Genetic Testing to Determine Trisomy 21 from Maternal Plasma DNA

Prospective review is recommended/required. Please check the member agreement for preauthorization guidelines.

Prospective review is not required.

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 3 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 non-invasive, 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.

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 non-invasive testing ranges from 60-96% 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, non-invasive, sequencing-based testing of maternal serum for fetal trisomy syndromes involves detection of fetal cell-free DNA fragments present in the plasma of pregnant women. As early as 8 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. Massively parallel sequencing (MPS; also known as next generation or “next-gen” sequencing) can be used to design assays for prenatal diagnosis of chromosomal trisomy. DNA fragments are first amplified by polymerase chain reaction (PCR); 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. Alternatively, chromosome-targeted sequencing can be used, which obviates the need for mapping to the reference human genome.

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. Additionally, in a euploid individual with normal chromosome numbers (e.g., the woman from whom the plasma sample was taken), the proportional contribution of DNA sequences per chromosome correlates with the relative size of each chromosome in the human genome. Any detectable difference from the euploid mean for each chromosome of interest is determined for the sample. A predetermined cutoff identifies samples that have abnormal chromosome numbers.

Published studies from all three commercially available tests have consistently demonstrated very high sensitivity and specificity for detecting Down syndrome (trisomy 21) in singleton pregnancies. Seven of the 8 published studies included only women at high-risk of trisomy 21. Direct evidence of clinical utility is not available. Eight studies were included that provided data on the sensitivity and specificity of the final, clinical nucleic acid sequencing-based assay of maternal plasma for trisomy 21 in singleton pregnancies.

Data from the 8 studies consistently reported a very high sensitivity and specificity of maternal plasma DNA sequencing-based tests for detecting trisomy 21 in high-risk women with singleton pregnancies. Only one of these studies included women at average-risk of trisomy 21. Thus, there is sufficient evidence that the tests are accurate when used in women with high-risk pregnancies, but the evidence on women with average-risk pregnancies is insufficient. For women with multiple pregnancies (multiple fetuses), there is insufficient evidence to draw conclusions about the diagnostic accuracy of these tests for detecting trisomy 21.

Based on the available evidence, as well as input from clinical vetting and recommendations from ACOG, nucleic acid sequencing-based testing for trisomy 21 may be considered medically necessary in women with high-risk singleton pregnancies who meet criteria and not medically necessary in women with average-risk singleton pregnancies.

**Medical Criteria:**

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

*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 or
- Fetal ultrasonographic findings indicating increased risk of aneuploidy or,
- History of previous pregnancy with a trisomy or
- Standard serum screening test positive for aneuploidy or
- Parental balanced robertsonian translocation with increased risk of fetal trisomy 13 or trisomy 21.

**Policy:**

*Preauthorization is required for BlueCHiP for Medicare and recommended for all other BCBSRI products.*

Nucleic acid sequencing-based testing of maternal plasma for trisomy 21 may be considered medically necessary in women with *high-risk singleton pregnancies undergoing screening for trisomy 21 when the patient meets the high risk criteria above.*

All other indications are not medically necessary as there is insufficient peer reviewed data to support efficacy.

**Coverage:**

Medicare excludes all screening (not just genetic screening) with certain statutory exceptions. Blue CHiP for Medicare provides no additional benefits for genetic screening. **Only** if the patient exhibits signs or symptoms of the disease would the test not be considered screening.

Benefits may vary between groups and contracts. Please refer to the appropriate Evidence of Coverage, Subscriber Agreement, or Benefit Booklet for applicable benefits/coverage.

**Coding:**

At this time, there is no specific CPT code for this testing. Claims should be submitted using 81599.

**Also known as:**
MaterniT21

**Related Topics:**
First-Trimester Detection of Down Syndrome Using Fetal Ultrasound Assessment of Nuchal Translucency Combined with Maternal Serum Assessment.

**Published:**
Provider Update, June 2013
Provider Update, September 2012
References:


History:

February 2013, Annual Review

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