

Protocol

Sequencing-Based Tests to Determine Trisomy 21 from Maternal Plasma DNA

(40121)

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| Medical Benefit | Effective Date: 07/01/13 | Next Review Date: 03/15 |
| Preauthorization | Yes | Review Dates: 03/13, 03/14 |

*The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. **Preauthorization is required.** 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.*

Description

National guidelines recommend that all pregnant women be offered screening for fetal chromosomal abnormalities, the majority of which are aneuploidies (an abnormal number of chromosomes). The trisomy syndromes are aneuploidies involving three copies of one chromosome. Trisomies 21, 18, and 13 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. Commercial noninvasive, sequencing-based testing of maternal serum for fetal trisomy 21, 18, and 13 has recently become available and has the potential to substantially alter the current approach to screening.

Background

Fetal chromosomal abnormalities occur in approximately one in 160 live births. The majority of fetal chromosomal abnormalities are aneuploidies, defined as an abnormal number of chromosomes. The trisomy syndromes are aneuploidies involving three copies of one chromosome. Trisomy 21 (Down syndrome, T21), trisomy 18 (Edwards syndrome, T18), and trisomy 13 (Patau syndrome, T13) are the most common forms of fetal aneuploidy that survive to birth. The most important risk factor for Down syndrome is maternal age, with an approximate risk of 1/1500 in young women that increases to nearly 1/10 by age 48.

Current national guidelines recommend that all pregnant women be offered screening for fetal aneuploidy (referring specifically to trisomy 21, 18, and 13) before 20 weeks of gestation, regardless of age. (1) Combinations of maternal serum markers and fetal ultrasound done at various stages of pregnancy are used, but there is not a standardized approach. 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 trisomy 21 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 trisomy 21, 18, and 13 has the potential to improve outcomes.

Commercial, noninvasive, sequencing-based testing of maternal serum for fetal trisomy syndromes has recently become available and has the potential to substantially alter the current approach to screening. The test technology involves detection of fetal cell-free 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, that is,

below about 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. (2)

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 shotgun sequencing (MPS; also known as next generation or “next-gen” 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 in order 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 and 13) in a single reaction. A statistical algorithm is used to determine the number of each type of chromosome.

In order to be clinically useful, the technology must be sensitive enough to detect a slight shift in DNA fragment counts among the small fetal fragment representation of a genome with a trisomic chromosome against a large euploid maternal background. Whether sequencing-based assays require confirmation by invasive procedures and karyotyping depends on assay performance. However, discrepancies between sequencing and invasive test results that may occur for biological reasons could make confirmation by invasive testing necessary at least in some cases, regardless of sequencing test performance characteristics.

Regulatory Status

None of the commercially available sequencing assays for detection of trisomy 21, 18 and 13 or other chromosomal abnormalities has been submitted to or reviewed by the U.S. Food and Drug Administration (FDA). Clinical laboratories may develop and validate tests in-house (laboratory-developed tests or LDTs; previously called “home-brew”) and market them as a laboratory service; LDTs must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories offering LDTs must be licensed by CLIA for high-complexity testing. Information on commercially available tests is as follows:

- In October 2011, Sequenom (San Diego, CA) introduced its MaterniT21™ test to test for trisomy 21, 18 and 13. The test is offered through the company’s CLIA laboratory, the Sequenom Center for Molecular Medicine. (Uses MPS; reports results as positive or negative.)
- In March 2012, Verinata Health (Redwood, CA) launched its Verifi® prenatal test for trisomy 21, 18, and 13. (Uses MPS and calculates a normalized chromosomal value [NPS]; reports results as one of three categories: No Aneuploidy Detected, Aneuploidy Detected, or Aneuploidy Suspected.)
- In May 2012, Ariosa Diagnostics (San Jose, CA) (formerly Aria) launched its Harmony™ test for trisomy 21 and 18, which is available from Integrated Genetics, a division of LabCorp. (Uses directed DNA analysis, results reported as risk score.)
- In March 2013, Natera (San Carlos, CA) introduced its Panorama™ prenatal test for detecting trisomy 21, 18 and 13, as well as for detecting select sex chromosome abnormalities. The test is available at ARUP Laboratories. (Uses SNP technology; results reported as risk score.)

Policy (Formerly Corporate Medical Guideline)

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

Nucleic acid sequencing-based testing of maternal plasma for trisomy 21 is considered **not medically necessary** in women with average-risk singleton pregnancies.

Nucleic acid sequencing-based testing of maternal plasma for trisomy 21 is considered **investigational** in women with twin or multiple pregnancies.

Policy Guideline

High-risk singleton pregnancies, as defined by the American College of Obstetricians and Gynecologists (ACOG) Committee Opinion, Number 454, December 2012 include women who meet at least one of the following criteria:

- Maternal age 35 years or older at delivery;
- Fetal ultrasonographic findings indicating increased risk of aneuploidy;
- History of previous pregnancy with a trisomy;
- Standard serum screening test positive for aneuploidy; or
- Parental balanced robertsonian translocation with increased risk of fetal trisomy 13 or trisomy 21.

This Protocol focuses on detection of trisomy 21, as it is the most common cause of human birth defects and provides the impetus for current maternal serum screening programs. Detection of trisomy 21 by DNA-based sequencing methods would likely be representative of the testing technology and interpretation for autosomal trisomy detection such as trisomy 18 and 13 (but not for aneuploidies of sex chromosomes). However, screening for these other trisomy syndromes is not currently the main intent of prenatal screening programs. The prevalence of other trisomy syndromes is much lower than the prevalence of trisomy 21. Also, the clinical implications of identifying trisomy 18 and 13 are unclear, as most fetuses with trisomy 18 and 13 do not survive to term.

Studies published to date 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. In the decision model conducted for the 2012 TEC Assessment, using an overall estimate for predictive value calculations, even in a high risk population, the predictive value of a positive result was only 83%. Thus, in the absence of substantial data to confidently characterize the false positive rate, a karyotyping test would be necessary to confirm a positive result.

In some cases, tissue samples from CVS or amniocentesis may be insufficient for karyotyping; confirmation by specific fluorescent in situ hybridization (FISH) assay is acceptable for these samples.

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.**

References

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

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