

Cell-free DNA prenatal screening

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Recent review date: 7/2024

Next review date: 11/2025

Policy contains: Aneuploidy; cell-free DNA; chromosome; prenatal screening; sequencing, trisomy.

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Coverage policy

Cell-free deoxyribonucleic acid (DNA) screening of gestational maternal plasma is clinically proven and, therefore, may be medically necessary for either (American College of Obstetricians and Gynecologists, 2020):

- Detection of trisomies 21, 18, and 13 regardless of maternal age or risk of chromosomal abnormality after nine to ten weeks gestation up to term.
- Follow-up to a positive serum analyte screening test for members who want to avoid an invasive diagnostic test.

Cell-free DNA for detecting other trisomies, sex chromosome aneuploidy, and other microdeletion syndromes is investigational/not clinically proven and, therefore, not medically necessary.

Pretest and posttest genetic counseling may be offered to all pregnant members to make an informed choice regarding prenatal genetic screening or diagnostic testing.

Limitations

No other limitations were identified for this policy.

Alternative covered services

- Serum analyte screening with or without fetal nuchal translucency ultrasound.
- Diagnostic testing using amniocentesis or chorionic villus sampling.

Background

Chromosomal abnormalities comprise absent or additional entire chromosomes (aneuploidy), microdeletions, duplications, and translocations of varying sizes. Aneuploidy can occur in sex and non-sex chromosomes. The most common sex chromosome aneuploidies are 47, XXY (Klinefelter syndrome) with a prevalence of one in 500 males and 45, X (Turner syndrome), which occurs in one in 2,500 births. Copy number variants occur in approximately 0.4% of pregnancies (American College of Obstetricians and Gynecologists, 2020).

A series of genetic disorders classified as trisomy features three copies of chromosomes in cells, instead of the usual two. Specific disorders include trisomy 21, which accounts for 95% of Down syndrome cases; trisomy 18, or Edwards syndrome; and trisomy 13, also known as Patau syndrome. The incidence of trisomy 21, 18, and 13 are one in 800 births; one in 5,000 births; and one in 16,000 births, respectively (Health Quality Ontario, 2019).

Causes of trisomies include non-disjunction (chromosomes do not properly separate in the egg or sperm); translocation (part of a chromosome becomes attached to another during egg or sperm formation); mosaicism (an error in cell division during early development of the embryo results in aneuploidy in some cells); and inheritance from a carrier patient (Health Quality Ontario, 2019).

Risk of aneuploidy increases with maternal age. The chance that a fetus has trisomy 21 rises from one in 1,480 in mothers age 20, to one in 35 in mothers age 45. Other risk factors include the presence of birth defects or soft markers on fetal ultrasound or prior pregnancy and a past family history of aneuploidy (Carlson, 2017).

Prognoses for these syndromes vary. Improvements in treatment have made it possible for many born with Down syndrome to live a full and meaningful life; current average life expectancy is over 60 years (Mayo Clinic, 2018). On the other hand, half of newborns with trisomy 18 will die in the first week of life, and only 5% to 10% live more than one year (Perlstein, 2020).

Ultrasound and serum screening in early pregnancy are traditional screening methods used to detect pregnancies at high risk for chromosomal abnormalities or birth defects. Several options for serum screening are available, each with their own testing criteria and optimal timing for use. While each of the screening methods can be used alone, a combined testing of ultrasound fetal nuchal translucency measurement and maternal serum biochemistry in early pregnancy (10 to 13 gestational weeks) is commonly used, along with consideration of maternal age. However, these screening tests are associated with high false negative and false positive rates (Carlson, 2017).

Cell-free DNA, also referred to as non-invasive prenatal testing, is a screening option that became available in the United States in 2011. Cell-free DNA from the pregnancy (placental origin) is separated from maternal plasma by centrifugation and then isolated and purified. Laboratory methods consist of either massive parallel shotgun sequencing or more targeted chromosome-selective, massive parallel sequencing or interrogation of single nucleotide polymorphisms. Small differences between fetal and maternal DNA sequences are used to detect aneuploidy. Positive results require additional diagnostic testing by chorionic villus sampling or amniocentesis, which can detect trisomy presence with certainty but are invasive and have a 1% chance of miscarriage. Cytogenic evaluations also can be used in diagnosing trisomy (Carlson, 2017).

Findings

Strong evidence supports improved sensitivity and specificity of prenatal cell-free DNA testing over traditional screening methods for detection of trisomies 21, 18, and 13 in singleton and twin pregnancies when used as a primary or secondary screen. In this role, the clinical utility is in reducing the number of false positive results and avoiding unnecessary invasive procedures. Positive cell-free DNA results require diagnostic confirmation by amniocentesis or chorionic villus sampling.

Evidence of cell-free DNA for detecting other trisomies, sex chromosome aneuploidy, and other microdeletion syndromes is emerging but insufficient for routine interrogation. Cell-free DNA testing appears to have sensitivity and specificity in excess of 90% but lower than that of trisomies 21, 18, and 13. The evidence suggests low positive predictive values for rare autosomal trisomies, explained in part by their rare occurrence, selection bias, and confirmation bias. However, cell-free DNA is the only laboratory-based prenatal screen capable of identifying all of these variants.

Guidelines

The American College of Medical Genetics and Genomics strongly recommends non-invasive prenatal screening over traditional screening methods for fetal trisomies 21, 18, and 13 in all singleton and twin pregnancies, and for sex chromosome aneuploidy in singleton pregnancies, based on high certainty of the evidence. The College conditionally recommends non-invasive prenatal screening for detection of 22q11.2 deletion syndrome based on moderate certainty of the evidence. There was insufficient evidence to recommend routine non-invasive prenatal screening for other microdeletions or rare autosomal trisomies. The College emphasized the importance of pre- and post-test genetic counseling (Dungan, 2023).

The American College of Obstetricians and Gynecologists (2020) issued the following recommendations relevant to genetic testing for trisomy:

- Cell-free DNA screening should be offered to all pregnant women regardless of maternal age or risk of chromosomal abnormality, as an alternative to serum screening with or without nuchal translucency ultrasound (Level of evidence: A).
- Cell-free DNA screening can be performed in twin pregnancies. Overall, performance of screening for trisomy 21 by cell-free DNA in twin pregnancies is encouraging, but the total number of reported affected cases is small. Accurate detection rates for trisomy 18 and 13 have not been determined (B).
- In multifetal gestations, there is a significant risk of an inaccurate test result if cell-free DNA is used in the presence of fetal demise, vanishing twin, or anomaly in one fetus (C).
- Patients should have one prenatal screening approach and should not have multiple screening tests performed simultaneously (A).
- Cell-free DNA testing is not equivalent to diagnostic testing. Positive screening tests for fetal aneuploidy should undergo genetic counseling and a comprehensive ultrasound evaluation with an opportunity for diagnostic testing to confirm results (A).
- A baseline sonogram may be useful prior to cell-free DNA screening, as some ultrasound findings detectable early in pregnancy may affect the timing of, the appropriateness of, and the ability to correctly interpret cell-free DNA testing. Cell-free DNA screening is not advised in the presence of fetal anomalies or a vanishing twin detected on ultrasound (B).
- The use of cell-free DNA screening as follow-up for patients with a screen positive serum analyte screening test is an option for patients who want to avoid a diagnostic test, but it may result in a delayed diagnosis (B).
- Genome-wide cell-free DNA screening for detecting large deletions or duplications is not recommended, because this testing has not been validated clinically and the screening accuracy in terms of detection and false-positive rates is not established.

Evidence reviews

Evidence of effectiveness of genetic screening methods for fetal aneuploidy are presented here. The majority of studies included high risk pregnant women who had undergone both cell-free DNA and invasive diagnostic

testing. Massive parallel sequencing was the most commonly used laboratory method. For detecting less common trisomy disorders, sex chromosome aneuploidies, and copy number variants, selection bias and incomplete confirmation of test results hamper more reliable estimates of diagnostic accuracy and predictive values:

- A systematic review of cell-free DNA testing in seven relevant studies of twin pregnancies found detection rates and false-positive rates for trisomy 21 (98.2% and 0.05%, $n = 56$); for trisomy 18 (88.9% and .03%, $n = 18$); and for trisomy 13 (66.7% and 0.19%, $n = 3$). Authors state that the observed cell-free DNA testing results for trisomy 21 of twins is similar to that of singletons, and superior to that of the first-trimester combined test or second-trimester biochemical testing (Gil, 2019).
- A systematic review of eight studies ($n = 32,121$) in the average-risk population showed the sensitivity of non-invasive prenatal testing for trisomy 21, 18, and 13 were 99.5%, 93.1%, and 92.7%, respectively. Overall sensitivity (86.7%) and false positive (0.1%) rates made non-invasive testing superior to traditional prenatal screening. Traditional prenatal screening is generally defined as ultrasound and other serum biomarkers that can detect conditions such as neural tube defects, other fetal structural abnormalities, and placental dysfunction. Authors note that positive tests should be confirmed by diagnostic testing (Health Quality Ontario, 2019).
- A Cochrane review included 65 studies of mixed high risk and general-risk pregnant populations. A total of 86,139 pregnancies, including 3,141 aneuploidies, found genomics-based non-invasive prenatal testing is highly sensitive and specific for detecting trisomy 21, 18 and 13 in high-risk pregnancies. However, authors conclude that evidence is insufficient to support replacing current invasive fetal karyotyping diagnostic tests in making decisions on pregnancy outcomes (Badeau, 2017).

In 2024, we deleted several older references, updated an American College of Obstetricians and Gynecologists guideline, added a guideline from the American College of Medical Genomics and Genetics, and added several new systematic reviews and meta-analyses. We modified the coverage to align with guideline recommendations. The evidence reviews are summarized, as follows:

- Cell-free DNA was highly accurate for detecting trisomies 21, 18, and 13 in both singleton and twin pregnancies. Diagnostic performance was variable for detecting rare autosomal trisomies and copy number variants. In terms of clinical utility, limited data from 10 studies suggests a reduction in diagnostic testing by 31% to 79% depending on the population, indication, and analytical method used. Data on the impact of testing on psychosocial outcomes was inconclusive (87 studies; Rose, 2022).
- For detecting rare autosomal trisomies (involving chromosomes other than 21, 18, 13) and the sex chromosomes, the positive predictive value of cell-free DNA is approximately 11% in combined populations of average and high risk (31 studies; Acreman, 2023).
- For detecting sex chromosome abnormalities, the pooled sensitivity, specificity, and positive predictive value of cell-free DNA testing was 94%, 99.5%, and 49.4%, respectively. The positive predictive value was higher for sex chromosome abnormalities with a supernumerary Y chromosome and lower for monosomy X (94 studies; $n = 1,531,240$; Bussolaro, 2023).
- For detecting trisomy 21, 18, 13, sex chromosomes, and additional findings in twin pregnancies affected by early single fetal demise (vanishing twin), limited data suggest cell-free DNA can detect common autosomal aneuploidies but at a higher false positive rate. The higher false positive rate may be a result of detection of cell-free DNA from the demised twin that was aneuploid (seven studies; van Eekhout, 2023).
- For detecting copy number variations, the pooled positive predictive value of cell-free DNA was approximately 33%. There were insufficient data to calculate sensitivity and specificity due to confirmation

bias favoring diagnostic testing only in high risk women (29 studies; n = 2,667; Wen, 2023).

References

On May 13, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “genetic testing” (MeSH), “maternal testing” (MeSH), “noninvasive prenatal testing” (MeSH), and “trisomy.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

12/2012: initial review date and clinical policy effective date: 8/2013

9/2014: Policy references updated.

9/2015: Policy references updated.

11/2016: Policy references updated.

11/2017: Policy references updated.

11/2018: Policy references updated. Policy ID changed from 02.01.01 to CCP.1002.

11/2019: Policy references updated.

2/2020: Policy references updated.

2/2021: Policy references updated. Policy title changed from “Maternal genetic testing” to “Maternal genetic testing for trisomy.”

2/2022: Policy references updated. Research remains unchanged on this subject. Appendix B added.

2/2023: Policy references updated.

7/2024: Policy references updated. Title changed and coverage modified.