Medical Policy
Noninvasive Prenatal Testing for Trisomy 21 Using Cell-Free Fetal DNA

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Policy Number: 628
BCBSA Reference Number: 4.01.21

Related Policies
- Down Syndrome Using Fetal Ultrasound Markers Combined with Maternal Serum Assessment, #443

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO BlueSM and Medicare PPO BlueSM Members

Nucleic acid sequencing-based testing of maternal plasma for trisomy 21 may be considered
MEDICALLY NECESSARY in women with high-risk singleton pregnancies as defined by the American
College of Obstetricians and Gynecologists (ACOG) Committee Opinion, December 2012, for 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.

(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.)

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 INVESTIGATIONAL in
women with twin or multiple pregnancies.

Prior Authorization Information
See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.

<table>
<thead>
<tr>
<th>Plan Type</th>
<th>Outpatient</th>
<th>Inpatient</th>
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<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>No</td>
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<td>Commercial PPO and Indemnity</td>
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<td>Medicare HMO Blue™</td>
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<td>Medicare PPO Blue™</td>
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CPT Codes / HCPCS Codes / ICD-9 Codes

The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member. A draft of future ICD-10 Coding related to this document, as it might look today, is included below for your reference.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81507</td>
<td>Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy</td>
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</table>

ICD-9 Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-9 diagnosis codes</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>V23.81</td>
<td>Elderly primigravida</td>
</tr>
<tr>
<td>V23.82</td>
<td>Supervision of high-risk pregnancy of elderly multigravida</td>
</tr>
<tr>
<td>V26.32</td>
<td>Other genetic testing of female</td>
</tr>
<tr>
<td>V28.89</td>
<td>Other specified antenatal screening</td>
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</tbody>
</table>

ICD-9 Procedure Codes

There is no specific ICD-9 procedure code for this service.

ICD-10 Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-10-CM Diagnosis codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>O09.511</td>
<td>Supervision of elderly primigravida, first trimester</td>
</tr>
<tr>
<td>O09.512</td>
<td>Supervision of elderly primigravida, second trimester</td>
</tr>
<tr>
<td>O09.521</td>
<td>Supervision of elderly multigravida, first trimester</td>
</tr>
<tr>
<td>O09.522</td>
<td>Supervision of elderly multigravida, second trimester</td>
</tr>
<tr>
<td>Z31.438</td>
<td>Encounter for other genetic testing of female for procreative management</td>
</tr>
<tr>
<td>Z36</td>
<td>Encounter for antenatal screening of mother</td>
</tr>
</tbody>
</table>

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.

**Background**

Fetal chromosomal abnormalities occur in approximately 1 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 3 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 1/1,500 in young women that increases to nearly 1/10 by age 48. (1)

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. (2) 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 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 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.

Thus, 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.

**Summary**

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. A 2012 TEC Assessment modeled comparative outcomes based on the published data on test performance, published estimates of standard screening performance, patient uptake of confirmatory testing, and miscarriage rates associated with invasive procedures. For each comparison and in each risk population, sequencing-based testing improved outcomes, i.e., increased the rate of Down syndrome detection and reduced the number of invasive procedures and procedure-related miscarriages. In the modeling, the negative predictive value of testing approached 100% across the range of aneuploidy risk, while the positive predictive value varied widely according to baseline risk. The variable positive predictive value highlights the possibility of a false positive finding and thus testing using karyotyping is necessary to confirm a positive result.

Based on the available evidence, including modeling in the TEC assessment, 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.

### Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>7/2014</td>
<td>Title changed to: Noninvasive Prenatal Testing for Trisomy 21 Using Cell Free Fetal DNA.</td>
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<tr>
<td>6/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
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<tr>
<td>2/2014</td>
<td>Coding information clarified</td>
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<tr>
<td>1/2014</td>
<td>Updated to add new CPT code 81507.</td>
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<tr>
<td>7/2013</td>
<td>New medical policy describing coverage and ongoing non-coverage.</td>
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<td></td>
<td>Effective 7/1/2013.</td>
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### Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

### References


