is secreted by the fetus and is present in the amniotic fluid and, therefore, also maternal serum (ACOG Practice Bulletin, Number 226).

#### Combined First-Trimester and Second-Trimester Screening

Combined first-trimester and second-trimester screening with either integrated, serum integrated, stepwise sequential, or contingent screening involving maternal serum analytes, NT, or both measurements provides a higher detection rate for trisomy 21, 18, and 13 than first- or second-trimester single point in time screening. Depending on the test selected, there is variable timing of results available to the patient (ACOG Practice Bulletin, Number 226).

#### Integrated Screening

With integrated screening, the patient undergoes a first-trimester NT ultrasound measurement and serum analyte screening (PAPP-A) followed by a second-trimester quad screen (hCG, AFP, inhibin A, and unconjugated estriol) and receives a single test result in the second trimester. All of these values are then incorporated into a single risk estimate to provide patient a second trimester risk of aneuploidy. The detection rate for trisomy 21 is 96%, the highest of any available serum screens other than cell-free DNA, with a 5% screen positive rate. Downsides to this approach include the relatively late availability of results, limiting the time in which patients and their provider may have to make important decisions about future care (ACOG Practice Bulletin, Number 226).

#### Serum Integrated Screening

In locations where an NT measurement by a certified ultrasonographer is unavailable, or if fetal position, maternal body habitus, or imaging properties preclude an accurate NT measurement, serum integrated screening, which includes only the first-trimester and second-trimester serum analytes, also is an option. Serum integrated screening has a lower detection rate than integrated screening that includes an NT measurement, but a similar detection rate to first-trimester screening (ACOG Practice Bulletin, Number 226).

#### Stepwise Sequential

The stepwise sequential screen involves performing the first-trimester screen (serum analytes and NT measurement). If the first-trimester screening result indicates that the risk of aneuploidy is greater than the laboratory's positive screening cutoff, the patient is notified and offered additional testing (diagnostic testing or cell-free DNA). If the first-trimester screening result indicates a lower risk than the cutoff level, the patient is informed that they have received a negative screening test result and quad screening is planned in the second trimester to receive a final combined numerical risk. The detection rate for trisomy 21 is 95%, with a 5% screen positive rate (ACOG Practice Bulletin, Number 226).

#### Contingent Screening

The contingent screen involves performing a first-trimester screen, after which women are stratified into high-, medium-, and low-risk groups. The high-risk group is offered additional testing (diagnostic testing or cell-free DNA). The low-risk group has no further testing. The intermediate-risk group is offered second-trimester quad screening. First-trimester and second-trimester results are used together to calculate a final risk of aneuploidy in patients at intermediate risk. The detection rate for trisomy 21 varies between 80% and 94% for this screening method, with a 5% screen positive rate (ACOG Practice Bulletin, Number 226).

#### **Screening for microdeletions**

Copy number variants (CNVs) are structural genomic variations in which sections of DNA are deleted or duplicated, resulting in an abnormal number of copies of that segment compared with the typical two copies found in the human genome. CNVs range widely in size—from thousands to millions of base pairs—and include both microdeletions (small losses of DNA) and microduplications (small gains of DNA) that are too small to be detected by a standard karyotype but can be identified by chromosomal microarray or sequencing-based methods.

Microdeletion syndromes are defined as a group of clinically recognizable disorders characterized by a small (< 5Mb) deletion of a chromosomal segment spanning multiple disease genes, each potentially contributing to the phenotype independently. The phenotype is defined as the set of observable characteristics of an individual resulting from the interaction of its genotype with the environment. Microdeletion testing can include, but is not limited to the following conditions or syndromes:

- 22q deletion syndrome (DiGeorge)
- 22q11 deletion syndrome (Shprintzen syndrome)
- 15q11.2 (Prader-Willi/Angelman syndromes)
- 5p deletion (Cri du chat syndrome)
- 1p36 deletion syndrome
- 4p deletion (Wolf-Hirschhorn syndrome)

In a systematic review of NIPT using cfDNA in general risk pregnancies conducted for the American College of Medical Genetics (ACMG), Rose et al., 2022 included 17 studies of screening for copy number variants (microdeletions and microduplications). Meta-analyses were not conducted due to study heterogeneity. Although screening identified a small number of copy number variants (CNVs), confirmatory testing was frequently unavailable and complete ascertainment of cases was lacking. Sample sizes in each study were relatively small and sensitivities varied greatly. Additionally, it was often difficult to distinguish between low- and high-risk cohort in individual studies. The study authors concluded that the performance of NIPT was significantly poorer when targeting CNVs than the common trisomies and additional outcome studies are needed to understand the unique clinical value of NIPT for CNVs when compared with other approaches.

In Practice Bulletin 226, ACOG stated “Screening for a limited number of microdeletions with cell-free DNA is available; however, this testing has not been validated clinically and is not recommended. Although microdeletions are relatively common when considered in aggregate, cell-free DNA panels only include a few specific clinically significant microdeletions and these are very rare. Therefore, the positive predictive value (PPV) for these disorders is much lower than for common trisomies. If a microdeletion is identified through cell-free DNA screening, it should be confirmed by diagnostic testing, as most positive results will be false-positive results because of the low prevalence of these disorders. If the diagnostic test confirms a microdeletion, the patient should be referred to a health care professional with genetics expertise to discuss the diagnosis and implications and to develop a management plan. For women who wish to evaluate their pregnancy for submicroscopic chromosomal changes, prenatal diagnostic testing with chromosomal microarray analysis from chorionic villus sampling or amniocentesis is recommended. At this time, there is no genetic screening test available to comprehensively screen for all copy number variants. Genome-wide cell-free DNA screening for large deletions or duplications is also offered by some laboratories. This testing evaluates the entire genome and is designed to detect abnormalities larger than those evaluated by cell-free DNA microdeletion screening. Screening for these ancillary disorders is not recommended because this testing has not been validated clinically and the screening accuracy with regard to detection and false-positive rate is not established.”

### **Screening for twin zygosity**

Twin gestations occur in approximately 1 in 30 live births in the United States and have a 4- to 10-fold increased risk of perinatal complications. Dizygous (DZ) twins are derived from two separately fertilized oocytes, with approximately 50% of their DNA being identical. They are characterized by two placentas, with two amniotic membranes and, nearly always, two chorions, i.e. dichorionic (DC). In contrast, monozygotic (MZ) twins arise from a single fertilized oocyte that splits into two embryos that have essentially 100% of their DNA in common. These pregnancies usually have separate amniotic sacs, but they can have one placenta, monochorionic (MC), or two placentas, dichorionic (DC). Thus, DZ twins are typically DC (DZDC), whereas MZ twins can be either monochorionic (MZMC) or dichorionic (MZDC). Although all twin pregnancies are at increased risk for pregnancy complications, MC twins are at the highest risk, requiring increased frequency of testing for twin-to-twin transfusion syndrome (TTTS), selective intrauterine growth restriction (SIUGR), twin anemia polycythemia sequence (TAPS), and twin reversed arterial perfusion syndrome (TRAP). Regardless of zygosity, MC twins generally have lower birthweights compared to DC twins. Both unequal placental sharing and the type of vascular anastomoses can contribute to birthweight discordancy in MC twins; MC twin pregnancies also have a higher frequency of preterm births than DC twins. Accurate determination of chorionicity is therefore critical for appropriate pregnancy risk assessment and management. Identification of chorionicity by ultrasound is generally considered to be accurate, provided the ultrasound is performed prior to 14 weeks of gestational age; the overall sensitivity and specificity for DC pregnancies are 99% and 95%, respectively, while for MC pregnancies, the sensitivity and specificity are 96% and 99%, respectively. In the second trimester, ultrasound assessment of chorionicity has lower sensitivity and lower specificity. Pathological examination of the placenta is considered the gold standard for establishing chorionicity, but placental examination can only be carried out after delivery (Quintero et al., 2026). NIPT using cell-free fetal DNA to determine zygosity in twin pregnancies could potentially inform decisions about early surveillance for TTTS and other MC twin-related abnormalities.

Quintero et al., 2026, reported results of a prospective observational study at 13 sites in the United States between October 2021 and March 2023, (ClinicalTrials.gov NCT05312814) that compared the ultrasound determination of chorionicity (DC or MC) with the results of cfDNA zygosity testing (DZ or MZ) in a cohort of twin pregnancies. The study was sponsored by Natera, Inc. Cell-free DNA (cfDNA) results, ultrasound findings, placental pathology, and maternal and newborn outcomes were collected. Dizygotic twins (DZ) on cell-free DNA were classified as dichorionic (DC). Monozygotic (MZ) twins on cell-free DNA were classified as monochorionic (MC) or DC based on placental pathology. Eligible patients had an ultrasound at less than 13 6/7 weeks of gestation that confirmed a twin pregnancy. The results of cfDNA testing results were

available to providers after the diagnosis of chorionicity had been attempted by ultrasound and were used in clinical management. Pregnancies with TTTS, SIUGR or TAPS or any other complication related to monochorionicity diagnosed prior to screening were excluded. The primary outcome was the overall frequency of cfDNA-determined monozygosity among twin pregnancies; the frequency of discordance between cfDNA-determined zygoty and ultrasound only chorionicity assessments; and the proportion of twin pregnancies with twin-twin transfusion syndrome (TTTS) that are diagnosed late as compared with historical rates. Of 137 twin pregnancies assessed, 110 were included in the analysis. Exclusions were due to missing placental pathology (n = 15), incomplete outcome data (n = 11), or missing cfDNA results (n = 1). Of the 110 patients included in the analysis, cfDNA testing established that 63 were DZ and 47 were MZ. These results were fully consistent with the chorionicity determined by placental pathology. Among 79 cases determined to be DC based on placental pathology, one (1.3%) had no recorded information on chorionicity from ultrasound, and one (1.3%) was misclassified as MC by ultrasound but was dizygous (DZ) by cfDNA, consistent with DC. This patient's BMI (20.6 kg/m<sup>2</sup>) did not appear to be a factor in determining a correct ultrasound diagnosis. Of the 31 cases determined to be MC by placental pathology, three (9.7%) had no recorded information for chorionicity on the ultrasound prior to prenatal cfDNA screening, and one (3.6%) was misclassified as DC by ultrasound. For this discrepant case, cfDNA testing showed MZ, consistent with MC on pathology. This patient's BMI was 27.7 kg/m<sup>2</sup>. For the four cases with missing data for chorionicity on the pre-cfDNA ultrasound, their ultrasounds were performed at 7–8 weeks gestation. Compared to MC pregnancies, DC pregnancies had significantly lower odds of delivering preterm (from 34 weeks to less than 37 weeks) (p = 0.03). Median gestational age at delivery was earlier for MZ twin pregnancies (35.0 weeks) compared to DZ (36.9 weeks, p=0.02). No significant differences were found between DC and MC twins in overall birthweights or birthweight percentiles. MZ twins, however, showed significantly lower birthweight percentiles than DZ twins (p=0.006). After adjusting for fetal sex and gestational age at birth, MZDC twins had significantly lower birthweights (p=0.006) and birthweight percentiles (p=0.004) than DZDC twins. Results of this study confirm that while assessment of chorionicity by first trimester ultrasound is generally accurate, incorrect ultrasound assignment can occur. This study demonstrates that cell free DNA zygoty determination identifies risk patterns and may guide management but does not evaluate improved clinical outcomes relative to usual care. The authors note that this is the first prospective study to assess the role of SNP-based cfDNA testing in helping to improve the accuracy of the ultrasound determination of chorionicity. More data are needed to fully assess how zygoty testing could be used in the prediction of twin preterm birth and low birthweight. Cell-free DNA testing may be particularly important for patients in the second or third trimester, without a first-trimester ultrasound, in whom the sonographic diagnosis of chorionicity is less reliable.

### **Single-gene disorders**

In a practice advisory on cell-free DNA screening for single-gene disorders published in 2019 and reaffirmed in 2021, ACOG stated, "Although this technology is available clinically and marketed as a single-gene disorder prenatal screening option for obstetric care providers to consider in their practice, often in presence of advanced paternal age, there has not been sufficient data to provide information regarding accuracy and positive and negative predictive value in the general population. For this reason, single-gene cell-free DNA screening is not currently recommended in pregnancy."

## **Analysis of Evidence (Rationale for Determination)**

Prenatal screening for chromosomal abnormalities is designed to provide an accurate assessment of a patient's risk of carrying a fetus with a chromosomal disorder. A wide variety of prenatal screening and diagnostic tests are available; each offers varying levels of information and performance, and each has relative advantages and limitations. When considering screening test characteristics, no one test is superior in all circumstances, which results in the need for nuanced, patient-centered counseling from the obstetric care professional and complex decision making by the patient.

The goal of carrier screening is to identify those at risk of transmitting a genetic disorder, traditionally focusing on autosomal recessive or X-linked conditions. Historically, criteria for screening have included: phenotype severity that may impact decision making, high prevalence of carriers in the screened population, established analytic validity of screening methods, predictable genotype–phenotype correlation, available prenatal diagnosis and reproductive options. Recent advancements in genomic technologies, such as next-generation sequencing (NGS), have enabled simultaneous screening of a large number of genes, identifying reproductive risks for dozens to hundreds of diseases. Although NGS facilitates carrier screening for a growing number of diseases simultaneously, developing a screening panel that meets the criteria to justify screening, including known positive and negative predictive values for each test remains a challenge. Uniformity across panels regarding the analytical validity and clinical utility are also a significant concern. Difficulties in interpreting a large number of sequence variants, in cases which a majority of them are variants of uncertain significance, represent the biggest stumbling block to large-scale implementation of NGS-based carrier screening.

Although initially non-invasive prenatal screening was used to screen for the common trisomies and sex chromosome aneuploidy in singleton pregnancies, many laboratories have adapted this technology to screen twin gestations. Furthermore, in some laboratories, the application has been expanded to screen for rare autosomal trisomies, as well as for both common and unique copy number variants. However, the positive predictive values for these conditions are significantly lower than the positive predictive values for common aneuploidies and large-scale outcome studies have not been performed, nor has clinical utility of screening for these rarer conditions been established (Rose et al., 2022). There is not enough research to show an improvement in health outcomes for non-invasive screening using fetal DNA to detect fetal microdeletion syndromes, fetal single-gene disorders, or twin zygosity. In addition, there are no evidence-based practice guidelines that recommend these types of testing. Therefore, non-invasive prenatal testing (NIPT) for fetal microdeletion syndromes, twin zygosity and single-gene disorders is considered investigational. This includes combination tests that include one or more investigational components.

## Coding

The following codes are included below for informational purposes only; inclusion of a code does not constitute or imply coverage or reimbursement.

Code	Description
59000	Amniocentesis; diagnostic
59001	Amniocentesis; therapeutic amniotic fluid reduction (includes ultrasound guidance)
59015	Chorionic villus sampling, any method
76805	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, after first trimester (> or = 14 weeks 0 days), transabdominal approach; single or first gestation
76810	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, after first trimester (> or = 14 weeks 0 days), transabdominal approach; each additional gestation
76813	Ultrasound, pregnant uterus, real time with image documentation, first trimester fetal nuchal translucency measurement, transabdominal or transvaginal approach; single or first gestation
76814	Ultrasound, pregnant uterus, real time with image documentation, first trimester fetal nuchal translucency measurement, transabdominal or transvaginal approach; each additional gestation (List separately in addition to code for primary procedure)
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81243	FMR1 (Fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; evaluation to detect abnormal

	(eg, expanded) alleles
81244	FMR1 (fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; characterization of alleles (eg, expanded size and promoter methylation status)
81329	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed
81412	Ashkenazi Jewish associated disorders (e.g., Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1
81420	Fetal chromosomal aneuploidy (e.g., 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
81422	Fetal chromosomal microdeletion(s) genomic sequence analysis (e.g., DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood
81443	Genetic testing for severe inherited conditions (e.g., cystic fibrosis, Ashkenazi Jewish-associated disorders [e.g., Bloom syndrome, Canavan disease, Fanconi anemia type C, mucopolysaccharidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (e.g., ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH)
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
81508	Fetal congenital abnormalities, biochemical assays of two proteins (PAPP-A, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score
81509	Fetal congenital abnormalities, biochemical assays of three proteins (PAPP-A, hCG [any form], DIA), utilizing maternal serum, algorithm reported as a risk score
81510	Fetal congenital abnormalities, biochemical assays of three analytes (AFP, uE3, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score
81511	Fetal congenital abnormalities, biochemical assays of four analytes (AFP, uE3, hCG [any form], DIA) utilizing maternal serum, algorithm reported as a risk score (may include additional results from previous biochemical testing)
81512	Fetal congenital abnormalities, biochemical assays of five analytes (AFP, uE3, total hCG, hyperglycosylated hCG, DIA) utilizing maternal serum, algorithm reported as a risk score
82105	Alpha-fetoprotein (AFP); serum
82106	Alpha-fetoprotein (AFP); amniotic fluid
82107	Alpha-fetoprotein (AFP); AFP-L3 fraction isoform and total AFP (including ratio)
84163	Pregnancy-associated plasma protein-A (PAPP-A)
84702	Gonadotropin, chorionic (hCG); quantitative
84704	Gonadotropin, chorionic (hCG); free beta chain

## References

1. ACOG Committee Opinion. Number 640. Noninvasive Prenatal Testing for Fetal Aneuploidy. September 2015. Reaffirmed 2017.
2. Norem CT, Schoen EJ, Walton DL, et al. Routine Ultrasonography Compared with Maternal Serum Alpha-fetoprotein for Neural Tube Defect Screening. *Obstet Gynecol.* 2005 Oct;106(4):747-52.

3. Bush MC, Malone FD. Down syndrome screening in twins. *Clin Perinatol*. 2005 Jun;32(2):373-86, vi.
4. Pandya PP, Snijders RJ, Johnson SP, et al. Screening for fetal trisomies by maternal age and fetal nuchal translucency thickness at 10 to 14 weeks of gestation. *Br J Obstet Gynaecol*. 1995 Dec;102(12):957-62.
5. Fan HC, Blumenfeld YJ, Chitkara U, et al. Noninvasive Diagnosis of Fetal Aneuploidy by Shotgun Sequencing DNA From Maternal Blood. *Proc Natl Acad Sci USA*. 2008;105(51):16266-71.
6. Chiu RWK, Cantor CR, Lo YMD. Non-invasive Prenatal Diagnosis by Single Molecule Counting Technologies. *Trends in Genetics*. 2009;25(7):324-30.
7. Cargill Y, Morin L, Morin L. No. 223-Content of a Complete Routine Second Trimester Obstetrical Ultrasound Examination and Report. *J Obstet Gynaecol Can*. 2017 Aug;39(8):e144-e149.
8. Sehnert AJ, Rhees B, Comstock D, et al. Optimal Detection of Fetal Chromosomal Abnormalities by Massively Parallel DNA Sequencing of Cell-Free Fetal DNA from Maternal Blood. *Clin Chem*. 2011;57(7):1-8.
9. Bianchi DW, Platt LD, Goldberg JD, et al. Genome-Wide Fetal Aneuploidy Detection by maternal Plasma DNA Sequencing. *Obstet Gynecol*. 2012;119(5):1-12.
10. Palomaki GE, Kloza EM, Lambert-Messerlian GM, et al. DNA sequencing of maternal plasma to detect Down syndrome: an international clinical validation study. *Genet Med*. Nov 2011;13(11):913-920.
11. Chiu RW, Akolekar R, Zheng YW, et al. Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study. *BMJ*. 2011;342:c7401.
12. Ashoor G, Syngelaki A, Wang E, et al. Trisomy 13 detection in the first trimester of pregnancy using a chromosome-selective cell-free DNA analysis method. *Ultrasound Obstet Gynecol*. 2013;41:21-25.
13. Nicolaides KH, Syngelaki A, Ashoor G, et al. Noninvasive prenatal testing for fetal trisomies in a routinely screened first-trimester population. *Am J Obstet Gynecol*. 2012;207:374.e1-6.
14. Gil MM, Quezada MS, Bregant B et al. Implementation of maternal blood cell-free DNA testing in early screening for aneuploidies. *Ultrasound Obstet Gynecol*. 2013; 42(1):34-40.
15. Wagner AJ, Mitchell ME, Tomita-Mitchell A. Use of cell-free fetal DNA in maternal plasma for noninvasive prenatal screening. *Clin Perinatol*. 2014 Dec;41(4):957-66.
16. Sarno L, Revello R, Hanson E, Akolekar R, Nicolaides KH. Prospective screening for trisomies by cell-free DNA testing of maternal blood in first trimester twin pregnancies. *Ultrasound Obstet Gynecol*. 2016 Mar 11.
17. Gekas J, Langlois S, Ravitsky V, et al. Non-invasive prenatal testing for fetal chromosome abnormalities: review of clinical and ethical issues. *Appl Clin Genet*. 2016 Feb 4;9:15-26.
18. Beulen L, Faas BH, Feenstra I, et al. The clinical utility of noninvasive prenatal testing in pregnancies with ultrasound anomalies. *Ultrasound Obstet Gynecol*. 2017 Jun;49(6):721-728.
19. Kibel M, Vanstone M. Reconciling ethical and economic conceptions of value in health policy using the capabilities approach: A qualitative investigation of Non Invasive Prenatal Testing. *Soc Sci Med*. 2017 Dec;195:97-104.
20. Breveglieri G, D'Aversa E, et al. Non-invasive Prenatal Testing Using Fetal DNA. *Mol Diagn Ther*. 2019 Feb 2.
21. National Government Services, Inc. Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000). Original Effective Date For services performed on or after 10/1/2015. Revision Effective Date For services performed on or after 07/13/2025. Available at: <https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=35000>. Accessed 01/24/2026.
22. National Government Services, Inc. LCD Reference Article: Billing and Coding: Molecular Pathology Procedures (A56199). Original Effective Date 01/01/2019. Revision Effective Date 10/01/2025. Available at: <https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=56199>. Accessed 01/24/2026.
23. Parham L, Michie M, Allyse M. Expanding Use of cfDNA Screening in Pregnancy: Current and Emerging Ethical, Legal, and Social Issues. *Curr Genet Med Rep*. 2017 Mar;5(1):44-53.

24. Carlson LM, Vora NL. Prenatal Diagnosis: Screening and Diagnostic Tools. *Obstet Gynecol Clin North Am.* 2017 Jun;44(2):245-256.
25. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics; Committee on Genetics; Society for Maternal-Fetal Medicine. Screening for Fetal Chromosomal Abnormalities: ACOG Practice Bulletin, Number 226. *Obstet Gynecol.* 2020 Oct;136(4):e48-e69.
26. Taglauer ES, Wilkins-Haug L, Bianchi DW. Review: cell-free fetal DNA in the maternal circulation as an indication of placental health and disease. *Placenta.* 2014 Feb;35 Suppl(Suppl):S64-8.
27. Dungan JS, Klugman S, Darilek S, et al; ACMG Board of Directors. Noninvasive prenatal screening (NIPS) for fetal chromosome abnormalities in a general-risk population: An evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2023 Feb;25(2):100336. Erratum in: *Genet Med.* 2023 Aug;25(8):100874.
28. Gregg AR, Rajkovic A. Cell-Free DNA Screening During Pregnancy. *JAMA.* 2019;321(3):308-9.
29. Gregg AR, Skotko BG, Benkendorf JL, et al. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. *Genet Med.* 2016;18(10):1056-65.
30. Gregg AR, Gross SJ, Best RG, et al. ACMG statement on noninvasive prenatal screening for fetal aneuploidy. *Genet Med.* 2013;15:395–398.
31. Grody WW, Thompson BH, Gregg AR, et al. ACMG position statement on prenatal/preconception expanded carrier screening. *Genet Med.* 2013;15:482–483. 3.
32. Driscoll DA, Gross SJ; Professional Practice and Guidelines Committee. First trimester diagnosis and screening for fetal aneuploidy. *Genet Med.* 2008 Jan;10(1):73-5.
33. Driscoll DA; Professional Practice and Guidelines Committee. Second trimester maternal serum screening for fetal open neural tube defects and aneuploidy. *Genet Med.* 2004 Nov-Dec;6(6):540-1.
34. ACOG Committee Opinion. Number 691. March 2017. Reaffirmed 2025. Carrier Screening for Genetic Conditions. *Obstet Gynecol.* 2017 Mar;129(3):e41-e55.
35. Sagaser KG, Malinowski J, Westerfield L, et al. Expanded carrier screening for reproductive risk assessment: An evidence-based practice guideline from the National Society of Genetic Counselors. *J Genet Couns.* 2023 Jun;32(3):540-557.
36. Fakh A, Spector-Bagdady K. Should Clinicians Leave "Expanded" Carrier Screening Decisions to Patients? *AMA J Ethics.* 2019 Oct 1;21(10):E858-864.
37. Edwards JG, Feldman G, Goldberg J, et al. Expanded carrier screening in reproductive medicine—points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. *Obstet Gynecol.* 2015;125(3):653–62.
38. ACOG Committee Opinion. Number 690, March 2017. Reaffirmed 2025. Carrier screening in the age of genomic medicine. *Obstet Gynecol.* 2017;129(3):595-596.
39. Gregg AR, Aarabi M, Klugman S, et al; ACMG Professional Practice and Guidelines Committee. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2021 Oct;23(10):1793-1806. Erratum in: *Genet Med.* 2021 Oct;23(10):2015.
40. Guha S, Reddi HV, Aarabi M, et al.; ACMG Laboratory Quality Assurance Committee. Laboratory testing for preconception/prenatal carrier screening: A technical standard of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2024 Jul;26(7):101137.
41. Deignan JL, Gregg AR, Grody WW, et al.; ACMG Board of Directors. Updated recommendations for CFTR carrier screening: A position statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2023 Aug;25(8):100867.
42. ACOG Committee Opinion No. 486: Update on carrier screening for cystic fibrosis. *Obstet Gynecol.* 2011 Apr;117(4):1028-1031.

43. Sun Y, Kong X, Zhao Z, Zhao X. Mutation analysis of 419 family and prenatal diagnosis of 339 cases of spinal muscular atrophy in China. *BMC Med Genet.* 2020 Jun 18;21(1):133.
44. Schneider A, Summers S, Tassone F, et al. Women with Fragile X-associated Tremor/Ataxia Syndrome. *Mov Disord Clin Pract.* 2020 Sep 23;7(8):910-919.
45. Liani V, Torrents C, Roller E, et al. Premutation Females with preFXTAS. *Int J Mol Sci.* 2025 Mar 20;26(6):2825.
46. Cabal-Herrera AM, Tassanakijpanich N, Salcedo-Arellano MJ, Hagerman RJ. Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS): Pathophysiology and Clinical Implications. *Int J Mol Sci.* 2020 Jun 20;21(12):4391.
47. Rose NC, Barrie ES, Malinowski J, et al. Systematic evidence-based review: The application of noninvasive prenatal screening using cell-free DNA in general-risk pregnancies. *Genetics in medicine: official journal of the American College of Medical Genetics.* 2022;24(7):1379-91.
48. ACOG Practice Advisory. Cell-Free DNA to Screen for Single-Gene Disorders. February 2019. Reaffirmed September 2024. Available at: <https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2019/02/cell-free-dna-to-screen-for-single-gene-disorders>.
49. Norwitz ER, McNeill G, Kalyan A, et al. Validation of a Single-Nucleotide Polymorphism-Based Non-Invasive Prenatal Test in Twin Gestations: Determination of Zygosity, Individual Fetal Sex, and Fetal Aneuploidy. *J Clin Med.* 2019;8(7).
50. The Fetal Medicine Foundation. MC twins: twin-to-twin transfusion syndrome. © 2026 The Fetal Medicine Foundation. Available at: <https://fetalmedicine.org/education/fetal-abnormalities/multiple-pregnancies/mc-twins-twin-to-twin-transfusion-syndrome>.  
Quintero R, Hurt KJ, Vora NL, et al. Ultrasound and SNP-based cell-free DNA zygosity testing in twin pregnancies. *J Matern Fetal Neonatal Med.* 2026 Dec;39(1):2614840.

## Policy history

Origination date:	03/28/2006
Review/Approval(s):	Technology Assessment Committee: 06/21/2006, 05/22/2012, 2/26/2014 ICD 10 CM codes mapped; 4/23/2014 correction due to ICD 10 CM implementation, 03/25/2015 (updated coding, references) 03/23/2016 (removed ICD-9 codes, added new code 0009M requiring prior authorization, updated references), 04/26/2017 (updated references), 02/28/2018 (added exclusion to NIPT criteria for multiple gestations, updated references), 02/27/2019 (removed ICD-10 codes, updated references), 03/27/2019 (added direction related to Spinal Muscular Atrophy testing to Genetic Testing Policy), 07/10/2021 (Added clarifying language related to Medicare Advantage, NaviCare and PACE under policy section), 01/28/2025 (annual review; added new paragraph for MassHealth ACO in Policy section; updated coverage criteria for cell-free DNA effective for dates of service on or after November 21, 2024; updated Exclusions, Coding, References), 01/27/2026 (annual review; added exclusions for noninvasive prenatal screening for fetal sex determination, combination tests that include one or more experimental and investigational components, and carrier screening for an inherited disorder performed more than once per lifetime; added new section for Carrier Screening for Genetic Disorders with adoption of InterQual® Criteria). Utilization Management Committee: 02/18/2025 (annual review; approved coverage criteria for cell-free DNA effective November 21, 2024), 02/17/2026 (annual review; approved new exclusions described above and new section for Carrier Screening for Genetic Disorders with adoption of InterQual® Criteria), 03/17/2026 (Under Expanded carrier screening panels, removed statement pertaining to CPT 81443: Limited evidence, requires Medical Director review, added paragraph related to ACMG recommendation, updated Summary of Evidence).

## Instructions for Use

Fallon Health complies with CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) of Medicare Contractors with jurisdiction for claims in the Plan's service area, and applicable Medicare statutes and regulations when making medical necessity determinations for Medicare Advantage members. When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health may create internal coverage criteria under specific circumstances described at § 422.101(b)(6)(i) and (ii).

Fallon Health follows Medical Necessity Guidelines published by MassHealth when making medical necessity determinations for MassHealth members. In the absence of Medical Necessity Guidelines published by MassHealth, Fallon Health may create clinical coverage criteria in accordance with the definition of Medical Necessity in 130 CMR 450.204.

For plan members enrolled in NaviCare, Fallon Health first follows CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) of Medicare Contractors with jurisdiction for claims in the Plan's service area, and applicable Medicare statutes and regulations when making medical necessity determinations. When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, or if the NaviCare member does not meet coverage criteria in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health then follows Medical Necessity Guidelines published by MassHealth when making necessity determinations for NaviCare members.

Each PACE plan member is assigned to an Interdisciplinary Team. PACE provides participants with all the care and services covered by Medicare and Medicaid, as authorized by the interdisciplinary team, as well as additional medically necessary care and services not covered by Medicare and Medicaid. With the exception of emergency care and out-of-area urgently needed care, all care and services provided to PACE plan members must be authorized by the interdisciplinary team.

Not all services mentioned in this policy are covered for all products or employer groups. Coverage is based upon the terms of a member's particular benefit plan which may contain its own specific provisions for coverage and exclusions regardless of medical necessity. Please consult the product's Evidence of Coverage for exclusions or other benefit limitations applicable to this service or supply. If there is any discrepancy between this policy and a member's benefit plan, the provisions of the benefit plan will govern. However, applicable state mandates take precedence with respect to fully-insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, federal mandates will apply to all plans.