Protocol

Genetic Testing for Noninvasive Prenatal Testing

(40121)

Medical Benefit		**Effective Date**: 01/01/18	**Next Review Date**: 09/18
Preauthorization	Yes	**Review Dates**: 03/13, 03/14, 11/14, 05/15, 7/15, 01/16, 09/16, 09/17	

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With singleton pregnancy	Interventions of interest are: • Noninvasive prenatal screening for trisomy 21, using cell-free fetal DNA	Comparators of interest are: • Conventional serum screening • Diagnostic testing • Standard care without screening	Relevant outcomes include: • Test accuracy • Test validity • Morbid events • Resource utilization
Individuals: • With singleton pregnancy	Interventions of interest are: • Noninvasive prenatal screening for trisomy 18, trisomy 13 or sex chromosome aneuploidies using cell-free fetal DNA	Comparators of interest are: • Conventional serum screening • Diagnostic testing • Standard care without screening	Relevant outcomes include: • Test accuracy • Test validity • Morbid events • Resource utilization
Individuals: • With twin or multiple pregnancy	Interventions of interest are: • Noninvasive prenatal screening for aneuploidies using cell-free fetal DNA	Comparators of interest are: • Conventional serum screening • Diagnostic testing • Standard care without screening	Relevant outcomes include: • Test accuracy • Test validity • Morbid events • Resource utilization
Individuals: • Pregnancy(cies)	Interventions of interest are: • Noninvasive prenatal screening for microdeletions using cell-free fetal DNA	Comparators of interest are: • Diagnostic testing • Standard care without screening	Relevant outcomes include: • Test accuracy • Test validity • Morbid events • Resource utilization

Description

National guidelines recommend that all pregnant women be offered screening for fetal chromosomal abnormalities, most of which are aneuploidies, an abnormal number of chromosomes. Trisomy syndromes are aneuploidies involving three copies of one chromosome. Trisomies 21 (T21), 18 (T18), and 13 (T13) are the most common forms of fetal aneuploidy that survive to birth. There are numerous limitations to standard screening for these disorders using maternal serum and fetal ultrasound. Noninvasive prenatal screening (NIPS) analyzing cell-free fetal DNA in maternal serum is a potential complement or alternative to conventional serum screening. NIPS using cell-free fetal DNA has also been proposed to screen for microdeletions.

Summary of Evidence

For individuals who have a singleton pregnancy who receive NIPS for T21 using cell-free fetal DNA, the evidence includes observational studies and systematic reviews. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. Published studies on commercially available tests and meta-analyses of these studies have consistently demonstrated very high sensitivity and specificity for detecting Down syndrome (T21) in singleton pregnancies. Most studies included only women at high risk of T21, but several studies, including one with a large sample size, have reported similar levels of diagnostic accuracy in average-risk women. Compared with standard serum screening, both the sensitivity and specificity of cell-free fetal DNA screening are considerably higher. As a result, screening with cell-free fetal DNA will result in fewer missed cases of Down syndrome, fewer invasive procedures, and fewer cases of pregnancy loss following invasive procedures. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a singleton pregnancy who receive NIPS for T18, T13, or sex chromosome aneuploidies using cell-free fetal DNA, the evidence includes observational studies, mainly in high-risk pregnancies, and systematic reviews. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. Meta-analyses of available data have suggested high sensitivities and specificities, but the small number of cases, especially for T13, makes definitive conclusions difficult. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have twin or multiple pregnancies who receive NIPS for aneuploidies using cell-free fetal DNA, the evidence includes several observational studies and a systematic review. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. The total number of cases of aneuploidy identified in these studies is small and is insufficient to draw conclusions about clinical validity. There is a lack of direct evidence of clinical utility, and a chain of evidence cannot be conducted due to insufficient evidence on clinical validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with pregnancy(ies) who receive NIPS for microdeletions using cell-free fetal DNA, the evidence includes several observational studies. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. The available studies on clinical validity have limitations (e.g., missing data on confirmatory testing, false-negatives), and the added benefit of NIPS compared with current approaches is unclear. Moreover, the clinical utility of NIPS for microdeletions remains unclear and has not been evaluated in published studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

Nucleic acid sequencing-based testing of maternal plasma for trisomy 21 may be considered **medically necessary** in women with singleton pregnancies (see Policy Guidelines) undergoing screening for trisomy 21.

Concurrent nucleic acid sequencing-based testing of maternal plasma for trisomy 13 and/or 18 and sex chromosomal aneuploidy ([SCA] i.e., Turner Syndrome, Kleinfelter Syndrome) may be considered **medically necessary** in women who are eligible for and are undergoing nucleic acid sequencing-based testing of maternal plasma for trisomy 21.

Non-invasive prenatal genetic testing for identification of chromosomal aneuploidy is considered **investigational** for women with twin or multiple pregnancies.

Nucleic acid sequencing-based testing of maternal plasma for trisomy 13 and/or 18, other than in the situations specified above, is considered **investigational**.

Nucleic acid sequencing-based testing of maternal plasma for microdeletions is considered **investigational**.

Nucleic acid sequencing-based testing of maternal plasma for trisomy 16 and 22 is considered **investigational**.

Policy Guidelines

This testing is necessary only once in an individual's lifetime.

Karyotyping would be necessary to exclude the possibility of a false positive nucleic acid sequencing–based test. Before testing, women should be counseled about the risk of a false positive test.

This protocol does not apply to pregnancies with a high clinical suspicion of fetal microdeletions for which invasive confirmatory testing is indicated.

In a 2015 committee opinion, the American College of Obstetricians and Gynecologists (ACOG) recommends that all patients receive information on the risks and benefits of various methods of prenatal screening and diagnostic testing for fetal aneuploidies, including the option of no testing.

Studies published to date on noninvasive prenatal screening for fetal aneuploidies report rare but occasional false positives. In these studies, the actual false positive test results were not always borderline; some were clearly above the assay cutoff value, and no processing or biological explanations for the false-positive results were reported. False-positive findings have been found to be associated with factors including placental mosaicism, vanishing twins and maternal malignancies. In its 2015 committee opinion, ACOG recommended diagnostic testing to confirm positive cell-free DNA tests, and that management decisions not be based solely on the results of cell free DNA testing. ACOG further recommends that patients with indeterminate or uninterpre-table (i.e., "no call") cell-free DNA test results be referred for genetic counseling and offered ultrasound evaluation and diagnostic testing because "no call" findings have been associated with an increased risk of aneuploidy.

As noted in the 2015 ACOG committee opinion, cell-free DNA screening does not assess risk of anomalies such as neural tube defects. Patients should continue to be offered ultrasound or maternal serum alpha-fetoprotein screening, regardless of the type of serum screening selected.

Genetics Nomenclature Update

Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Human Genome Variation Society nomenclature is recommended by the Human Genome Variation Society, the Human Variome Project, and the Human Genome Organization.

The American College of Medical Genetics and Genomics and Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Medicare Advantage

For Medicare Advantage fetal chromosomal microdeletions genomic sequence analysis is unlikely to impact therapeutic decision-making in the clinical management of the patient and is considered **not medically necessary**.

Background

Fetal Aneuploidy

Fetal chromosomal abnormalities occur in approximately one in 160 live births. Most fetal chromosomal abnormalities are aneuploidies, defined as an abnormal number of chromosomes. The trisomy syndromes are aneuploidies involving three copies of one chromosome. The most important risk factor for trisomy syndromes is maternal age. The approximate risk of a trisomy 21 (T21; Down syndrome)–affected birth is one in 1100 at age 25 to 29. The risk of a fetus with T21 (at 16 weeks of gestation) is about one in 250 at age 35 and one in 75 at age 40.[1]

T21 is the most common chromosomal aneuploidy and provides the impetus for current maternal serum screening programs. Other trisomy syndromes include T18 (Edwards syndrome) and T13 (Patau syndrome), which are the next most common forms of fetal aneuploidy, although the percentage of cases surviving to birth is low and survival beyond birth is limited. The prevalence of these other aneuploidies is much lower than the prevalence of T21, and identifying them is not currently the main intent of prenatal screening programs. Also, the clinical implications of identifying T18 and T13 are unclear, because survival beyond birth is limited for both conditions.

Fetal Aneuploidy Screening

Current national guidelines recommend that all pregnant women be offered screening for fetal aneuploidy (referring specifically to T21, T18, and T13) before 20 weeks of gestation, regardless of age.[2] Standard aneuploidy screening involves combinations of maternal serum markers and fetal ultrasound done at various stages of pregnancy. The detection rate for various combinations of noninvasive testing ranges from 60% to 96% when the false-positive rate is set at 5%. When tests indicate a high risk of a trisomy syndrome, direct karyotyping of fetal tissue obtained by amniocentesis or chorionic villous sampling (CVS) is required to confirm that T21 or

another trisomy is present. Both amniocentesis and CVS are invasive procedures and have an associated risk of miscarriage. A new screening strategy that reduces unnecessary amniocentesis and CVS procedures and increases detection of T21, T18, and T13 could improve outcomes. Confirmation of positive noninvasive screening tests with amniocentesis or CVS is recommended; with more accurate tests, fewer women would receive positive screening results.

Commercial, noninvasive, sequencing-based testing of maternal serum for fetal trisomy syndromes is now available. The test technology involves detection of cell-free fetal DNA fragments present in the plasma of pregnant women. As early as eight to 10 weeks of gestation, these fetal DNA fragments comprise 6% to 10% or more of the total cell-free DNA in a maternal plasma sample. The tests are unable to provide a result if fetal fraction is too low, (i.e., below 4%). Fetal fraction can be affected by maternal and fetal characteristics. For example, fetal fraction was found to be lower at higher maternal weights and higher with increasing fetal crown-rump length.[3]

Cell-Free DNA Analysis Methods

Sequencing-based tests use one of two general approaches to analyzing cell-free DNA. The first category of tests uses quantitative or counting methods. The most widely used technique to date uses massively parallel sequencing (MPS; also known as next-generation sequencing). DNA fragments are amplified by polymerase chain reaction; during the sequencing process, the amplified fragments are spatially segregated and sequenced simultaneously in a massively parallel fashion. Sequenced fragments can be mapped to the reference human genome to obtain numbers of fragment counts per chromosome. The sequencing-derived percent of fragments from the chromosome of interest reflects the chromosomal representation of the maternal and fetal DNA fragments in the original maternal plasma sample. Another technique is direct DNA analysis, which analyzes specific cell-free DNA fragments across samples and requires approximately a tenth the number of cell-free DNA fragments as MPS. The digital analysis of selected regions (DANSR™) is an assay that uses direct DNA analysis.

The second general approach is single nucleotide polymorphism (SNP)–based methods. These use targeted amplification and analysis of approximately 20,000 SNPs on selected chromosomes (e.g., 21, 18, 13) in a single reaction. A statistical algorithm is used to determine the number of each type of chromosome.

At least some of the commercially available cell-free DNA prenatal tests also test for other abnormalities including sex chromosome abnormalities and selected microdeletions. Sex chromosome aneuploidies (e.g., 45,X [Turner syndrome]; 47,XXY, 47,XYY) occur in approximately one in 400 live births. These aneuploidies are typically diagnosed postnatally, sometimes not until adulthood, such as during an evaluation of diminished fertility. Alternatively, sex chromosome aneuploidies may be diagnosed incidentally during invasive karyotype testing of pregnant women at high risk for Down syndrome. Potential benefits of early identification (e.g., the opportunity for early management of the manifestations of the condition), must be balanced against potential harms that can include stigmatization and distortion of a family's view of the child.

Copy Number Variants and Clinical Disorders

Microdeletions (also known as submicroscopic deletions) are defined as chromosomal deletions that are too small to be detected by microscopy or conventional cytogenetic methods. They can be as small as one and three megabases (Mb) long. Along with microduplications, microdeletions are collectively known as copy number variants (CNVs). CNVs can lead to disease when the change in copy number of a dose-sensitive gene or genes disrupts the ability of the gene(s) to function and effects the amount of protein produced. A number of genomic disorders associated with microdeletion have been identified which may be associated with serious clinical features such as cardiac anomalies, immune deficiency, palatal defects, and developmental delay as in DiGeorge syndrome. Some of the syndromes (e.g., DiGeorge) have complete penetrance yet marked variability in clinical expressivity. A contributing factor is that the breakpoints of the microdeletions may vary, and there may be a correlation between the number of haplo-insufficient genes and phenotypic severity.

Fetal Detection of CNVs

A proportion of microdeletions are inherited and some are de novo. Accurate estimates of the prevalence of microdeletion syndromes during pregnancy or at birth are not available. Risk of a fetus with a microdeletion syndrome is independent of maternal age. There is little population-based data and most studies published to date base estimates on phenotypic presentation. The 22q11.2 (DiGeorge) deletion is the most common microdeletion associated with a clinical syndrome. According to the GeneTests database, current estimates of prevalence range from one in 4000 to one in 6395 live births.[3] Prevalence estimates for other microdeletions are between one in 5000 and one in 10,000 live births for 1p36 deletion syndrome, between one in 10,000 and one in 30,000 for Prader-Willi syndrome, and between one in 12,000 and one in 24,000 for Angelman syndrome. The above figures likely underestimate the prevalence of these microdeletion syndromes in the prenatal population because the population of mutation carriers includes phenotypically normal or very mildly affected individuals.

Routine prenatal screening for microdeletion syndromes is not recommended by national organizations. Current practice is to offer invasive prenatal diagnostic testing in selected cases to women when a prenatal ultrasound indicates anomalies (e.g., heart defects, cleft palate) that could be associated with a particular microdeletion syndrome. Samples are analyzed using fluorescence in situ hybridization, chromosomal microarray analysis, or karyotyping. In addition, families at risk (e.g., those known to have the deletion or with a previous affected child) generally receive genetic counseling and those who conceive naturally may choose prenatal diagnostic testing. Most affected individuals, though, are identified postnatally based on clinical presentation and may be confirmed by genetic testing. Using 22q11.2 deletion syndrome as an example, although clinical characteristics vary, palatal abnormalities (e.g., cleft palate) occur in approximately 69% of individuals, congenital heart disease in 74%, and characteristic facial features are present in a majority of individuals of northern European heritage.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of noninvasive prenatal screening tests using cell-free fetal DNA. Commercially available tests include but are not limited to the following:

- VisibiliT™ (Sequenom Laboratories, now LabCorp) tests for T21 and T18, and tests for sex.
- MaterniT21™ PLUS (Sequenom Laboratories) tests for T21, T18, and T13 and fetal sex aneuploidies. The enhanced sequencing series includes testing for trisomies 16 and 22 and seven microdeletions: 22q deletion syndrome (DiGeorge syndrome), 5p (cri du chat syndrome), 15q (Prader-Willi and Angelman syndromes), 1p36 deletion syndrome, 4p (Wolf-Hirschhorn syndrome), 8q (Langer-Giedion syndrome), and 11q (Jacobsen syndrome). The test uses MPS and reports results as positive or negative. The enhanced sequencing series is offered on an opt-out basis.
- Harmony™ test. (Ariosa Diagnostics was acquired by Roche 2015) tests for T21, T18, and T13. Uses directed DNA analysis, results reported as risk score.
- Panorama™ (Natera) is a prenatal test for detecting T21, T18, and T13, as well as select sex chromosome abnormalities. It uses single-nucleotide variant technology; results reported as risk score. An extended panel tests for five microdeletions: 22q deletion syndrome (DiGeorge syndrome), 5p (cri du chat syndrome), 15q11-13 (Prader-Willi and Angelman syndromes), and 1p36 deletion syndrome. Screening for 22q11.2 will be included in the panel unless the opt-out option is selected; screening for the remaining four microdeletions is offered on an opt-in basis.

- Verifi® (Illumina; formerly Verinata Health) is a prenatal test for T21, T18, and T13. The test uses MPS and calculates a normalized chromosomal value; reports results as one of three categories: no aneuploidy detected, aneuploidy detected, or aneuploidy suspected.
- InformaSeqSM (Integrated Genetics) is a prenatal test for detecting T21, T18, and T13, with optional additional testing for select sex chromosome abnormalities. Uses Illumina platform and reports results in similar manner.
- QNatal™ Advanced (Quest Diagnostics) tests for T21, T18, and T13.

Related Protocols

Carrier Screening for Genetic Diseases

Genetic Testing for Developmental Delay and Autism Spectrum Disorder

Invasive Prenatal (Fetal) Diagnostic Testing

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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