

## Medical Policy



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### Title: Sequencing-based Tests to Determine Trisomy 21 from Maternal Plasma DNA

#### Professional

Original Effective Date: June 10, 2013  
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#### 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.

## 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.
- In March 2012, Verinata Health (Redwood, CA) launched its verifi® prenatal test for trisomy 21, 18, and 13.
- 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.
- Natera (San Carlos, CA) plans to introduce its prenatal test for detecting aneuploidy in late 2012.

## POLICY

- A. 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.)
- B. Nucleic acid sequencing-based testing of maternal plasma for trisomy 21 is considered **not medically necessary** in women with average-risk singleton pregnancies.
- C. Nucleic acid sequencing-based testing of maternal plasma for trisomy 21 is considered **experimental / investigational** in women with twin or multiple pregnancies.

## Policy Guidelines

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:

1. Maternal age 35 years or older at delivery;
2. Fetal ultrasonographic findings indicating increased risk of aneuploidy;
3. History of previous pregnancy with a trisomy;
4. Standard serum screening test positive for aneuploidy; or

5. Parental balanced robertsonian translocation with increased risk of fetal trisomy 13 or trisomy 21.

This policy 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.

## **RATIONALE**

### **Literature Review**

The policy is based on a 2012 TEC Assessment and also includes a search of the MEDLINE database and national practice guidelines/position statements through November 2012. The Assessment focused on detection of trisomy 21/Down syndrome because the majority of published data was concentrated on this trisomy, large numbers of cases were included in several publications, and all companies had published data regarding the detection of trisomy 21. The Assessment also reviewed the available data for detection of trisomy 18 and 13. The TEC Assessment and the policy both limit their scope to the evaluation of tests that are available in the United States.

Assessment of a diagnostic technology such as maternal plasma DNA sequencing tests typically focuses on 3 parameters: 1) analytic validity; 2) clinical validity (i.e., sensitivity and specificity) in appropriate populations of patients; and 3) demonstration that the diagnostic information can be used to improve patient health outcomes (clinical utility). The evidence on these 3 questions, as summarized in the TEC assessment, is described below.

### **What is the analytic validity of the available maternal plasma DNA sequencing-based tests?**

No studies were identified that provided direct evidence on analytic validity. Each of the commercially available tests uses massively parallel sequencing (MPS; also called next generation sequencing), a relatively new technology but not an entirely new concept for the clinical laboratory. Currently, there are no recognized standards for conducting clinical sequencing by MPS. On June 23, 2011, the U.S. Food and Drug Administration (FDA) held an exploratory, public meeting on the topic of MPS, in preparation for an eventual goal of developing "a transparent evidence-based regulatory pathway for evaluating medical devices/products based on NGS [next generation sequencing] that would assure safety and effectiveness of devices marketed for clinical diagnostics." (3) The discussion pointed out the differences among manufacturers' sequencing platforms and the diversity of applications, making it difficult to generate specific regulatory phases and metrics. It was suggested that "the process may need to be judged by the accuracy and fidelity of the final result." A consistent discussion trend was that validation be application-specific. Thus, technical performance may need to be more closely linked to intended use and population and may not be generalizable across all sequencing applications. Each of the companies currently offering a maternal plasma DNA sequencing test for fetal trisomy 21 has developed a specific procedure for its private, CLIA-licensed laboratory where all testing takes place.

#### Conclusions:

Although all currently available commercially available tests use MPS, actual performance and interpretive procedures vary considerably. Clinical sequencing in general is not standardized or regulated by the FDA or other regulatory agencies, and neither the routine quality control procedures used for each of these tests, nor the analytic performance metrics have been published.

### **What is the clinical validity of the available maternal plasma DNA sequencing-based tests for trisomy 21 compared to the gold standard of karyotype analysis?**

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. (4-12) Tests from 3 commercial sources were identified: 2 studies used the Sequenom test, 2 studies used the Verinata test and 4 studies used the Ariosa Diagnostics test. Studies are underway by a fourth manufacturer, Natera. Six studies were entirely prospective, and 2 retrospectively evaluated archived samples. Seven of 8 studies were industry-funded; in the 8<sup>th</sup>, testing was provided gratis.

With one exception, the enrolled study populations included women at increased risk due to increased age and/or standard screening results or because they were already scheduled for amniocentesis or chorionic villous sampling (CVS). Nicolaidis and colleagues evaluated archived samples from women attending their routine first pregnancy visit at 11-14 weeks' gestation. (9) Studies generally included women at a wide range of gestational ages (e.g., 8-36 weeks or 11-20 weeks) spanning first and second trimesters.

The approach to analysis varied. Some studies analyzed samples from all enrolled women and others analyzed samples from all women with pregnancies known to have a trisomy syndrome and selected controls (i.e., nested case-control analysis within a cohort). All studies but one evaluated the results of maternal fetal DNA testing in comparison to the gold standards of

karyotyping or, in individual cases when a sample did not allow karyotyping, fluorescence in situ hybridization (FISH) for specific trisomies. Because they were evaluating an average-risk population, Nicolaides et al. had karyotyping results for only a small percentage of women in their study; for the rest of the enrollees, chromosomal status was determined by phenotype at birth obtained from medical records.

Sample sizes of the studies ranged from 119 to 1,988 patients. These numbers represent the samples analyzed, including euploid controls; in some studies, samples were drawn from larger available cohorts of collected samples. All studies included testing for trisomy 21. Eight studies additionally tested for trisomy 18 and 4 studies additionally tested for trisomy 13. There were fewer cases of T18 (range: 3-59) and T13 (range: 1-14) per study compared to T21. Four studies had 50 or more cases of T21, and one study, Palomaki et al. 2011, (5) had 212 cases.

The sensitivity and specificity estimates of testing for trisomy 21 in singleton pregnancies were uniformly high. The sensitivity ranged from 99.1% to 100%, and the specificity ranged from 99.7% to 100%.

Detection of trisomy 21 in twin pregnancies was systematically evaluated in only one study, published in 2012 by Canick and colleagues; the study used the Sequenom test. (13) All 7 cases of twin pregnancies with Down syndrome were correctly classified. Five of these were discordant, where one twin had T21 aneuploidy and the other did not; 2 were concordant where both twins had T21 aneuploidy.

#### Conclusions:

Data from 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, there is insufficient evidence to draw conclusions about the diagnostic accuracy of these tests for detecting trisomy 21.

#### **What is the clinical utility of the available maternal plasma DNA sequencing-based tests for aneuploidy?**

No comparative studies were evaluated that compared health outcomes in patients managed using the maternal plasma DNA tests compared to standard screening tests.

As part of the 2012 TEC Assessment, a decision model was constructed to model health outcomes of sequencing-based testing for trisomy 21 compared to standard testing. The primary health outcomes of interest included the number of cases of aneuploidy correctly identified, the number of cases missed, the number of invasive procedures potentially avoided (i.e., with a more sensitive test), and the number of miscarriages potentially avoided as a result of fewer invasive procedures. The results were calculated for a high-risk population of women age 35 years or older (estimated antenatal prevalence of T21: 0.95%), and an average risk population including women of all ages electing an initial screen (estimated antenatal prevalence of T21: 0.25%). For women testing positive on initial screen and offered an invasive, confirmatory procedure, it was assumed that 60% would accept amniocentesis or CVS. Sensitivities and specificities for both standard and sequencing-based screening tests were

varied to represent the range of possible values; estimates were taken from published studies whenever possible.

According to the model results, sequencing-based testing improved outcomes for both high-risk and average risk women. As an example, assuming there are 4.25 million births in the U.S. per year (14) and two-thirds of the population of average risk pregnant women (2.8 million) accepted screening, the following outcomes would occur for the 3 screening strategies under consideration:

- Standard screening. Of the 2.8 million screened with the stepwise sequential screen, 87,780 would have an invasive procedure (assuming 60% uptake after a positive screening test and a recommendation for confirmation), 448 would have a miscarriage, and 3,976 of 4,200 (94.7%) trisomy 21/Down syndrome cases would be detected.
- Sequencing as an alternative to standard screening. If sequencing-based testing were used instead of standard screening, the number of invasive procedures would be reduced to 7,504 and the number of miscarriages reduced to 28, while the cases of Down syndrome detected would increase to 4,144 of 4,200 (97.6% of total), using conservative estimates.
- Sequencing following standard screening. Another testing strategy would be to add sequencing-based testing only after a positive standard screen. In this scenario, invasive procedures would be further decreased to 4,116, miscarriages would remain at 28, but fewer Down syndrome cases would be detected (3,948 of 4,200, 94.0% of total).. Thus, while this strategy has the lowest rate of miscarriages and invasive procedures, it detects fewer cases than sequencing-based testing alone.

At least two decision models have also been presented in industry-funded publications, each using a different commercially available test and published estimates of sensitivity and specificity. Findings of both these models are similar to the TEC Assessment model in that detection of T21 is increased and miscarriage rates are decreased using sequencing-based testing compared to standard screening. Both of the studies specifically model use of sequencing-based tests offered to women who have had a positive standard screening test.

Garfield and Armstrong published a study modeling use of the Verinata test. (15) In the model, women were eligible for screening following a positive first-trimester or second-trimester screening test or following a second-trimester ultrasound. The model assumed that 71% of women at average risk and 80% of women at high risk would choose the test. In a theoretical population of 100,000 pregnancies, the detection rate of T21 increased from 148 with standard testing to 170 with verifi® testing. In addition, the number of miscarriages associated with invasive testing (assumed to be 0.5% for amniocentesis and 1% with CVS) was reduced from 60 to 20.

Palomaki and colleagues modeled use of the Sequenom sequencing-based test offered to women after a positive screening test, with invasive testing offered only in the case of a positive sequencing-based test. (4) As in the TEC Assessment, they assumed 4.25 million births in the U.S. per year, with two-thirds of these receiving standard screening. The model assumed a 99% detection rate, 0.5% false positive rate, and 0.9% failure rate for sequencing-based testing. Compared to the highest performing standard screening test, the addition of sequencing-based screening would increase the Down syndrome detection rate from 4,450 to 4,702 and decrease the number of miscarriages associated with invasive testing from 350 to 34.

It is important to note that all of the above models include confirmatory invasive testing for positive screening tests. Sequencing-based testing without confirmatory testing carries the risk of misidentifying normal pregnancies as positive for trisomy. Due to the small but finite false positive rate, together with the low baseline prevalence of trisomy in all populations, a substantial percent of positive results on sequencing tests could be false positive results.

Conclusions:

There is no published direct evidence that managing patients using sequencing-based testing improves health outcomes compared to standard screening. Modeling studies using published estimates of diagnostic accuracy and other parameters predict that sequencing-based testing as an alternative to standard screening will lead to an increase in the number of Down syndrome cases detected and a large decrease in the number of invasive tests and associated miscarriages.

**Ongoing Clinical Trials**

Prenatal Non-invasive Aneuploidy Test Utilizing SNPs [single nucleotide polymorphism] Trial (PreNATUS) (NCT01545674) (16): This is a prospective, blinded study evaluating the diagnostic accuracy of the Natera test for diagnosing aneuploidies (chromosomes 13, 18, 21) and sex aneuploidy (X and Y). It includes women with singleton pregnancies at high or moderate risk for trisomy who were planning on undergoing invasive testing. Gestational age of the fetus is between 8 weeks 0 days and 23 weeks 6 days. The estimated enrollment is 1,000 participants and the expected date of study completion is December 2012.

Non-invasive Chromosomal Examination of Trisomy study (NEXT) (NCT01511458) (17): This is a prospective blinded case-control study comparing the Aria test for trisomy 21 with standard first-trimester prenatal screening (maternal serum testing and nuchal translucency). Cases will consist of patients with trisomy 21 pregnancies confirmed by genetic testing, and controls will consist of patients without trisomy 21 pregnancies, as confirmed by genetic testing or live birth. The study is sponsored by Aria Diagnostics. The estimated enrollment is 25,000 individuals. The expected date of study completion is July 2013.

Comparison of Aneuploidy Risk Evaluations (CARE) (NCT01663350) (18): This prospective observational study is comparing diagnostic accuracy of the Verinata Health prenatal aneuploidy test and conventional non-invasive screening. The study will include all risk levels. Entry criteria include adult women with clinically confirmed pregnancy at gestational age of at least 8 weeks who plan to complete or who have completed prenatal serum screening. The study is sponsored by Verinata Health; expected enrollment is 3,000 women. The expected date of study completion is not available.

Clinical Evaluation of the SEQuReDx T21 Test in Low Risk Pregnancies (NCT01597063) (19): This is a prospective study and includes pregnant women between 10-22 weeks' gestation who are at low risk for trisomy 21 aneuploidy (i.e., no positive prenatal screening tests, and no personal or family history of Down syndrome). Blood samples will be collected at a scheduled prenatal care visit and analyzed with the SEQuReDX T21 test; pregnancies will be followed until the birth outcome is recorded. The study is sponsored by Sequenom; estimated enrollment is 1,600. The expected date of study completion is August 2013.



### **Clinical Input Received through Physician Specialty Societies and Academic Medical Centers**

Input was received through 3 physician specialty societies and 4 academic medical centers in 2012. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

There was consensus that sequencing-based tests to determine trisomy 21 from maternal plasma DNA may be considered medically necessary in women with high-risk singleton pregnancies undergoing screening for trisomy 21. Input was mixed on whether sequencing-based tests to determine trisomy 21 from maternal plasma DNA may be considered medically necessary in women with average-risk singleton pregnancies. An American College of Obstetricians and Gynecologists (ACOG) Genetics Committee Opinion, included as part of the specialty society's input, does not recommend the new tests at this time for women with singleton pregnancies who are not at high-risk of aneuploidy. There was consensus that sequencing-based tests to determine trisomy 21 from maternal plasma DNA are investigational for women with multiple pregnancies. In terms of an appropriate protocol for using sequencing-based testing, there was consensus that testing should not be used as a single-screening test without confirmation of results by karyotyping. There was mixed input on use of the test as a replacement for standard screening tests with karyotyping confirmation and use as a secondary screen in women with screen positive on standard screening tests with karyotyping confirmation. Among the 5 reviewers who responded to the following questions (which did not include ACOG), there was consensus that the modeling approach is sufficient to determine the clinical utility of the new tests and near-consensus there is a not a need for clinical trials comparing a screening protocol using the new tests to a screening protocol using standard serum screening prior to initiation of clinical use of the tests.

### **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.

### Practice Guidelines and Position Statements

In November 2012, the American College of Obstetricians and Gynecologists (ACOG) released a committee opinion on noninvasive testing for fetal aneuploidy. (20) The Committee Opinion was issued jointly with the Society for Maternal-Fetal Medicine Publications Committee. ACOG recommended that maternal plasma DNA testing be offered to patients at increased risk of fetal aneuploidy. They did not recommend that the test be offered to women who are not at high risk or women with multiple gestations. ACOG further recommended that women be counseled prior to testing about the limitations of the test and recommended confirmation of positive findings with CVS or amniocentesis. The document noted that the content reflected emerging clinical and scientific advances and is subject to change as additional information becomes available. The Committee Opinion did not include an explicit review of the literature.

The International Society for Prenatal Diagnosis (ISPD) published a rapid response statement on October 24, 2011 regarding non-invasive tests based on the presence of cell-free fetal nucleic acids in maternal plasma. (21) ISPD considers these tests to be advanced screening tests, requiring confirmation through invasive testing. They further suggest that trials are needed in low-risk populations and in sub-populations such as twin pregnancies and in vitro fertilization donor pregnancies.

The National Society of Genetic Counselors (NSGC) published a position statement on their website regarding noninvasive prenatal testing of cell-free DNA in maternal plasma. (1) The NSGC supports this testing "as an option for patients whose pregnancies are considered to be at an increased risk for certain chromosome abnormalities." They recommend that the test be offered in the context of informed consent and that patients whose results are abnormal be offered standard confirmatory (i.e., invasive) testing.

### **CODING**

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) 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 of these services as it applies to an individual member.**

#### CPT/HCPCS

- |       |  |
|-------|--|
| 81479 | Unlisted molecular pathology procedure   |
| 81504 | Oncology (tissue of origin), microarray gene expression profiling of >2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores ( <i>New code, effective January 1, 2014</i> ) |
| 81507 | 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 ( <i>New code, effective January 1, 2014</i> )                      |
| 81599 | Unlisted multi analyte assay with algorithmic analysis   |

- At this time, there is no specific CPT code for this testing so an unlisted code would be used.
- Effective in 2013, the unlisted Multianalyte Assays with Algorithmic Analyses (MAAA) code 81599 would be used if the test involves an algorithmic analysis. The unlisted molecular pathology code 81479 is available when the test does not involve an algorithmic analysis.
- Effective January 1, 2014, there will be a specific MAAA CPT code for the Ariosa Diagnostics Harmony™ Prenatal Test: 81507 [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].

### ICD-9 DIAGNOSES

V23.81 Elderly primigravida  
 V26.33 Genetic counseling  
 V28.89 Other specified antenatal screening

### ICD-10 Diagnosis (*Effective October 1, 2014*)

O09.511 Supervision of elderly primigravid, first trimester  
 O09.512 Supervision of elderly primigravida, second trimester  
 O09.513 Supervision of elderly primigravida, third trimester  
 O09.519 Supervision of elderly primigravida, unspecified trimester  
 Z31.5 Encounter for genetic counseling  
 Z36 Encounter for antenatal screening of mother

### **REVISIONS**

06-10-2013	Policy added to the bcbsks.com web site on 05-10-2013. Effective on 06-10-2013, 30 days after posting.
06-10-2013	(Posted 06-07-2013) In Coding section <ul style="list-style-type: none"> <li>▪ Added CPT code: 81479</li> <li>▪ Updated Coding information</li> </ul>
12-31-2013	In Coding section: <ul style="list-style-type: none"> <li>▪ Added CPT codes: 81504 and 81507 (<i>New codes, effective January 1, 2014</i>)</li> <li>▪ Added ICD-10 Diagnosis codes (<i>Effective October 1, 2014</i>)</li> </ul> Updated Reference section

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