Test Specific Guidelines

Non-Invasive Prenatal Screening

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Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
Non-Invasive Prenatal Screening for Fetal Aneuploidy	81420
Non-Invasive Prenatal Screening for Fetal Aneuploidy with Risk Score	81507
Non-Invasive Prenatal Screening for Fetal Chromosomal Microdeletions	81422
Non-Invasive Prenatal Screening for Single-Gene Mutations	81105-81479
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What Is a Chromosome Abnormality?

Definition

A chromosome abnormality is any difference in the structure, arrangement, or amount of genetic material packaged into the chromosomes.[1]

Humans usually have 23 pairs of chromosomes. Each chromosome has a characteristic appearance that should be the same in each person.

Chromosome abnormalities can lead to a variety of developmental and reproductive disorders. Common chromosome abnormalities that affect development include Down syndrome (trisomy 21), trisomy 18, trisomy 13, Turner syndrome, and Klinefelter syndrome.

About 1 in 150 live births involve some type of chromosome abnormality that results in an abnormal fetal or neonatal phenotype, and a higher percentage of pregnancies are affected but lost during pregnancy. About 6%-11% of stillbirths or neonatal deaths are associated with a chromosome abnormality.[2,3]

The risk of having a child with an extra chromosome, notably Down syndrome, increases as a woman gets older.[3] However, many babies with Down syndrome are born to women under 35 and the risk of having a child with other types of chromosome abnormalities, such as Turner syndrome or 22q11 deletion syndrome, is not related to maternal age. Therefore, prenatal screening for Down syndrome and certain other chromosome abnormalities is now routinely offered to all pregnant women. As a result, prenatal diagnosis via amniocentesis or chorionic villus sampling (CVS) is now also an option for most pregnant women.

Test Information

Non-invasive prenatal screening (NIPS, also called prenatal cell-free DNA screening or cfDNA screening) is performed on a maternal plasma sample generally collected after 9 weeks' gestation.[4]

Testing methodology relies on the presence of cell-free placental DNA in maternal circulation.[4] Approximately 10% of cell-free DNA in maternal circulation is of placental origin.[5]

Analysis of cell-free placental DNA is performed to identify pregnancies at increased risk for chromosomal aneuploidy. Detection rates for trisomies 21, 18, and 13 are greater than 98%, with false positive rates of less than 0.5%.[4]

Some laboratories also test for sex chromosome aneuploidies (such as Turner syndrome or Klinefelter syndrome) and rare chromosome microdeletion syndromes (such as 22q11 deletion syndrome or 1p36 microdeletion syndrome), with variable performance.

Each commercial or academic laboratory offering NIPS has a proprietary platform and bioinformatics pipeline.

Chromosome analysis via CVS and amniocentesis is also routinely available for diagnosis of fetal chromosome abnormalities in pregnancy.

Guidelines and Evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2016) published a position statement regarding Non Invasive Prenatal Screening (NIPS), recommending the following:[5]

"Informing all pregnant women that NIPS is the most sensitive screening option for traditionally screened aneuploidies (i.e., Patau, Edwards, and Down syndrome)."

"Informing all pregnant women of the availability of the expanded use of NIPS to screen for clinically relevant copy number variations (CNV's) when the following conditions can also be met:"

"Obstetric care providers should discuss with their patients the desire for prenatal screening as opposed to diagnostic testing (i.e., CVS or amniocentesis)."

"Obstetric care providers should discuss with their patients the desire for maximum fetal genomic information through prenatal screening."

"Obstetric care providers should inform their patients of the higher likelihood of false-positive and false-negative results for these conditions as compared to results obtained when NIPS is limited to common aneuploidy screening."

"Obstetric care providers should inform their patients of the potential for results of conditions that, once confirmed, may have an uncertain prognosis."

"Referring patients to a trained genetics professional when an increased risk of aneuploidy is reported after NIPS."

"Offering diagnostic testing when a positive screening test result is reported after NIPS."

"Offering diagnostic testing for a no-call NIPS result due to low fetal fraction if maternal blood for NIPS was drawn at an appropriate gestational age. A repeat blood draw is NOT appropriate."

"Informing all pregnant women, as part of pretest counseling for NIPS, of the availability of the expanded use of screening for sex chromosome aneuploidies."

Offering aneuploidy screening other than NIPS in cases of significant obesity.

The ACMG specifically recommended against the following:

"NIPS to screen for genome-wide CNVs. If this level of information is desired, then diagnostic testing (e.g., chorionic villous sampling or amniocentesis) followed by CMA is recommended."

"NIPS to screen for autosomal aneuploidies other than those involving chromosomes 13, 18, and 21."

The American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (ACOG, 2019) issued a practice advisory on the use of cell-free DNA to screen for single-gene disorders stating the following:[6]

"The continued innovation in cell-free technology combined with the desire for a maternal blood test to predict the risk for fetal genetic disorders during a pregnancy has broadened the application of cell-free DNA screening beyond aneuploidy to single-gene disorders. Examples of single-gene disorders include various skeletal dysplasias, sickle cell disease and cystic fibrosis. Although this technology is available clinically and marketed as a single-gene disorder prenatal screening option for obstetric care providers to consider in their practice, often in presence of advanced paternal age, there has not been sufficient data to provide

information regarding accuracy and positive and negative predictive value in the general population. For this reason, single-gene cell-free DNA screening is not currently recommended in pregnancy."

The American College of Obstetricians and Gynecologists and Society for Maternal Fetal Medicine

In 2020, The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal Fetal Medicine (SMFM) published a joint practice bulletin stating the following:[7]

"Prenatal genetic screening (serum screening with or without nuchal translucency [NT] ultrasound or cell-free DNA screening) and diagnostic testing (chorionic villus sampling [CVS] or amniocentesis) options should be discussed and offered to all pregnant women regardless of maternal age or risk of chromosome abnormality." [Level A Recommendation: based on good and consistent scientific evidence]

"If screening is accepted, patients should have one prenatal screening approach, and should not have multiple screening tests performed simultaneously." [Level A Recommendation: based on good and consistent scientific evidence]

"Cell-free DNA is the most sensitive and specific screening test for the common fetal aneuploidies. Nevertheless, it has the potential for false-positive and false-negative results. Furthermore, cell-free DNA testing is not equivalent to diagnostic testing." [Level A Recommendation: based on good and consistent scientific evidence]

"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. Given the small number of affected cases it is difficult to determine an accurate detection rate for trisomy 18 and 13." [Level B Recommendation: based on limited or inconsistent scientific evidence]

American Society of Human Genetics and European Society of Human Genetics

A 2015 joint statement by the American Society of Human Genetics (ASHG)/European Society of Human Genetics (ESHG) includes the following recommendations:[8]

"NIPT offers improved accuracy when testing for common autosomal aneuploidies compared with existing tests such as cFTS. However, a positive NIPT result should not be regarded as a final diagnosis… Thus women should be advised to have a positive result confirmed through diagnostic testing, preferably by amniocentesis, if they are considering a possible termination of pregnancy."

"Expanding NIPT-based prenatal screening to also report on sex chromosomal abnormalities and microdeletions not only raises ethical concerns related to information and counseling challenges but also risks reversing the important

reduction in invasive testing achieved with implementation of NIPT for aneuploidy, and is therefore currently not recommended."

The International Society for Prenatal Diagnosis

The International Society for Prenatal Diagnosis (ISPD) first issued a position statement on NIPT in January 2011 and then updated its recommendations in April 2013 and again in April 2015. ISPD summarizes that:[9]

"The following protocol options are currently considered appropriate:"

"cfDNA screening as a primary test offered to all pregnant women."

"cfDNA secondary to a high risk assessment based on serum and ultrasound screening protocols."

"When cfDNA screening is extended to microdeletion and microduplication syndromes or rare trisomies the testing should be limited to clinically significant disorders or well-defined severe conditions."

The ISPD issued a position statement (2020) on cfDNA screening for Down syndrome in twin and triplet pregnancies. The statement compared cfDNA screening to other screening methods available for multiple gestation pregnancies, focusing on test characteristics. This approach is in contrast to other professional guidelines that compare the performance of cfDNA in twin pregnancies to that reported for cfDNA screening in singleton pregnancies. ISPD summarized:[10]

"The use of first trimester cfDNA screening for the common autosomal trisomies is appropriate for twin pregnancies due to sufficient evidence showing high detection and low false positive rates with high predictive values. Moderate."

"The finding of an increased risk on a cfDNA screening test in multiple pregnancies should be followed by counseling and an offer of diagnostic testing to confirm results. Strong."

The National Society of Genetic Counselors

The National Society of Genetic Counselors (NSGC, 2021) issued a position statement regarding the use of prenatal cell-free DNA screening:[11]

"The National Society of Genetic Counselors believes that all pregnant patients, regardless of aneuploidy risk, should have access to prenatal aneuploidy screening using cell-free DNA (cfDNA)."

"Patients who receive increased risk or inconclusive/atypical results should receive post-test genetic counseling with a knowledgeable healthcare provider, such as a genetic counselor. In such cases, confirmatory diagnostic testing may be indicated, and patients should be counseled that no irreversible actions should be taken based on the cfDNA screening alone."

Society of Obstetricians and Gynaecologists of Canada

The Society of Obstetricians and Gynaecologists of Canada (SOGC, 2017) stated: "Routine cfDNA screening for fetal microdeletions is not currently recommended (II-2B)."[12]

Selected Relevant Publications

Selected relevant publications pertaining to twin pregnancies, microdeletion testing, and single gene testing.

Twin pregnancies

Evidence for clinical validity and clinical utility of NIPS is insufficient to assess the risk of fetal aneuploidy in twin pregnancies.[10,13-21] Only three of 10 professional society statements allow or recommend cfDNA screening in twin pregnancies.[10] Well-designed clinical validity and clinical utility studies evaluating the performance of NIPS to detect T21, T18, and T13 aneuploidies in twin pregnancies in the general obstetric population are needed.

Microdeletion syndromes testing

A few clinical validity studies have evaluated noninvasive prenatal screening (NIPS) to detect known and likely pathogenic microdeletions in microdeletion syndromes.[15,22-31] Based on the few number of cases across each study, detection rates were more than 97% with less than 1% rate of false positives. However, a significant limitation is the lack of positive predictive values (PPVs) and negative predictive values (NPVs) to estimate clinical utility, which are screening metrics crucial for clinical decision-making.

Overall, the evidence base is insufficient to permit definitive conclusions about the performance of NIPS to assess the risk of microdeletion syndromes. Larger, well-designed clinical validity studies assessing test performance and clinical utility studies assessing pregnancy outcomes are needed before NIPS can be adopted for routine use in general or average-risk obstetric populations.

Single gene disorders testing

There are very few clinical studies evaluating the performance of NIPS to assess the risk of single-gene disorders.[32-36] The bulk of the available peer-reviewed evidence consists of small case reports, small case series, and general review or clinical opinion articles discussing the feasibility and application of emerging technical platforms for this indication.

The evidence base is insufficient to permit definitive conclusions regarding the performance of NIPS to assess the risk of single-gene disorders. Larger well-designed clinical validity and clinical utility studies evaluating NIPS for this indication in the general obstetric population are needed.

Criteria

Cell-free DNA-based Prenatal Screening for Fetal Aneuploidy

Genetic Counseling:

Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Prenatal Screening:

Prenatal cell-free DNA screening for fetal aneuploidy (e.g. trisomy 13, 18, and 21) is considered medically necessary when all of the following criteria are met:

Singleton pregnancy, AND

Gestational age within the window validated by the selected testing laboratory, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

Prenatal cell-free DNA screening is not considered medically necessary in the following circumstances:

Singleton pregnancies in which the demise of a twin has occurred.

Multiple gestation pregnancies, which may be defined by the presence of one of the following ICD codes: O30.X. O31.X.

More than one prenatal cell-free DNA screen performed per pregnancy defined as no more than one paid prenatal cell-free DNA screen procedure code within 10 weeks.

When karyotyping, aneuploidy FISH, and/or cytogenomic microarray analysis (CMA) have already been performed on the pregnancy, defined as any of these procedure codes paid within 10 weeks of the prenatal cell-free DNA screen.

Prenatal Cell-Free DNA Screening for Chromosome Microdeletions

This test is considered investigational and/or experimental.

Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.

In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

Prenatal Cell-Free DNA Screening for Single-Gene Mutations

This test is considered investigational and/or experimental.

Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.

In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

Billing and Reimbursement Considerations

Non-specific procedure codes (e.g. 81479, 81599, 84999) or any procedure codes that do not accurately describe the test methodology performed (e.g. 88271) are not eligible for reimbursement.

Screening for aneuploidy of the X and Y chromosomes and/or detection of less common trisomies, are not separately reimbursable under these coverage guidelines. Additional procedure codes billed with cell-free DNA screening for this purpose are not eligible for reimbursement.

Prenatal diagnosis by amniocentesis or CVS following NIPS is generally only indicated when NIPS results are abnormal or additional information becomes available throughout the pregnancy that suggests additional risk factors. Amniocentesis or CVS billed after NIPS is subject to medical necessity review.

Other Considerations

Maternal serum screening for aneuploidy and non-invasive prenatal screening (prenatal cell-free DNA screening) should not be performed concurrently.

If non-invasive prenatal screening (prenatal cell-free DNA screening) has been successfully performed in the current pregnancy, other aneuploidy screening (by first or second trimester screening or integrated, step-wise sequential, or contingent sequential screening) is not indicated. Maternal serum screening for neural tube defects (AFP-only) is indicated.

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