Cell-Free Fetal DNA Testing

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➲ Instructions for Use

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Related Commercial Policies

- Chromosome Microarray Testing (Non-Oncology Conditions)
- Preimplantation Genetic Testing and Related Services

Community Plan Policy

- Cell-Free Fetal DNA Testing

Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans.

Coverage Rationale

Cell-Free Fetal DNA testing using maternal plasma to determine fetal genotype is proven and medically necessary when the individual undergoing testing is alloimmunized or at risk for alloimmunization due to maternal RhD status or the presence of red cell antigen antibodies and all the following:

- Paternal genotyping shows heterozygosity for RhD or paternal RhD status is unknown
- Indicated invasive diagnostic testing (e.g., amniocentesis, chorionic villus sampling) for fetal genotyping has been offered and declined

Due to insufficient evidence of efficacy, Cell-Free Fetal DNA testing using maternal plasma is considered unproven and not medically necessary for indications beyond screening for trisomies 21, 18, and 13 and sex chromosome Aneuploidy. This includes but is not limited to the following:

- Testing for the sole purpose of determining Twin Zygosity
- Genome-wide or exome-wide screening (e.g., MaterniT® Genome)
- Cell-Free Fetal DNA expanded panel testing (panels that include testing beyond trisomies 21, 18, and 13 and sex chromosome Aneuploidy)
- Screening for the following:
  - Microdeletions/microduplications/copy number variations
  - Single-gene disorders (e.g., Vistara™, PreSeek™)
  - Fetal antigen status other than RhD

Genetic Counseling

Genetic counseling is strongly recommended prior to fetal screening or prenatal diagnosis in order to inform persons being tested about the advantages and limitations of the test as applied to a unique person.

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Medical Records Documentation Used for Reviews

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the guidelines titled Medical Records Documentation Used for Reviews.

Definitions

Aneuploidy: A normal human cell has 23 pairs of chromosomes. An abnormal number of chromosomes in a human cell is called Aneuploidy. This includes trisomy, in which there is an extra chromosome present, or monosomy, in which a chromosome is missing. Aneuploidy can impact any of the chromosomes, including sex chromosomes. Down syndrome (trisomy 21) is a common Aneuploidy. Patau syndrome (trisomy 13) and Edwards syndrome (trisomy 18) are other notable aneuploidies (American College of Obstetricians and Gynecologists Dictionary, 2026).

Cell-Free Fetal DNA: Small fragments of fetal DNA from the placenta that move freely in the pregnant individual's blood. These fragments can be analyzed via a Noninvasive Prenatal Screening test (American College of Obstetricians and Gynecologists Dictionary, 2026).

Comparative Genomic Hybridization: Comparative Genomic Hybridization is a technology that can be used for the detection of genomic copy number variations. Tests can use a variety of probes or single-nucleotide polymorphisms to provide copy number and gene-differentiating information. All platforms share in common that individual and reference DNA are labeled with dyes or fluorescing probes and hybridized on the array. A scanner then measures differences in intensity between the probes, and the data are expressed as having greater or less intensity than the reference DNA (South et al., 2013).

Noninvasive Prenatal Testing/Screening: A common term used to describe different types of analysis of Cell-Free Fetal DNA (Allyse and Wick, 2018).

Twin Zygosity: Zygosity refers to the type of conception. Dizygotic (nonidentical, fraternal) twins result from multiple ovulations with (near) synchronous fertilization of two separate ova by two separate sperm cells. Dizygotic twins thus share the same genetic relationship as nontwin siblings and share approximately 50% of genes. Monozygotic twins (so-called identical twins) are generated by division of a zygote that originated from the fertilization of one single ovum by one single sperm cell (De Paepe, 2023).

Whole-Genome Sequencing: Whole-Genome Sequencing determines the sequence of the entire DNA in a person or a tissue type, such as a tumor, which includes the protein-making (coding) as well as noncoding DNA elements (MedlinePlus, 2021).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other policies and guidelines may apply.

CPT Code	Description
0060U	Twin zygosity, genomic targeted sequence analysis of chromosome 2, using circulating cell-free fetal DNA in maternal blood
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

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CPT Code	Description
0489U	Obstetrics (single-gene noninvasive prenatal test), cell-free DNA sequence analysis of 1 or more targets (e.g., 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 (e.g., 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
0632U	Red blood cell antigen (fetal RhD gene analysis), multiplex polymerase chain reaction (PCR) and next-generation sequencing (NGS) of circulating cell-free DNA (cfDNA), plasma from pregnant individuals known to be RhD negative, reported as detected or not detected
0633U	Obstetrics (single-gene noninvasive prenatal test), cell-free DNA (cfDNA), next-generation sequencing (NGS) analysis of 1 or more targets (eg, CFTR, SMN1, HBB, HBA1, HBA2) to identify paternally inherited pathogenic variants and to determine fetal inheritance of maternal mutation, using maternal blood sample, algorithm reported as a fetal risk score
0663U	Obstetrics (fetal platelet antigen noninvasive prenatal test [NIPT]), cell-free DNA (cfDNA) sequence analysis for detection of fetal presence or absence of 1 human platelet antigen or more (HPA-1a, HPA-1b, HPA-3a, HPA-5b, and others) when performed, reported as maternal/fetal incompatibility detected or not detected per selected antigen
81422	Fetal chromosomal microdeletion(s) genomic sequence analysis (e.g., DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood
81479	Unlisted molecular pathology procedure

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Description of Services

During pregnancy, cell-free DNA from the placenta circulates in a pregnant individual's blood. Cell-Free Fetal DNA from this blood can be screened for common Aneuploidies (trisomies 21, 18, and 13) as well as other genetic anomalies, with testing offered as early as 9 to 10 weeks' gestation. Available tests use different methodologies and algorithms for data analysis. These tests may identify women with an increased risk of having a child with a genetic disorder, but they cannot conclusively diagnose, confirm, or exclude the possibility of a genetic condition. Only conventional prenatal diagnostic testing (i.e., by chorionic villus sampling or amniocentesis) can definitively diagnose fetal genetic conditions (Society for Maternal-Fetal Medicine, 2025).

Clinical Evidence

RHD Genotyping

Moise et al. (2025) developed a comprehensive clinical practice guideline for managing pregnancies complicated by red blood cell alloimmunization through the formation of four multidisciplinary expert working groups that conducted systematic reviews and meta-analyses followed by a Delphi consensus process to determine appropriate recommendations. The groups comprised experts in (1) trauma and transfusion, (2) hematology, (3) maternal-fetal medicine/obstetrics, and (4) neonatology; they ultimately produced seven core recommendations and 32 practice points outlining standardized management from early detection through intrauterine transfusion therapy. These recommendations emphasize the importance of early fetal risk assessment using maternal cell-free fetal DNA (cffDNA) as well as surveillance for fetal anemia and the selective use of intravenous immunoglobulin, when necessary. A noted limitation in the development of these guidelines includes variable evidence quality across reviewed topics due to the low volumes of published evidence. As such, some of the recommendations were based on indirect or limited data. The recommendation for the use of maternal cffDNA was based on moderate confidence in evidence quality. Despite some limitations in the evidence base, the guideline offers a structured, consensus-driven approach to standardizing care for alloimmunized pregnancies, with the use of maternal cffDNA as a key recommendation.

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Mateus-Nino et al. (2025) performed a retrospective cohort study that evaluated the clinical performance of a next-generation sequencing (NGS) cell-free DNA (cfDNA) assay to detect fetal RhD status among 401 racially and ethnically diverse, nonalloimmunized, RhD-negative, pregnant patients receiving care across four health centers in the United States. The cfDNA results demonstrated perfect concordance with neonatal serology, yielding 100% sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) while also identifying 10 patients with non-*RHD* gene deletions such as *RHDΨ* and *RHD-CE-D* hybrid variants. Clinicians appeared to use cfDNA information to guide Rh immunoglobulin (RhIG) administration patterns; RhIG was administered to 93% of pregnant patients with cfDNA results that indicated an RhD-positive fetus compared with 75% of pregnant patients in whom cfDNA results indicated an RhD-negative fetus. Although the researchers found that the cfDNA assay was highly accurate and their results support recommendations to offer cfDNA screening for fetal Rh status as an option to prophylactic use of RhIG for all nonalloimmunized, RhD-negative individuals, the study did have some limitations. These include its retrospective design, modest sample size, and administration of RhIG per clinician discretion. In addition, the study was sponsored by and authors had affiliations with a commercial laboratory (BillionToOne), which may introduce bias.

Gilstrop et al. (2025) conducted a clinical validation study to assess the performance of an NGS-based, prenatal cfDNA test for fetal *RHD* status in pregnant individuals with an RhD-negative phenotype. The key inclusion criteria included passing quality metrics for samples; available previous prenatal cfDNA results for fetal aneuploidy; documented RhD-negative serological results for the pregnant person; available newborn RhD serology results; maternal genotype results identifying the individual as having an *RHD* deletion or *RHD-CE-D* hybrid genotype; and identification of the pregnancy as singleton or monozygotic twin based on single-nucleotide polymorphism (SNP)–based testing. Demographic and clinical data were included to evaluate how well the results would apply to the U.S. population. Maternal and fetal *RHD* genotypes were assessed using prospective cfDNA NGS. Investigators were blinded to the fetal RhD status during the analysis. The cohort comprised 655 pregnant individuals, representing a diverse distribution of races and ethnicities in the RhD-negative U.S. population. The reported results showed no false-negative results; all 356 fetuses were accurately identified as RhD positive (sensitivity, 100%; 95% CI, 98.9%-100%). Among the 297 RhD-negative fetuses, 295 were correctly identified as RhD negative (specificity, 99.3%; 95% CI, 97.6%-99.8%). In fetuses with a negative RhD phenotype, the cfDNA test was able to accurately identify three who carried the fetal RhD pseudogene (*RHDΨ*) genotype. Of note, cfDNA fetal *RHD* was not reported in two cases. According to the authors, the assay demonstrated high performance and achieved 100% sensitivity, 99.3% specificity, a PPV of 98.4%, and an NPV of almost 100% beginning at 9 weeks of gestation. They suggested that implementing this test could conserve the U.S. RhD immunoglobulin supply by decreasing the need for unnecessary blood products in up to 40% of RhD-negative pregnant individuals. The study's strengths include the following: the cohort was large and racially diverse; serological truth was available for all newborns; and the three most common *RHD* variants were evaluated. A limitation is that potential sampling bias existed due to the nonrandom cohort of individuals with previous SNP-based cfDNA screening. In addition, the study was funded by and the majority of authors were associated with the manufacturer (Natera) of the test under study, creating additional potential for bias. Despite these limitations, the authors asserted that their results support the use of prenatal cfDNA screening as a highly sensitive and specific tool for assessing fetal RhD status in a diverse U.S. population.

In a 2024 (updated 2025) Hayes Clinical Utility Evaluation, the use of cfDNA testing for *RHD* genotypes to direct treatment with anti-D immunoglobulin prophylaxis in RhD-negative, nonalloimmunized pregnancies was assessed. Nine applicable studies that met the inclusion criteria were identified and analyzed. Overall, this low-quality body of evidence indicates that the number of unnecessary anti-D prophylaxis injections was reduced when cfDNA RhD testing was performed. Based on these data, clinical utility is inferred (Hayes utility score of 3/probable) due to the widely established test accuracy and the availability of safe and effective treatment. Existing clinical practice guidelines and/or position statements weakly support the use of cfDNA testing in these cases.

In a 2021 systematic review and meta-analysis, Alshehri and Jackson evaluated the application of cfDNA for fetal *RHD* genotyping in conjunction with quantitative maternal alloantibody analysis for the early diagnosis of pregnancies at risk of hemolytic disease of fetus and newborn. A total of 19 studies from January 2006 to April 2020 were included in the analysis. The researchers found that cfDNA testing was highly sensitive and specific (as early as 11 weeks' gestation) with regard to early *RHD* genotyping, with a preference for high-throughput platforms, and feel that this evidence supports the inclusion of cfDNA testing, along with maternal alloantibody quantitation, in routine pregnancy management. They noted that knowledge of parental ethnicity is key for the correct interpretation of cfDNA results and quantitative screening results and that cfDNA testing would lead to less anxiety and inconvenience for pregnant individuals. The authors concluded that future large-scale studies that evaluate cfDNA non-*RHD* genotyping, including varying ethnic groups and with the presence of clinically significant alloantibodies, are needed.

A 2020 Ontario Health Technology Assessment evaluated the accuracy, clinical utility, and cost-effectiveness of noninvasive fetal RhD blood group genotyping in RhD-negative pregnant individuals. The evaluation included a literature search, which identified six systematic reviews that addressed the test accuracy and 11 studies that addressed clinical

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utility. Test accuracy was found to be high across all the systematic reviews and indicated that implementation of fetal cfDNA testing for the RhD genotype could lead to avoidance of unneeded RhIG [Grading of Recommendations Assessment, Development, and Evaluation (GRADE): low], good adherence to targeted RhIG prophylaxis (GRADE: very low), and high uptake of genotyping (GRADE: low). In addition, alloimmunization may not increase with the use of fetal cfDNA RhD genotyping for targeting prenatal RhIG prophylaxis, and unnecessary monitoring and invasive procedures in alloimmunized pregnant individuals may be reduced (both GRADE: very low). The Health Technology Assessment concluded that overall, fetal cfDNA testing for fetal RhD blood group genotyping is an accurate test to detect RhD incompatibility and help steer the management of RhD-negative pregnancies, but only low- to very low-quality evidence was identified to indicate that fetal cfDNA testing for RhD genotype would lead to the avoidance of unnecessary RhIG prophylaxis, high adherence to the targeted RhIG programs, and high uptake of genotyping. Studies by Yang et al. (2019) and Mackie et al. (2017), discussed in the evidence below, and Saramago et al. (2018), previously discussed in this policy, were included in this Health Technology Assessment.

A prospective cohort systematic review and meta-analysis was performed by Yang et al. (2019; included in the 2020 Ontario Health Technology Assessment discussed above) to assess the diagnostic accuracy of high-throughput noninvasive prenatal testing (NIPT) for fetal RhD status in RhD-negative women who were not known to be sensitized to the RhD antigen. The databases that were scanned for this meta-analysis included MEDLINE, Embase, and the Science Citation Index; these were searched through February 2016. Included for review were 3,921 identified studies. The study population included RhD-negative pregnant women known to not be sensitized to the RhD antigen, and the index test was high-throughput cfDNA on maternal plasma. Serological cord blood testing at birth was considered to be the reference standard, and eligible studies were required to report diagnostic accuracy data, including true-positive, false-positive, true-negative, and false-negative absolute numbers. The diagnostic accuracy of NIPT varied by gestational age, with data suggesting that NIPT was consistently accurate any time after the first trimester. The false-negative rate (those incorrectly classified as RhD negative) was 0.34% (95% CI, 0.15%-0.76%), and the false-positive rate (incorrectly classified as RhD positive) was 3.86% (95% CI, 2.54%-5.82%). Because this study was a meta-analysis, the authors stated that the original articles and several of the included studies were deemed to be at a high risk of bias due to the selected populations and the reference standards. The authors concluded that the use of NIPT for fetal RhD screening in all RhD-negative women is possible. Results would significantly reduce the need for unnecessary prenatal anti-D prophylaxis while marginally increasing the risk of sensitization due to false-negative results.

Manfroi et al. (2018) performed fetal *RHD* genotyping with polymerase chain reaction (PCR) using cfDNA from maternal plasma to determine the diagnostic accuracy of noninvasive fetal genotyping at different gestational ages. A commercial multiple-exon assay was used to determine the accuracy of fetal *RHD* genotyping. Samples from RhD-negative women (n = 367) with RhD-positive partners or partners with unknown RhD phenotype were collected between 24 and 28 weeks' gestation; due to the lack of available first-trimester samples, the analysis was restricted to 24 to 28 weeks, during which fetal genotyping is usually performed for prenatal RhIG administration. Neonatal results were provided for 284 pregnancies. The reported sensitivity and specificity were 100% and 97.5%, respectively. Diagnostic accuracy was 96.1%, including nine of 284 inconclusive results. The low number of early gestational age samples is a weakness of the study, and the authors attributed a false-negative result to this. The authors concluded that cfDNA for *RHD* genotyping is an accurate and reliable tool for fetal immunoprophylaxis.

Saramago et al. (2018) conducted a Health Technology Assessment on the use of cfDNA to determine fetal RhD status. The authors searched MEDLINE and other databases, from inception to February 2016, for studies of high-throughput prenatal cfDNA tests of maternal plasma to determine fetal RhD status in RhD-negative pregnant women who were not known to be sensitized to the RhD antigen. The inclusion criteria for all reviews included pregnant women who were RhD negative and not known to be sensitized to the RhD antigen. For examining diagnostic accuracy, the inclusion criteria were prospective cohort studies that reported absolute numbers; for clinical effectiveness, the inclusion criteria included studies that used high-throughput NIPT, in which anti-D prophylaxis was given. The clinical outcomes were reported. The inclusion criteria for implementation outcomes were any publication that reported issues related to the implementation of or practical advice relating to NIPT. Eight studies were included in the diagnostic accuracy review, seven studies were included in the clinical effectiveness review, and 12 studies were included in the review of implementation. The meta-analysis found that women in the studies were at least at 11 weeks of gestation or later and mostly Caucasian with singleton pregnancies. The false-negative rate (at risk of sensitization) was 0.34%, and the false-positive rate (receiving unnecessary anti-D prophylaxis) was 3.86%. Clinical outcome data were limited to confirm the true sensitization rate, but there was no evidence of potential adverse effects. The authors concluded that there were limited data on the clinical effectiveness of NIPT for fetal RhD status, and more studies are needed for non-Caucasian individuals and multiple gestations.

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Screening for Rare Aneuploidies

The use of cfDNA for the determination of aneuploidies other than trisomies 13, 18, and 21 and sex chromosome aneuploidies is still in the early stages of development. Evidence, at this time, is limited and has shown a high number of false-positive results.

Suo et al. (2026) conducted a large, retrospective cohort study that evaluated the performance of expanded NIPT for the detection of fetal aneuploidies, including sex-chromosome aneuploidies (SCAs), rare autosomal aneuploidies (RAAs), and copy number variations (CNVs), in 9,708 pregnancies screened at a maternity and child health hospital in China between March 2021 and August 2024. All screen-positive cases [n = 192 (1.98%)] were offered invasive diagnostic confirmation; 158 patients underwent amniocentesis with chromosomal microarray analysis (CMA). Test performance was assessed by determining the sensitivity, specificity, PPV, and NPV for each category of genetic anomaly. Of the 158 cases in which CMA was performed, 51 were true positives and 107 were false positives, resulting in an overall PPV of 32.3% (95% CI, 25.3%-40.2%). High sensitivity and specificity were attained for common trisomies T13, T18, and T21 and SCAs, with PPVs of 88.5%, 30.0%, 15.4%, and 57.7%, respectively, but substantially lower PPVs were calculated for RAAs (20.0%) and CNVs, especially the latter, which showed a PPV of only 14.6% despite a high NPV (99.99%) and one false-negative result. The authors concluded that expanded NIPT is highly effective for detecting common trisomies and SCAs but yields modest predictive performance for CNVs and RAAs. They emphasized the need for confirmatory invasive testing and genetic counseling for all positive results. Noted limitations include the study's retrospective, single-center design; researchers' reliance on confirmatory testing in only a subset of screen-positive cases; and lack of systematic maternal genomic testing to confirm maternal-origin CNVs, which may contribute to false-positive results. Further high-quality investigation across diverse populations is recommended to validate these findings and assess long-term outcomes.

Yan et al. (2025) included a total of 33,079 pregnant patients in a retrospective analysis of prenatal diagnostic results and pregnancy outcomes of cases in which a high risk of rare autosomal trisomies (RATs) was detected via cfDNA prenatal testing. The study, which took place at a reproductive medical facility in China, identified 66 cases in which the fetus was found to be at a high risk of RATs, for a detection rate (DR) of 0.20% (66 of 33,079). Of the 66 identified cases, seven patients opted not to undergo amniocentesis. The prenatal diagnostic procedures did not confirm corresponding RATs in any of the remaining 59 cases in which amniocentesis was performed. Five patients were lost to study follow-up, and one patient terminated their pregnancy for personal reasons. Full-term pregnancy/birth occurred in 50 of the 60 patients with reported outcomes (83.33%), while 10 (16.67%) experienced some type of adverse outcome (preterm birth, miscarriage, intrauterine growth restriction, fetal abnormality related to placental hemangioma, hydronephrosis, or diagnosed chromosomal abnormality). The authors noted that because most fetuses with RATs do not survive beyond 12 weeks' gestation, RATs identified by cfDNA testing after 12 weeks are typically indicative of placental mosaicism and not fetal trisomy. However, the presence of trisomic cells in the placenta can disrupt normal placental development, which can lead to adverse pregnancy outcomes. They recommended further study that examines pregnancy outcomes in cases of RATs.

Yang et al. (2025) conducted a retrospective study to evaluate the clinical performance of expanded NIPT (NIPT-plus) and compare its effectiveness in screening for chromosomal aneuploidies with that of standard NIPT. The study included screening results, confirmatory invasive testing results, and follow-up data from pregnant women who underwent either NIPT (6,792 cases) or NIPT-plus (5,237 cases). The researchers calculated the PPV, sensitivity, specificity, and other indicators for different types of chromosomal abnormalities with NIPT and NIPT-plus. In the NIPT-plus samples, the average number of unique reads was 5.26 times greater than that in the standard NIPT samples. No significant difference in the PPV or positive rate between NIPT-plus and NIPT was identified for screening chromosomal aneuploidies. The high-risk group had a greater PPV than the low-risk group, but in the NIPT-plus group, no significant difference in the PPV between the low-risk and high-risk groups was discovered. Pregnant patients in the study had a higher rate of confirmatory invasive testing for common trisomies, SCAs, and CNVs than for RAAs. The rate of pregnancy termination was higher for common trisomies, RAAs, and CNVs than for SCAs. Both NIPT and NIPT-plus screening had a sensitivity of 100% and a specificity of over 0.99 for common trisomies and SCAs, with no detected cases of false-negatives, indicating that both tests are effective in screening for the common trisomies and SCAs, even though NIPT-plus has approximately five times more sequencing data than standard NIPT. The authors concluded that these findings demonstrate that both NIPT and NIPT-plus are effective in screening for common trisomies, SCAs, and RAAs in different groups of pregnant individuals, and although NIPT-plus can effectively screen for pathogenic CNVs due to the increased amount of sequencing performed, it does not improve detection of common trisomies, SCAs, and RAAs compared with standard NIPT. Noted limitations of this study include that (1) it is too early to determine if a newborn has SCAs or CNVs 3 months post partum because symptoms of pathogenic CNVs and SCAs may not appear until childhood and that (2) the study excluded screening-positive instances, without confirmatory invasive testing results, as well as those lost to follow-up, which could impact the accuracy of the results and conclusions of this study. In addition, the software used for the analysis of CNVs was limited to only pathogenic or likely pathogenic, which did not allow for the comprehensive evaluation of CNV detection efficiency.

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Konya et al. (2024) assessed the specificity and accuracy of genome-wide cfDNA prenatal testing for RATs and structural chromosome abnormalities to help determine the clinical utility of this testing in a recent systematic review and meta-analysis. Both the screening accuracy in and pregnancy outcomes of cases in which testing revealed rare chromosomal abnormalities were analyzed. Overall, 17 studies were included, with a total of 740,076 cfDNA fetal tests performed. Of the 740,076 tests, 1,738 of these were positive for RATs. Two methodologies were used to determine true-positive cases; the first was a confirmed methodology in which only cases that were verified by diagnostic genetic testing were considered true positives with a definitive diagnosis, and the second was an extended methodology in which, in addition to cases confirmed by genetic testing, intrauterine fetal death and termination of pregnancy due to an abnormality, confirmed by ultrasound, were also considered true positives (no definitive diagnosis was made in these cases, but it was likely that the fetus was affected). The pooled PPV using the confirmed method was 0.07. Using the extended method, the pooled PPV was 0.13. The pooled false-positive rate among all prenatal cfDNA tests was 0.0020. The heterogeneity was high (I^2 = 95%). Many cases of RAT that were identified by cfDNA testing were not confirmed in the fetus; this is most often due to placental mosaicism, which also increases the risk of adverse pregnancy outcomes and warrants increased prenatal monitoring. The highest rates of true positives were found for trisomies 16, 22, and 2, using the confirmed method. With the use of the extended method, the highest rates of true positives were found for trisomies 15, 16, and 22. Overall, the meta-analysis revealed frequency data related to rare chromosomal abnormalities, test-positive rates, and accurate PPV for each chromosomal abnormality (this varied widely between chromosomes), which may assist clinicians with pre- and posttest counseling and decision-making. The authors asserted that their findings indicate that prenatal screening for rare chromosome abnormalities with cfDNA can lead to the early identification of individuals who may be candidates for verification of fetal status via invasive diagnostic testing. Further investigation into the clinical utility of screening for rare chromosomal abnormalities is required before this testing can be incorporated into standard practice. Publications by Zhang et al. (2023) and Van Opstal et al. (2018), discussed below, and Scott et al. (2018), Wan et al. (2018), Pertile et al. (2017), and Fiorentino et al. (2017), previously discussed in this policy, were included in this systematic review and meta-analysis.

Acreman et al. (2023) sought to determine the PPV of cfDNA screening for RATs in another recent systematic review and meta-analysis. This analysis included 31 studies, with 1,703 pregnant individuals tested. This evaluation found the pooled PPV for the diagnosis of RATs to be 11.46% (95% CI, 7.80%-15.65%). Heterogeneity was high (I^2 = 82%). When the analysis was restricted to five studies with a low risk of bias, the pooled PPV was 9.13%. No assessment of sensitivity and specificity was performed because the majority of studies only ordered confirmatory testing for individuals whose results showed them to be high risk. The researchers maintained that these findings provide helpful information for clinicians and also for pregnant individuals who may be considering expanded testing for conditions beyond the common trisomies; they noted that this testing is not currently recommended by professional societies. They further indicated that in situations in which there is a strong clinical suspicion of aneuploidy (e.g., abnormal ultrasound), cfDNA testing is considerably inferior to invasive diagnostic testing. Publications by Van Opstal et al. (2018), discussed below, and van der Meij et al. (2019), Xue et al. (2019), Brison et al. (2018), Scott et al. (2018), Wan et al. (2018), and Pertile et al. (2017), previously discussed in this policy, were included in this systematic review and meta-analysis.

To evaluate the application of NIPT for screening rare autosomal abnormalities, a study was conducted in 81,518 pregnant participants who had undergone NIPT at a Chinese hospital between May 2018 and March 2022 (Zhang et al., 2023). Samples deemed to be high risk were evaluated with amniotic fluid karyotyping and CMA, with pregnancy outcomes recorded. NIPT identified 292 cases (0.36%) of rare autosomal abnormalities in the cohort. Overall, 140 of these (0.17%) were RATs. Of the 140 pregnancies with RATs detected, 102 participants agreed to invasive testing for confirmation. Five of these participants were found to have a true positive (PPV, 4.90%). CNVs were identified in 152 samples (0.19%); 95 participants agreed to CMA testing, which confirmed a true-positive result in 29 pregnancies (PPV, 30.53%). Clinical information was acquired in 81 of the 97 cases with false-positive RAT results. Of these, 37 (45.68%) had adverse perinatal outcomes, including a higher incidence of small for gestational age babies, intrauterine growth retardation, and preterm birth. Based on these results, the authors indicated that NIPT is not recommended for screening for RATs.

Hayes (2021; updated 2024) published a Clinical Utility Evaluation that addressed the use of cfDNA screening for fetal RATs in singleton and twin pregnancies. The report asserted that the use of this screening in singleton pregnancies leads to confirmatory testing in some women, but a few of the women with confirmed RAAs used the final diagnostic results for pregnancy management decisions. Of those who underwent confirmatory diagnostics based on the RAA cfDNA screening, more than 50% of the cases were found to be false positives. Overall, the published evidence regarding the use of RAA fetal testing in singleton pregnancy is very low in quality and insufficient to come to any conclusions regarding clinical utility at this time. With regard to fetal RAA testing in twin pregnancies, there were no identified peer-reviewed studies that assessed clinical utility in individuals with twin pregnancies; evidence is thus insufficient to draw conclusions related to the clinical utility of this RAA testing in twin pregnancies.

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Van Opstal et al. (2018) reported on the presence of rare trisomies and other abnormalities found by the TRIDENT (Trial by Dutch Laboratories for Evaluation of Noninvasive Prenatal Testing) study. The TRIDENT study was a trial in which NIPT was offered as an alternative for pregnant women considering an invasive prenatal diagnostic test between April 2014 and April 2015. NIPT testing was performed using whole-genome shallow massively parallel shotgun sequencing. Of 3,306 enrolled cases, 753 were analyzed only for chromosomes 21, 13, and 18. The remaining 2,553 were analyzed for all chromosomes and for segmental subchromosomal abnormalities. Results were reported in 2,527 cases. In 78, a common trisomy was found, and follow-up information was reported elsewhere. Overall, 41 cases of another type of chromosome abnormality were identified. One case of reported trisomy 8 was terminated at a private clinic before any follow-up was available. In the remaining 40 cases, 10 were confirmed to be true positives. These included two cases of trisomy 9, which were confirmed to be mosaic in the fetus. Both resulted in live births with multiple congenital anomalies. One case of a dual trisomy 15 and trisomy 22 was reported, and fetal tissue confirmed a mosaic trisomy 15. The pregnancy resulted in a live birth with no identifiable anomalies. One trisomy 22 was identified, confirmed as a mosaic trisomy 22. The pregnancy had multiple anomalies and was terminated. Six of the 10 cases were genomic imbalances that included dup 2p, del 6q, del 80/dup 8q, del 9p, del 12q, and del 18p. All were confirmed through amniocentesis. In 22 of the 40 positive cases, placental testing confirmed that confined placental mosaicism was the likely cause of the NIPT results, and in this group, there were 10 infants with some impact, ranging from small for gestational age to having multiple congenital anomalies. The authors concluded that genome-wide screening for NIPT results in the identification of chromosomal aberrations other than trisomy 13, 18, or 21 in approximately one-third of screen-positive results, and this information is important for pregnancy management.

Other Prenatal Screening Using Cell-Free DNA

The evidence is insufficient to support the use of other types of prenatal screening using cfDNA, such as screening for microdeletions and CNVs, and/or the use of cfDNA for prenatal exome and genome sequencing. Further validation studies are needed to determine the sensitivity, specificity, and PPV of cfDNA used for these purposes.

Scott et al. (2025) conducted a 4-year retrospective study that assessed the ways in which chromosomal anomalies that were missed by genome-wide NIPT (gwNIPT) could be detected through other clinical methods. The study involved 919 singleton pregnancies that underwent first-line gwNIPT followed by confirmatory invasive testing (chorionic villus sampling or amniocentesis) at two multisite, specialty obstetric ultrasound and prenatal screening clinics in Australia. All cases of microdeletions and microduplications were also evaluated regardless of the screening pathway. The authors found that 338 of the 919 cases had a single chromosomal abnormality, including nine false-negative gwNIPT results (2.9%) and 26 (7.7%) abnormalities that gwNIPT was unable to detect (18 microdeletions/duplications and eight triploidies). Just three of the missed cases (9%) had a markedly increased nuchal translucency, showing that nuchal translucency assessment alone is a poor detector of potential chromosomal abnormalities. Instead, approximately 90% of anomalies missed by gwNIPT were discovered via invasive prenatal testing that was performed because of growth restriction, structural anomalies, failed NIPT, or low pregnancy-associated plasma protein A results identified during pre-NIPT, 13-, or 20-week ultrasounds. Limitations include the retrospective design and the older, private practice population (median age, 33 years) from which the study group was selected; not all patients in the population underwent gwNIPT or detailed 13-week ultrasounds. In addition, some cases with chromosomal abnormalities that were not identified by NIPT likely resulted in miscarriage, underwent invasive testing elsewhere, or had chromosomal anomalies that went undetected antenatally. Based on the results of this study, the authors determined that while gwNIPT has significant diagnostic limitations, the majority of missed chromosomal abnormalities are nonetheless identified when early ultrasound findings or biochemical indicators prompt invasive testing, underscoring the essential role of comprehensive prenatal management.

Soster et al. (2025) conducted a retrospective review of more than 1,500 samples from 1,472 triplet pregnancies undergoing prenatal cfDNA screening to evaluate test performance for common aneuploidies, analyzing indications, demographic patterns, screen-positive rates, no-call rates, and available pregnancy or neonatal outcomes. The study found a mean patient age of 34 years and mean gestational age of 13 weeks, with advanced pregnant patient age as the most common indication (> 60% of cases). Results revealed 13 screen-positive cases (1.01%) and a 17.32% no-call rate. Outcome data were available for only 147 pregnancies (including all positive screens); no false-positive or false-negative results were identified. The authors concluded that cfDNA screening is a reasonable option for triplet pregnancies, given the lack of alternatives, with performance likely approaching that seen in twins, despite higher no-call rates. However, the study is limited by incomplete data (including outcomes) due to the retrospective design and inherent rarity of triplet pregnancies, which restricted the ability to fully evaluate test sensitivity and specificity at scale. In addition, all authors had affiliations with the laboratory performing the screening test, which introduced potential bias.

Hammer et al. (2024) analyzed 380,000 pregnant individuals with both average- and high-risk pregnancies in a study to assess the clinical performance of whole-genome sequencing–based cfDNA screening, including 22q11.2 detection. The cfDNA screening test (Prequel, Myriad Genetics, Inc.), which incorporates the amplification of fetal fraction (FF), was administered to 379,428 individuals who met the study eligibility requirements. Of all individuals, 76 received a positive

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result on the screening test for a de novo 22q11.2 microdeletion; this equates to a screen-positive rate of one in 4,992. Overall, 22 of the 76 had diagnostic test results available, and all 22 of these were confirmed as true positives, yielding a PPV of 100% (95% CI, 84.6%-100%). In addition, ultrasound results for pregnancies that screened positive were consistent with findings associated with 22q11.2 deletion syndrome. Because the performance of the test is dependent on FF, the distribution of FF in the screen-positive and screen-negative groups was compared to determine whether test performance could have been different between the two groups; no significant difference was found, indicating that the test performed similarly between the two groups. Because 22q11.2 deletion syndrome is a rare finding, this study did not assess sensitivity, specificity, or NPV. The authors suggested that the prevalence and severity of 22q11.2 deletion syndrome warrant screening with a cfDNA assay using FF amplification for all pregnant individuals. Although the study individuals were diverse in ethnicities, body mass index, and testing indications, they were commercially ascertained, so there is uncertainty regarding whether the cohort is representative of a general pregnancy population. In addition, although outcomes were obtained for 74 screen-positive cases, clinical information was incomplete for 17 of those. Lastly, the high PPV in this study may be related to the fact that diagnostic testing was performed primarily in those who had ultrasound findings that suggested possible 22q11.2 deletion syndrome. Further investigation that explores test sensitivity, specificity, and NPV as well as detailed outcome information across all individuals are needed.

Soster et al. (2024) detailed outcomes in a small cohort of individuals with screen-positive results for trisomy 20 in another study that used prenatal genome-wide cfDNA. These individuals represented a subset of individuals from a larger cohort in which screening was done for RAAs (Mossfield et al., 2022). In all, 10 cases with screen-positive results for trisomy 20, nine of which had diagnostic information available, were reviewed. The one case without diagnostic information was a pregnancy that ended in fetal demise. Of the nine cases in which diagnostic information was available, all nine had normal diagnostic results after amniocentesis. One case had a mosaic partial duplication rather than a full trisomy 20, which could explain the assay showing trisomy 20. Only one case in the cohort had placental testing; the result was discordant with the cfDNA testing result. Confined placental mosaicism could not be ruled out for the rest of the cases in the cohort due to the lack of placental testing. Half of the 10 cases had adverse pregnancy outcomes, suggesting the possible presence of underlying confined placental mosaicism or mosaic/full fetal trisomy 20, but this could not be confirmed. This cohort was made up of mainly individuals of advanced maternal age (AMA). The authors recommended further study that includes larger cohorts and individuals of average risk.

Liu et al. (2024) performed a retrospective review that investigated the use of noninvasive prenatal screening (NIPS) to detect CNVs in fetuses with ultrasound soft markers (USMs) in pregnancies not involving AMA. The study included pregnancies with isolated USMs in the second trimester from January 2020 to December 2022 at West China Second University Hospital, Sichuan University. NIPS was performed in the Department of Medical Genetics. The results included 6,647 pregnant women who were screened using the Berry Genomics NIPS algorithm. Those with positive NIPS results underwent amniocentesis for prenatal diagnosis. The results were analyzed and compared among different USMs. Overall, 96 pregnancies were positive for fetal chromosome anomalies, including 37 aneuploidies and 59 CNVs. The PPVs for trisomy 21, trisomy 18, trisomy 13, and sex chromosome aneuploidies were 66.67%, 80.00%, 0%, and 30.43%, respectively. NIPS sensitivity for aneuploidies was 100%. For CNVs, the PPV was 35.59%, with a false-positive rate of 0.57%. Six pathogenic CNVs were identified, with two detected by NIPS and four missed (three below the NIPS resolution limit and one false negative). Aneuploidies were more common in fetuses with an absent or hypoplastic nasal bone, while pathogenic CNVs were more frequent in fetuses with an aberrant right subclavian artery. Study limitations include the following: (1) 8.23% of pregnant women were lost to follow-up, making it difficult to accurately assess the sensitivity and specificity of NIPS for detecting CNVs due to unclear clinical outcomes; (2) 45 fetuses had birth defects, but 43 did not undergo postpartum CMA, preventing confirmation of pathogenic CNVs; and (3) the number of USMs varied across categories, with only seven cases of mild ventriculomegaly but over 5,000 cases of echogenic intracardiac focus, potentially leading to selection bias. Per the authors, future research goals will include a focus on reestablishing contact with parents of fetuses who were lost to follow-up to determine the presence or absence of birth defects and the identification of more cases with both NIPS-derived significant CNVs and postpartum CMA results to better assess NIPS accuracy for CNVs. The researchers stated that their results indicate that while NIPS is highly sensitive for detecting common aneuploidies/SCAs and has moderate PPVs for CNVs in non-AMA pregnant women with fetal USMs, it appears to have limited ability to detect pathogenic CNVs. The authors strongly recommended additional prenatal diagnosis when NIPS indicates CNVs and advised against using NIPS for CNV screening in non-AMA pregnant women with fetal USMs, particularly in fetuses with an aberrant right subclavian artery.

Maya et al. (2023) sought to (1) evaluate the theoretical value-add of two types of cfDNA screening expansions in pregnancies with no evidence of major structural abnormalities over standard cfDNA testing (13, 18, 21, X, and Y) and (2) also assess them in terms of the added value of CMA in a retrospective cohort study. The study was based on the CMA results in pregnant patients with normal ultrasounds who had undergone amniocentesis between January 2013 and February 2022. Of the 8,605 pregnancies assessed, 1.4% (n = 122) had clinically significant CMA results. Standard cfDNA testing would have theoretically identified 36.1% of these. In addition to aneuploidies that were detectable with

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standard cfDNA testing, three cases that were detectable with expanded cfDNA testing (including commonly found microdeletions) and nine cases that were detectable with genome-wide cfDNA screening (excluding common microdeletions) were identified in the overall cohort. The researchers asserted that of the clinically significant CMA findings, standard cfDNA screening would miss 63.9%, and genome-wide cfDNA screening would miss 54.1%. cfDNA screening that was expanded to include detection of microdeletions would increase value over standard cfDNA testing by approximately 0.035%, and genome-wide cfDNA screening, including large CNVs, would result in an increase in value of approximately 0.14%; these results are far lower than the value-add of CMA (0.91%).

Several recent studies have explored the accuracy of cfDNA testing for the identification of microdeletion/microduplication syndromes (MMSs) and nonsyndromic CNVs. Yang et al. (2022) assessed 19,068 singleton pregnancies that had been screened with cfDNA testing using high-throughput sequencing. Of 170 participants whose testing revealed abnormalities, 113 (66.5%) opted for invasive testing. The PPV of CNV sequencing for all types of CNVs that were detected in the study was 35.4% (61.5% for pathogenic MMSs and 27.6% for nonsyndromic CNVs). Although performance for MMSs was relatively high, the low PPV for nonsyndromic CNVs led the authors to conclude that the use of expanded cfDNA testing would likely increase unnecessary invasive tests and potentially lead to inappropriate terminations of pregnancy.

In a prospective study that assessed the performance of expanded NIPT (Zou et al., 2023), the PPV of the NIPT expanded test for CNVs was found to be 51.72%. Using a clinically available genome-wide cfDNA assay (Sequenom) to test 701 pregnant participants, Soster et al. (2023) found that when the CNVs evaluated were at least 7 megabases (Mb) and the test was specific to specific microdeletions, the sensitivity was 93.8%, specificity was 97.3%, PPV was 63.8%, and NPV was 99.7% compared with microarray testing. However, when out-of-scope CNVs were included as false negatives, the sensitivity fell to 63.8%. The authors of this study indicated that microarray testing via amniocentesis provides the most accurate and thorough assessment of fetal CNVs, but genome-wide cfDNA testing may be an option for individuals who decline or are otherwise unable to undergo invasive diagnostic testing; however, diagnostic testing would still be required to confirm screen-positive results. Further study is recommended to explore the potential clinical utility and assess the impact of reducing the size threshold of CNVs.

The accuracy of NIPT-plus in the detection of clinically significant fetal CNVs was the subject of a prospective analysis of 31,260 singleton pregnancies from June 2017 to December 2020 (Xue et al., 2022). Among the 31,260 pregnant participants who underwent NIPT-plus testing at a single hospital in Fuzhou, China, results were obtained for 31,256. A high risk of clinically significant CNVs was detected in 221 participants (0.71%). Of them, 18 refused further evaluation. Overall, 203 underwent invasive testing for a prenatal diagnosis, which revealed 78 true-positive cases and 125 false-positive cases. Overall, the PPV was 38.42%, and the false-positive rate was 0.40%. Where known MMSs were identified (n = 27), the PPVs were as follows: 75% for DiGeorge syndrome; 80% for 22q11.22 microduplication syndrome; 50% for Prader-Willi syndrome; and 50% for cri-du-chat syndrome. The remaining significant fetal CNVs (n = 175) had a combined PPV of 46.5% for CNVs greater than 10 Mb and 28.57% for CNVs of 10 Mb or less. Overall, the results indicate that NIPT screening had relatively high performance for identification of 22q11.2 microduplication syndrome and DiGeorge syndrome in this study but low/moderate detection for other clinically significant CNVs. Further high-quality studies, with larger and more diverse populations, increased depth of sequencing, and improved algorithms, are needed.

A 2022 (updated 2025) Hayes Clinical Utility Evaluation addressed cfDNA screening for fetal chromosome CNVs in individuals with twin or singleton pregnancies. There were no peer-reviewed studies that evaluated the clinical utility of cfDNA screening for fetal CNVs in individuals with an identified twin pregnancy. Although some evidence suggests that the use of cfDNA screening for fetal CNVs in singleton pregnancies may lead to confirmatory diagnostic testing in some women, it is unknown if additional CNV testing will impact the rate of confirmatory diagnostic testing from common aneuploidy cfDNA screening. Among individuals who underwent confirmatory diagnostic testing based on the CNV cfDNA result, there was a high rate of false-positive results. The current published evidence is of low quality and currently does not support conclusions regarding clinical utility.

The results of a multicenter, prospective, observational study that was designed to assess the performance of SNP-based cfDNA screening for the detection of 22q11.2 deletion syndrome were published by Dar et al. (2022). The study also assessed the prevalence of 22q11.2 deletion syndrome and the performance of an updated cfDNA algorithm, which the researchers blinded to the pregnancy outcome. Enrollees from 21 centers in six countries participated, undergoing SNP-based cfDNA screening specific to 22q11.2 deletion syndrome. Either prenatal or newborn DNA samples were requested in all cases so that genetic confirmation using chromosomal microarrays could be performed. Overall, 20,887 participants were enrolled, and a genetic outcome was available for 87.6% (18,289). Twelve 22q11.2 deletion syndrome cases were confirmed in this cohort (including five nested deletions), which yielded a prevalence of one in 1,524. Of the total cohort, cfDNA screening identified 17,976 cases as low risk for 22q11.2 deletion syndrome and 38 cases as high risk, with 275 cases being nonreportable. Ultimately, nine of 12 cases of 22q11.2 were identified, equating to a sensitivity of 75%, specificity of 99.84%, and PPV of 23.7%. The NPV was 99.98%. No cases with a nonreportable outcome resulted in a

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diagnosis of 22q11.2 deletion syndrome. The updated algorithm identified 10 of 12 cases and led to a lower false-positive rate and an increased PPV of 52.6%. The authors concluded that cfDNA screening for 22q11.2 deletion syndrome can detect most affected cases, with a low false-positive rate, and has the ability to detect smaller, nested deletions. However, the overall confirmed number of cases of 22q11.2 deletion syndrome in this study was low, limiting the ability to accurately calculate PPV, as stratified by risk factors. In addition, the estimates of DRs for rare conditions are associated with wide CIs; finally, there were varied indications for testing, and prevalence rates may not reflect the risk in the average population. In addition, the study was funded by Natera, which is the maker of a test that includes 22q11.2 microdeletion screening.

Cui et al. (2019) evaluated the clinical utility of NIPT for the detection of CNVs by reporting on 161 pregnancies with ultrasound findings and negative NIPT results for chromosomal aneuploidy. Fetal CNVs were diagnosed by CNV sequencing; fetal and parental karyotypes were obtained by G-banding. NIPT revealed 11 CNVs of ≥ 1 Mb in nine samples, including two CNVs in each one of two separate samples. CNV sequencing on amniotic fluid was performed for 137 samples and 24 samples of fetal tissue. Fetal karyotypes were obtained for 78 cases, and seven cases were diagnosed as abnormal. The sensitivity and specificity of NIPT for detecting CNVs of > 1 Mb were 83.33% and 99.34%, respectively. The PPV and NPV were 90.91% and 98.68%, respectively. The sensitivity and specificity for CNVs of 1 Mb to 5 Mb were higher than for those of ≥ 5 Mb. The authors claimed that NIPT can be performed for pregnancies with structural fetal anomalies for CNV detection; however, due to the residual chromosomal aneuploidy risks for pregnancies with soft ultrasound markers, women with structural ultrasound anomalies should be offered invasive procedures for diagnosing CNVs. This study is difficult to generalize to the average screening population, as only pregnancies with ultrasound anomalies and negative NIPT results were selected for analysis. Future studies are needed for NIPT and CNV detection.

DiGeorge syndrome, also known as velocardiofacial syndrome or 22q11 deletion syndrome, is one of the most common microdeletion syndromes, with an incidence of one in 3,000 to 6,000 births. Affected individuals have a wide array of clinical manifestations, including congenital heart defects, immune dysfunction, hypocalcemia, mild to severe learning disabilities, and an increased risk of mental health disorders. Ravi et al. (2018) reported on the clinical validity of an SNP-based NIPT assay to detect fetal 22q11.2 deletions during pregnancy. Women from six prenatal centers were enrolled in the study and underwent invasive prenatal diagnosis for a variety of reasons. At the time of blood draw, information about gestational age, maternal age and weight, and time between the invasive procedure and blood draw was collected. Samples from participants who were at less than 9 weeks' gestation, had a fetal demise, had atypical 22q distal deletions on invasive testing, or had equivocal invasive test results were excluded. Participants with inconclusive or no-call NIPT results were also excluded, and no redraws were requested. The study was internally blinded but ultimately included 10 participants with confirmed fetal 22q11.2 deletions and 390 with unaffected pregnancies. The mean age was 28 years, and the gestational age averaged 21 weeks for affected pregnancies and 12.8 weeks for unaffected pregnancies. Samples were tested at Natera using a massively multiplexed PCR amplification targeting SNPs covering chromosomes 13, 18, 21, 22, X, and Y. The target set contained 13,926 distinct genetic loci, including 1,351 SNPs spanning a 2.91-Mb section of the 22q11.2 region that constitutes approximately 87% of all deletions detected in individuals with the 22q11.2 deletion syndrome. Risk status for 22q11.2 deletion was assigned as high or low risk or risk unchanged/no call. High-risk calls with maternally deleted haplotypes were sequenced at a higher depth of read to confirm high-risk status. For cases with an FF of 2.8% to 6.5%, the sample was evaluated only for the presence or absence of the paternally inherited haplotype. Of the 10 affected pregnancies, nine were identified as test positive or high risk. Of the 390 unaffected samples, one false positive was found. Overall, the study found the sensitivity to be 90% and the specificity to be 99.7%; based on a prevalence of 22q11.2 deletions of one in 1,442 in pregnancy, the estimated PPV was 19.6%.

Gross et al. (2016) evaluated the ability of an SNP-based NIPT test to detect 22q11 deletion syndrome in a commercial laboratory. A retrospective analysis was performed in 21,948 consecutive samples for fetal aneuploidy and microdeletion screening that were received over a 6-month period from February to August 2014. The demographic information received included indication for testing, gestational age, maternal date of birth, maternal weight, and whether the mother was a known microdeletion carrier. A paternal sample was requested but not required, and 5,912 (26.9%) cases included a paternal sample. Prior to the analysis of 22q11.2, the standard panel testing for aneuploidy at chromosomes 13, 18, 21, X, and Y was conducted; samples that failed quality control at this step were not evaluated for 22q11.2. This region was analyzed by 672 SNPs targeting the 2.91-Mb loci associated with the 22q11.2 deletion syndrome. Fetal results were predicted based on the pattern of SNPs, FF, and paternal results, when available. Overall, 95 cases were reported as high risk. Of these, 84 had some outcome data available. Invasive testing was performed in 48 cases, and 11 had postnatal testing; testing was declined by the remaining patients. Of those with follow-up diagnostic testing, 11 were true positives, and 50 were false positives. In total, 77 high-risk patients had ultrasound data available. Of them, 26 had anomalies observable on ultrasound, of which nine were true positives. There were three pregnancy terminations related to the screening results of 22q11.2 deletion, two of which were confirmed as true positive. The authors concluded that the

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availability of genetic counseling and other resources to manage high-risk 22q11.2 cases is an important aspect of this screening test.

While individually rare, subchromosomal abnormalities occur in 1.6% of pregnancies. Helgeson et al. (2015) reported on the development of an algorithm to be applied to cfDNA testing to support identifying 5pdel, 22q11del, 15qdel, 1p36del, 4pdel, 11qdel, and 8qdel in routine testing. Low-coverage whole-genome massively parallel sequencing was used to analyze cfDNA and used a statistical method to search for consistently underrepresented regions, followed by a decision tree to differentiate whole-chromosome events from regional deletions. A cohort of 175,393 high-risk pregnancies was used to test the algorithm. Samples were collected from October 2013 to October 2014. In total, 55 cases were screen positive for subchromosomal events. Outcome data were available for 53 cases. Chromosome microarray or fluorescence in situ hybridization confirmed the findings in 41 cases (77%). Nine cases did not have confirmational testing but had clinical features on ultrasound consistent with the deletion. Three cases were false positives. The false-negative rate and sensitivity were not conclusively determined.

Fetal Antigen Testing (Other Than for RhD Status)

There is a lack of evidence in the peer-reviewed literature that supports the use of cfDNA testing to determine fetal antigen status (other than RhD) in pregnant individuals who are alloimmunized for specific antigens. Additional study, including high-quality trials focused on the impact to clinical outcomes, is needed.

Clausen and van der Schoot (2025) focused on the use of cffDNA testing for blood group antigen genotyping as a diagnostic tool for the prediction of hemolytic disease of the fetus and newborn in pregnancies in which the pregnant individual was immunized. The authors indicated that these noninvasive tests have demonstrated high performance accuracy and predicted that the use of cffDNA blood group antigen genotyping will soon be expanded in clinical practice. Anticipated challenges include the use of this testing in mixed ethnic populations and the need for improvement of care in many low-income countries around the world.

Rego et al. (2024) conducted a multicenter prospective cohort study to evaluate the accuracy of NGS-based quantitative cfDNA analysis for fetal antigen genotyping in participants with alloimmunized pregnancies. The study included 156 participants with alloimmunized pregnancies who were undergoing clinical fetal antigen cfDNA analysis between 10 0/7 and 37 0/7 weeks of gestation at 120 clinical sites. After delivery, neonatal buccal swabs were collected between 0 and 270 days of life and were sent to an outside independent laboratory for antigen genotyping. The laboratory was blinded to the fetal cfDNA results. Concordance between cfDNA analysis results and neonatal genotype was determined for 465 antigen calls for the following antigens: K1 (n = 143), E (124), C (60), Fy a (50), c (47), and D(RhD) (41). The 465 calls included 145 in which the fetus was antigen positive and 320 in which the fetus was antigen negative, resulting in 100% sensitivity, specificity, and accuracy. The authors concluded that cfDNA analysis is highly sensitive and specific for determining fetal antigen genotype as early as 10 weeks of gestation in individuals with alloimmunized pregnancies. They determined that with 100% accuracy and no need for paternal testing or invasive procedures, the assay has the potential to provide informative results about fetal risk to more alloimmunized individuals compared with the traditional approach and can streamline clinical management while improving equitable access to care. Noted limitations include overrepresentation of participants identifying as White; however, the no-call rate for the assay did not differ across varying races and ethnicities. In addition, many authors had affiliations with the manufacturer of the test under study, creating a potential for bias.

Alford et al. (2023) used quantitative counting template technology in the development of an NGS-based fetal cfDNA screening test that was then used to identify RhD, C, c, K (Kell), and Fy^a (Duffy) fetal antigen genotypes present in the blood of pregnant participants in an ethnically diverse population in the U.S. The use of the quantitative counting template was leveraged to allow for highly specific and sensitive quantification and identification of paternally derived fetal antigen alleles in cfDNA. In an analytical validation that included 1,061 preclinical samples, use of the test to determine fetal antigen status was found to have a sensitivity of 100% (95% CI, 99%-100%) and specificity of 100% (95% CI, 99%-100%). An independent evaluation of two duplicate plasma samples was performed for 1,683 clinical samples, which showed precision of 99.9%. The “no results” rate (in clinical practice) was 0% in 711 RhD-negative, nonalloimmunized pregnant participants and 0.1% in 769 cases in which the participant was alloimmunized. Clinical validation demonstrated that fetal cfDNA testing results were 100% concordant with neonatal antigen genotype serology results in a corresponding 23 RhD-negative pregnancies and 93 antigen evaluations in 30 alloimmunized pregnant participants. The researchers concluded that NGS-based fetal antigen cfDNA testing has the potential to detect more fetuses at risk for hemolytic disease than the standard practice, which relies on paternal genotyping and invasive diagnostics, thereby limiting results due to the lack of adherence or faulty attribution of paternity. The authors proposed that integration of fetal cfDNA testing for the detection of fetal antigens into care for both alloimmunized and RhD-negative, nonalloimmunized pregnant individuals could increase efficiency in prenatal care and potentially reduce unneeded treatment and supervision. While these data show promise, additional high-quality studies that measure the impact of this testing on clinical outcomes are

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needed. In addition, the majority of the authors of this study are noted to be affiliated with a fetal cfDNA test manufacturer, which creates a risk of bias.

Single-Gene Disorders

The use of cfDNA testing to evaluate single-gene disorders is in the early stages of development. The evidence available is limited and contains small sample sizes. Further studies, with larger numbers of individuals, are needed to determine the clinical utility of this approach.

Zhang et al. (2025) conducted a prospective pilot study to assess the clinical utility of an NIPT approach that analyzes plasma cfDNA using targeted NGS to detect variants in 34 genes linked to neurodevelopmental and other syndromic dominant single-gene disorders. The study first validated the method using retrospective samples, then applied it to 567 pregnancies, yielding 535 analyzable cases, of which 11 (2.1%) carried pathogenic or likely pathogenic variants; three of these were paternally inherited, and eight were de novo mutations. Of note, five of the positive cases had normal ultrasound findings. The NIPT results were compared with invasive prenatal or postnatal genetic diagnosis obtained via whole-exome sequencing and Sanger sequencing. The researchers reported 100% sensitivity (95% CI, 71.7%-100%) and 100% specificity (95% CI, 99.0%-100%), observing no false positives or false negatives. They concluded that NIPT using cfDNA to screen for dominant single-gene disorders accurately detected both paternally inherited and de novo dominant variants in this cohort, suggesting that it has the potential to offer clinically meaningful information, even when ultrasound appears normal. Noted limitations include the reliance on a restricted 34-gene panel, limiting detection scope, and a lack of reported long-term or population-diverse follow-up, which may constrain generalizability.

Wynn et al. (2023) endeavored to strengthen the evidence supporting the use of single-gene testing to assess the fetal risk of autosomal recessive conditions in the largest clinical validation of carrier screening with reflex to single-gene NIPT (sgNIPT) in a general population setting to date. Specifically, the clinical performance of carrier screening with reflex to sgNIPT was evaluated for four conditions: cystic fibrosis, spinal muscular atrophy, α-thalassemias, and β-hemoglobinopathies. Pregnancy outcome records from individuals who had undergone this testing were reviewed, and a comparison of neonatal outcomes with the fetal risk predicted by the sgNIPT test was performed. A total of 42,067 pregnant individuals from 811 unique practices throughout 45 states and Puerto Rico underwent carrier screening. Of these, 7,538 carriers (17.9%) reflexed to sgNIPT. Fetal/neonatal outcomes were obtained from 528 individuals, including 25 impacted pregnancies. High concordance was found between sgNIPT results and neonatal/fetal outcomes. The sgNIPT assay was found to have a sensitivity of 96% (95% CI, 79.65%-99.90%), specificity of 95.2% (95% CI, 92.98%-96.92%), average PPV of 50.0% (95% CI, 35.23%-64.77%), and NPV of 99.8% (95% CI, 98.84%-99.99%). The overall performance of carrier screening with reflex to sgNIPT was determined to have a sensitivity of 92.4% and a specificity of 99.9%. These were not impacted by partner carrier screening or misattributed paternity, in contrast to the traditional carrier screening workflow, for which the sensitivity is 35% and maximum PPV is 25%. Based on the results above, the authors asserted that carrier screening with reflex to sgNIPT has good performance in a general population and should be considered as first-line testing in many situations, including cases in which a biological partner sample is not available. They indicated that the test used was able to identify high-risk pregnancies related to autosomal recessive conditions with high sensitivity and specificity and has the potential to increase access to actionable health information. Noted limitations include the collection of outcomes that relied on individual and provider reporting; of the over 42,000 individuals initially screened, outcomes were received for 528, including only 25 affected neonates. In addition, the authors of this study had affiliations with a test manufacturer that provided financial support for this study, which created a potential for bias.

Adams et al. (2023) conducted a clinical pilot study that sought to determine the utility of single-gene NIPS (sgNIPS) in a group of high-risk pregnant individuals. The sgNIPS panel screened for pathogenic variants in 30 genes. Pregnant individuals who qualified for study participation had one or more of the following indications: (1) sperm age of ≥ 40 years, (2) nuchal translucency of ≥ 3.5 mm, (3) fetal anomaly, and (4) family history of a condition included for assessment in the panel. Individuals were offered concurrent diagnostic testing. A total of 228 individuals completed sgNIPS testing, and of them, eight (3.5%) had a positive result. No false-positive or false-negative results were identified in 78 individuals who underwent diagnostic testing. Ultimately, 41 of the participating individuals received a molecular diagnosis, but 34 of them (82.9%) were outside the scope of the sgNIPS test. Positive results from sgNIPS testing impacted medical management in five individuals. The researchers concluded that sgNIPS has the potential to detect prenatal diagnoses earlier, which may lead to better monitoring and focused genetic assessment, but diagnostic testing is still preferred when clinically indicated. Additional high-quality validation studies are needed to establish the value-add for sgNIPS before this testing can be implemented broadly.

To assess the performance of carrier screening for cystic fibrosis, hemoglobinopathies, and spinal muscular atrophy with reflex sgNIPS, Hoskovec et al. (2023) conducted a study in an unselected population of 9,151 pregnant patients in the United States. Screening for carrier status of noted conditions was performed, and 1,669 samples (18.2%) were found to be heterozygous for at least one pathogenic variant and reflexed to sgNIPS. The results of sgNIPS were compared with

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outcomes identified via parent surveys or provider reports for 201 newborns. Overall, informative results were obtained for 98.7% of pregnancies, including either a negative carrier report or, for those identified as heterozygous for a pathogenic variant, an sgNIPS result. In the subgroup with outcomes information, the NPV of sgNIPS was found to be 99.4% (95% CI, 96.0%-99.9%), and the average PPV of sgNIPS was 48.3% (95% CI, 36.1%-60.1%). A key factor was the use of personalized PPVs, which accurately reflected the proportion of impacted pregnancies in each PPV range; all pregnancies in which sgNIPS fetal risk was found to be greater than nine of 10 (90% PPV) were indeed affected. The authors concluded that prenatal screening with sgNIPS is an option that can provide accurate fetal risk, without a paternal screening test, and results can be used for counseling and pregnancy management. The study has limitations, including the low number of outcomes collected and a relatively high rate of no-call results (1.3%) among the patients, all of whom were heterozygous for a pathogenic variant. In addition, outcomes were determined via newborn screening and not through molecular diagnosis, which is the gold standard. Further research that includes larger cohorts and more complete collection of outcomes as well as studies that focus on the impact of carrier screening with sgNIPS on clinical practice are needed.

Young et al. (2020) performed a retrospective analysis of noninvasive prenatal diagnosis (NIPD) single-gene testing for pregnancies at risk of cystic fibrosis, spinal muscular atrophy, and X-linked Duchenne muscular dystrophy (DMD)/Becker muscular dystrophy (BMD) by using the relative haplotype dosage (RHDO) method. RHDO uses a capture-based, targeted enhancement that is followed by massive parallel sequencing and analysis by RHDO. The requirements for NIPD using RHDO include a known family history of a disorder, confirmed molecular diagnosis, and necessary reference samples when possible. RHDO allows both paternal and maternal inheritance to be determined by measuring allelic imbalance between two haplotypes in cfDNA, with phasing conducted through SNP sequencing; multiple single-gene disorders can be performed during the same sequencing run, and the same assay can be used for all families at risk for a particular condition, which eliminates preliminary workup prior to pregnancy. RHDO for DMD/BMD was performed in at-risk pregnancies following confirmation of a male fetus by cfDNA and required maternal haplotype with a male reference sample (previous affected, previous unaffected, other male relative affected, or unaffected maternal grandfather) providing the mutated or normal haplotype. Due to the 12% chance of DMD/BMD gene recombination, RHDO was performed in both directions: 5' to 3' and 3' to 5'. For cystic fibrosis/spinal muscular atrophy, maternal and paternal haplotypes, in addition to a reference child (e.g., previously affected child, an unaffected noncarrier child) or a carrier child if the parents had different mutations, were used for phasing. From September 2016 to October 2019, 152 at-risk pregnancies were referred to the West Midlands Regional Genetics Laboratory. Follow-up genetic testing was performed in 70 of the 146 pregnancies for which a diagnostic result was issued. In all cases, follow-up testing confirmed the RHDO result, and no discrepancies were reported, demonstrating 100% concordance. In an additional 39 cases, no postnatal discrepancies were reported as of the time of study publication. The authors concluded that NIPD by RHDO can be performed clinically for both autosomal recessive and X-linked disorders, with high sensitivity and specificity. However, this study is difficult to generalize to a nonselected population, as the families selected needed to have a known family history of the disorder. In addition, this study had a lack of follow-up data for many cases. In conclusion, the authors emphasized the importance of (1) prenatal counseling for individuals undergoing NIPD for single-gene disorders and (2) access to NIPT for routine aneuploidy screening at 10 weeks of pregnancy. Further testing is needed to validate this method for clinical use.

Zhang et al. (2019) developed and reported a clinical validation experience with a novel method for noninvasive prenatal sequencing for a panel of causative genes for frequently occurring monogenic, dominant disorders. Maternal cfDNA was barcoded and enriched and analyzed by NGS for target regions of 30 genes. Low-level fetal variants were then determined by a statistical analysis adjusted for NGS read count and FF. Likely pathogenic and pathogenic variants were confirmed by a secondary amplicon-based cfDNA test. Clinical testing was performed in 422 pregnancies with or without ultrasound findings. Of these 422 cases, 390 had negative testing, and 32 had positive results. Follow-up testing on cases was limited and only included 233 of the 422 original cases. The researchers stated that this study revealed 20 true positives, 127 true negatives, zero false positives, and zero false negatives. A significant limitation of this study is the lack of follow-up data for many cases; therefore, the clinical sensitivity and specificity are limited to only cases with outcomes. The authors concluded that by using this novel NIPT NGS method, a large number of dominant, monogenic disorders can be identified; however, additional validation studies are needed.

Xiong et al. (2018) conducted a feasibility study in individuals of Southeast Asian descent to determine if targeted sequencing and relative mutation dosage can be used to correctly identify maternal β-thalassemia mutations in cfDNA. Samples were collected from 49 couples who were at risk of having a child with β-thalassemia, and genomic DNA was evaluated from the parents, cfDNA, and either amniocentesis or chorionic villus sampling. Common *HBB* mutations were targeted using nested PCR. Relative mutation dosage was used to determine if the fetus had the wild-type allele or the maternal carrier allele. Overall, 48 of the samples were able to be classified using cfDNA (98%). The correct result was obtained in 44 of the 48 cases (91.7%), and there was one false positive and three false negatives. The overall sensitivity was 87.5%, and the specificity was 95.8% for the inheritance of the maternal allele.

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Clinical Practice Guidelines

American College of Medical Genetics and Genomics (ACMG)

The ACMG published a guideline (Dungan et al., 2023) that addresses the use of prenatal cfDNA screening for fetal chromosome abnormalities in general-risk populations. The guideline is largely based on the results of the 2022 ACMG systematic review (Rose et al.) and used the GRADE Evidence to Decision framework to establish recommendations. The evidence reliably demonstrates better accuracy of prenatal cfDNA screening compared with traditional screening techniques for trisomies 13, 18, and 21 in both singleton and twin-gestation pregnancies, and the guideline notes that the identification of RATs and other microdeletion syndromes with prenatal cfDNA screening is an emerging area of interest. Specific recommendations are as follows:

- Prenatal cfDNA screening for fetal trisomies 13, 18, and 21 is recommended over traditional screening methods for all pregnant patients with singleton-gestation pregnancies (strong recommendation based on high certainty of evidence).
- Prenatal cfDNA screening for fetal trisomies is recommended over traditional screening methods for twin-gestation pregnancies (strong recommendation based on high certainty of evidence).
- Prenatal cfDNA screening should be offered to patients with single-gestation pregnancies to assess for fetal SCA (strong recommendation based on high certainty of evidence).
- The ACMG suggests offering prenatal cfDNA screening for 22q11.2 deletion syndrome to all pregnant patients (conditional recommendation based on moderate certainty of evidence).
- Currently, there is insufficient evidence for the recommendation of routine screening for CNVs other than 22q11.2 deletions (no recommendation due to the lack of clinically relevant evidence and validation).
- Currently, there is insufficient evidence to either recommend or not recommend prenatal cfDNA screening for the identification of RATs (no recommendation due to the lack of clinically relevant evidence).

In addition to the above recommendations, the ACMG guideline indicates that the most frequent explanation for no-call results in prenatal cfDNA screening is insufficient FF. Low FF has been linked to varying adverse pregnancy outcomes, but definitive rates of pregnancy complications and standard monitoring practices have not been determined. The ACMG also notes that certain pregnancy factors can interfere with the performance of prenatal cfDNA screening; vanishing twin syndrome is a known example.

American College of Obstetricians and Gynecologists (ACOG)

In a 2026 practice advisory, ACOG endorses the *Society for Maternal-Fetal Medicine Consult Series #74: Cell-Free DNA Screening for Aneuploidies: Updated Guidance*. This practice advisory, detailed below, replaces ACOG *Practice Bulletin No. 226, Screening for Fetal Chromosomal Abnormalities*.

ACOG's *NIPT Summary of Recommendations* includes the following:

- Prenatal genetic screening options, including serum screening with or without nuchal translucency ultrasound or cfDNA screening and diagnostic testing with chorionic villus sampling or amniocentesis, should be discussed and offered to all pregnant patients regardless of age or risk of chromosomal abnormality.
- If screening is accepted, patients should have one prenatal screening approach; multiple screening tests should not be performed simultaneously.
- cfDNA is the most sensitive and specific screening test for the most common fetal aneuploidies. However, the potential for false-positive and false-negative results exists. Importantly, cfDNA testing is not equivalent to diagnostic testing.
- Patients whose screening tests are positive for fetal aneuploidy should undergo genetic counseling and a comprehensive ultrasound evaluation, with an opportunity for further diagnostic testing to confirm results.
- Patients whose screening tests are negative should be informed that although this result substantially decreases their risk of the targeted aneuploidy, it does not ensure that the fetus is unaffected. Other genetic disorders that are not part of the screening/testing should be reviewed.
- In cases of cfDNA screening test results that are not reported by the laboratory or are uninterpretable (a no-call test result), patients should be informed that test failure is associated with an increased risk of aneuploidy. They should undergo further genetic counseling and be offered a comprehensive ultrasound evaluation and diagnostic testing.
- cfDNA screening used as a follow-up for patients with a screen-positive serum analyte screening test result is an option for patients who want to avoid invasive diagnostic testing. Patients must be informed that this approach could delay a definitive diagnosis and will fail to identify some fetuses with chromosomal abnormalities.
- No method of aneuploidy screening that includes a serum sample is as accurate in twin gestations as it is in singleton pregnancies; this information should be part of pretest counseling performed in patients with multiple gestations. Overall, the performance of screening for trisomy 21 by cfDNA in twin pregnancies is encouraging, but the total number of reported affected cases is small. As such, it is difficult to determine an accurate DR for trisomies 18 and 13.

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- Prenatal screening and prenatal diagnosis should be offered to all patients regardless of previous preimplantation genetic testing, as preimplantation genetic testing is not uniformly accurate.
- In multifetal gestations, if fetal demise, a vanishing twin, or an anomaly is identified in one fetus, a significant risk of an inaccurate test result exists when serum-based aneuploidy screening or fetal cfDNA screening is used. In these cases, patients should be counseled, and diagnostic testing should be offered.
- When unusual or multiple aneuploidies are detected by cfDNA, affected patients should be referred for genetic counseling and maternal-fetal medicine consultation.

(ACOG, 2026)

In 2024, ACOG published a clinical practice update to *Practice Bulletin No. 192, Management of Alloimmunization During Pregnancy*. The update addresses paternal and fetal genotyping in the management of pregnancy alloimmunization, stating that fetal antigen genotyping is recommended in situations in which the paternal genotype is heterozygous or unknown. The clinical practice update makes the following recommendations:

- "Paternal *RHD* zygosity testing using genotypic analysis is recommended for RhD alloimmunization risk assessment. It may be reasonable to defer or discontinue fetal surveillance for anemia in the setting of paternal genotyping that is *RHD* homozygous negative.
- Because cfDNA testing possesses performance characteristics that appear comparable with those of molecular testing, while avoiding the rare complications and costs associated with diagnostic genetic testing, it is reasonable to use it as an alternative tool for fetal *RHD* testing among alloimmunized patients with potentially at-risk pregnancies who decline amniocentesis.
- cfDNA for the assessment of selected non-RhD red blood cell antigens may be considered for pregnant patients declining amniocentesis, after weighing cost, access, and the encouraging-yet-limited data supporting its use."

An ACOG practice advisory recognizes the emerging technology and availability of cfDNA screening for single-gene disorders but emphasizes that there is insufficient evidence to demonstrate the accuracy, PPV, and NPV for general population use (ACOG, 2019; reaffirmed 2024). For this reason, ACOG does not recommend single-gene cfDNA screening in pregnancy.

ACOG's *Practice Bulletin No. 181*, which addresses the prevention of RhD alloimmunization (2017; reaffirmed 2024), notes that cfDNA testing is being used to determine fetal *RHD* status and select candidates for antenatal anti-D immunoglobulin prophylaxis. The bulletin reports that studies have shown high rates of sensitivity and specificity for fetal *RHD* status determination in the first trimester; however, at current costs, noninvasive assessment of fetal *RHD* status is not recommended for routine use at this time.

American College of Obstetricians and Gynecologists (ACOG)/Society for Maternal-Fetal Medicine (SMFM)

Pregnancy at 35 years of age or older is the focus of *Obstetric Care Consensus #11*, developed jointly by ACOG and the SMFM (2023). In this consensus, ACOG and the SMFM recommend that prenatal genetic screening options (serum screening with or without nuchal translucency ultrasound or cfDNA screening) as well as diagnostic testing (chorionic villus sampling or amniocentesis) be discussed and offered to all pregnant patients regardless of their risk of chromosomal abnormality or age. Each patient has the right to either pursue or decline genetic screening and diagnostic testing (GRADE 1A; strong recommendation, high-quality evidence).

In *Practice Bulletin Number 231*, ACOG and the SMFM (2021) address prenatal screening for fetal chromosome abnormalities in multifetal-gestation pregnancies, indicating that all women with multifetal gestations, regardless of age, are candidates for screening for fetal chromosome abnormalities; however, no method of fetal chromosome abnormality screening, including serum samples, will be as accurate in twin gestations as it is in singleton gestations. The bulletin asserts that it is important to include this information in the counseling process for patients with multiple-gestation pregnancies. No data exist for serum screening for high-order multiple gestations (e.g., triplets or quadruplets). Analyzing risk vs benefit for screening/diagnostic testing in patients carrying multiple fetuses is complex. cfDNA screening can be performed in twin pregnancies; however, because there is a smaller number of reported affected cases than in singleton pregnancies, it is challenging to determine the accurate DR for trisomies 18 and 13. Since twin fetuses in a single pregnancy each contribute variable amounts of cfDNA, it is possible that a fetus with a chromosomal abnormality would contribute less fetal DNA, thereby masking the aneuploid test result. Although recent studies have suggested that the sensitivity for trisomy 21 with cfDNA in twin pregnancies may be similar to that in singletons, there has been a higher rate of test failure in twins.

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International Society for Prenatal Diagnosis (ISPD)

To update information regarding current technologies, implementation practices, and clinical experiences, the ISPD published a new position statement on the use of NIPT for fetal chromosomal conditions in 2023. The consensus position offered by the ISPD is summarized as follows:

- NIPT is the most accurate screening test for the common autosomal aneuploidies (trisomies 21, 13, and 18) in unselected singleton populations and those at known increased probability. It can be offered in primary or contingent screening models, with context-specific considerations in local health policy influencing decisions and implementation models.
- False-positive results occur with NIPT. Therefore, the ISPD strongly recommends that all patients with a "high chance" NIPT result have genetic counseling and be offered diagnostic testing, particularly if the termination of pregnancy is being considered.
- FF is an important quality-control metric, but substantial variation exists between laboratories and test methodologies. Laboratories should perform their own internal validation of their limit of detection and threshold for no-call results.
- Providers (laboratory and clinicians) should have established clinical pathways for the management of patients with a no-call result. This may include a detailed ultrasound, offer of repeat NIPT, alternative screening test, and/or diagnostic testing.
- If technically relevant, protocols for the identification and disclosure of suspected malignancy should be developed by laboratories.
- NIPT for SCA is sufficiently accurate to be offered alongside autosomal aneuploidy screening, with specific pretest counseling and consent. However, other societal, economic, cultural, and ethical factors may need to be considered in health policy decisions regarding population-based screening for the sex chromosomes.
- There are insufficient data to assess the performance and clinical utility of routine NIPT for RATs, subchromosomal imbalances, and microdeletion/duplication syndromes. Further research is required to evaluate these applications of NIPT, but if offered as part of local practice, there should be protocols in place to manage high-risk results and detailed platform-specific counseling available both prior to and post testing.
- At least one early first-trimester scan for dating, diagnosis of multiple pregnancy, and confirmation of fetal viability should be offered before performing NIPT.
- Fetuses with ultrasound abnormalities, including a nuchal translucency measurement of ≥ 3.5 mm, should be offered diagnostic testing and evaluation with chromosomal microarray regardless of the prior NIPT result.
- The ethical implementation of NIPT requires attention to provision of quality pretesting counseling, equity of access, and access to appropriate downstream clinical services.
- All stakeholders, including health care consumers, should be involved in determining local implementation models and future directions for NIPT.

(Hui et al., 2023)

National Institute for Health and Care Excellence (NICE)

A 2016 (updated 2021) NICE guideline (DG25) recommends the use of high-throughput cfDNA testing for the fetal *RHD* genotype to guide decisions regarding antenatal prophylaxis with anti-D immunoglobulin (dependent on a cost threshold) to reduce the unnecessary use of blood products in pregnant women. This recommendation was based on a comprehensive review of studies that assessed diagnostic accuracy, assessment of clinical outcomes, evaluation of implementation issues, and cost effectiveness.

National Society of Genetic Counselors (NSGC)

In a 2025 position statement, the NSGC states its belief that all pregnant patients, regardless of aneuploidy risk, should have access to prenatal screening using cfDNA. They recommend that health care providers present cfDNA for aneuploidy as a topic within the context of other prenatal screening and testing options, including the option of pursuing diagnostic testing as a first-line approach or declining any screening or testing altogether. Discussions should also include individual preferences, values, and needs as well as the limitations and benefits of genetic screening with cfDNA. They further recommend careful consideration of the test's PPV, particularly in rare disorders.

Society for Maternal-Fetal Medicine (SMFM)

In the 2025 *Consult Series #74*, the SMFM updated its guidance on the appropriate application of cfDNA screening, including the use of cfDNA to detect sex chromosome aneuploidies and microdeletions as well as its application in multifetal-gestation pregnancies. The following recommendations are provided:

- cfDNA screening for trisomies 21, 18, and 13 should be routinely offered to all obstetric patients (GRADE 1B).
- cfDNA screening is recommended as the most sensitive and specific method for detecting trisomies 21, 18, and 13 in all patient populations; patients retain the choice to accept or decline screening and diagnostic testing after counseling (GRADE 1B).

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- Screening for sex chromosome aneuploidies should be offered only as an opt-in component of cfDNA testing and should be preceded by appropriate pretest counseling (GRADE 1C).
- Routine general population cfDNA screening for microdeletion syndromes should not be performed. Patients specifically requesting 22q11.2 deletion screening should receive pretest counseling; those desiring CNV information should be offered diagnostic testing instead (GRADE 1C).
- cfDNA screening should be used as a first-line option for trisomy 21 detection in twin gestations (GRADE 1B).
- cfDNA screening for trisomies 18 and 13 should be offered in twin gestations, given consistently high DRs, despite limited case numbers (GRADE 1B).
- cfDNA screening should not be used to assess SCA in twin gestations or any aneuploidy in higher-order multiples due to insufficient supporting data (GRADE 1C).
- cfDNA screening should not be used routinely for genome-wide assessment of large copy number deletions or duplications (GRADE 1C).

GRADE system:
- 1A. Strong recommendation, high-quality evidence.
- 1B. Strong recommendation, moderate-quality evidence.
- 1C. Strong recommendation, low-quality evidence.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Laboratories that perform DNA-based tests are regulated by the FDA under the Clinical Laboratory Improvement Amendments. Refer to the following website for more information: https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clinical-laboratory-improvement-amendments-clia. (Accessed February 20, 2026)

A list of nucleic acid–based tests that have been cleared or approved by the FDA Center for Devices and Radiological Health is available at: https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests. (Accessed February 20, 2026)

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Policy History/Revision Information

Date	Summary of Changes
10/01/2026	**Applicable Codes** • Updated list of applicable CPT codes to reflect quarterly edits; added 0663U **Supporting Information** • Archived previous policy version 2026T0560MM

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates.

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