DNA Sequencing versus Standard Prenatal Aneuploidy Screening

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ABSTRACT

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A complete list of members of the Comparison of Aneuploidy Risk Evaluations (CARE) Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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BACKGROUND

In high-risk pregnant women, noninvasive prenatal testing with the use of massively parallel sequencing of maternal plasma cell-free DNA (cfDNA testing) accurately detects fetal autosomal aneuploidy. Its performance in low-risk women is unclear.

METHODS

At 21 centers in the United States, we collected blood samples from women with singleton pregnancies who were undergoing standard aneuploidy screening (serum biochemical assays with or without nuchal translucency measurement). We performed massively parallel sequencing in a blinded fashion to determine the chromosome dosage for each sample. The primary end point was a comparison of the false positive rates of detection of fetal trisomies 21 and 18 with the use of standard screening and cfDNA testing. Birth outcomes or karyotypes were the reference standard.

RESULTS

The primary series included 1914 women (mean age, 29.6 years) with an eligible sample, a singleton fetus without aneuploidy, results from cfDNA testing, and a risk classification based on standard screening. For trisomies 21 and 18, the false positive rates with cfDNA testing were significantly lower than those with standard screening (0.3% vs. 3.6% for trisomy 21, P<0.001; and 0.2% vs. 0.6% for trisomy 18, P=0.03). The use of cfDNA testing detected all cases of aneuploidy (5 for trisomy 21, 2 for trisomy 18, and 1 for trisomy 13; negative predictive value, 100% [95% confidence interval, 99.8 to 100]). The positive predictive values for cfDNA testing versus standard screening were 45.5% versus 4.2% for trisomy 21 and 40.0% versus 8.3% for trisomy 18.

CONCLUSIONS

In a general obstetrical population, prenatal testing with the use of cfDNA had significantly lower false positive rates and higher positive predictive values for detection of trisomies 21 and 18 than standard screening. (Fundied by Illumina; ClinicalTrials.gov number, NCT01663350.)
NONINVASIVE PRENATAL TESTING performed with the use of massively parallel sequencing of cell-free DNA (cfDNA testing) in maternal plasma came into use in clinical prenatal care in the United States in late 2011. This transition occurred after multiple clinical validation studies all showed high sensitivities, specificities, and negative predictive values for detection of the most common autosomal aneuploidies.\(^1\)\(^-\)\(^9\) Plasma samples for the validation studies were either acquired retrospectively from populations with known karyotypes or collected prospectively from high-risk populations to ensure an adequate enrichment of aneuploid fetal samples for testing. The results of these studies were sufficiently robust to allow the International Society for Prenatal Diagnosis,\(^10\) the National Society of Genetic Counselors,\(^11\) and the American College of Obstetricians and Gynecologists and the Society for Maternal–Fetal Medicine\(^12\) to publish committee opinions stating that cfDNA testing could be offered to pregnant women at high risk for fetal aneuploidy as a screening option after counseling.

With the integration of cfDNA testing into prenatal care for high-risk women, questions surrounding its performance in low-risk pregnant women have emerged. On the basis of studies of small numbers of pregnant women in their own clinics, some private obstetrical practices in the United States have begun to offer cfDNA testing as a primary screening option to all patients in place of the current standard of care (serum biochemical assays with or without measurement of the thickness of fetal nuchal translucency on ultrasonography).\(^13\)

Outside the United States, two larger studies have been conducted in low-risk populations.\(^14\)\(^,\)\(^15\) In one study involving 1741 pregnant women 35 years of age or younger who were undergoing second-trimester serum triple screening for fetal aneuploidy at two clinics in China (with availability of pregnancy outcomes or karyotype), cfDNA testing outperformed standard screening in sensitivity (100.0% vs. 54.5%), specificity (99.9% vs. 85.9%), and positive predictive value (91.7% vs. 2.4%).\(^14\) Another study, which was conducted at a single clinic in the United Kingdom, compared the performance of first-trimester combined screening at 12 weeks’ gestation with cfDNA testing performed at 10 weeks in all women who presented for prenatal evaluation (median maternal age, 36.7 years). These investigators also found that the performance of cfDNA testing was superior to that of standard screening, although outcomes were incomplete for continuing pregnancies at the time of publication.\(^15\)

Although these findings are encouraging, the cited studies examined narrowly defined populations and screening algorithms that do not represent the more complex and variable approaches currently used in the United States. Recently, there have been multiple appeals for evidence concerning the performance characteristics of cfDNA testing and its clinical usefulness in the general obstetric population.\(^16\)\(^,\)\(^17\) Here, we describe the results of the Comparison of Aneuploidy Risk Evaluations (CARE) study, a prospective, blinded, multicenter observational study comparing the results of noninvasive prenatal cfDNA testing for fetal autosomal aneuploidy with the results of conventional screening for trisomy 21 (Down’s syndrome) and trisomy 18 (Edwards’ syndrome) in a general obstetrical population, with outcomes included. The primary objective was the comparison of false positive rates with the use of each method. A secondary end point compared false positive rates for trisomy 13 (Patau’s syndrome) in a subset of pregnant women in whom standard screening results included a risk assessment for trisomy 13. We also compared fetal cfDNA fractions in low-risk patients and those in high-risk patients in the CARE study population to assess the potential effects of demographic differences on test performance.\(^18\)

**METHODS**

**PATIENTS AND DATA COLLECTION**

From July 2, 2012, to January 4, 2013, we enrolled pregnant women who were undergoing routine obstetrical care at 21 medical centers in 14 states. The institutional review board at each institution approved the studies. Written informed consent was obtained from all patients.

To be eligible for the study, pregnant women had to be at least 18 years of age and had to be carrying a fetus with a gestational age of at least 8 weeks. All patients had planned to undergo or had completed standard prenatal serum screening for fetal aneuploidy during the first or second trimester (with or without first-trimester measurement of nuchal translucency). The protocol did not require that the blood sample for cfDNA testing be drawn concurrently with the sample used for standard aneuploidy screening. Results
of cfDNA testing were not returned to either the patients or their practitioners. By these criteria, women beyond the second trimester were eligible for enrollment if standard screening was completed and results were available. The enrollment criteria allowed for invasive prenatal procedures (chorionic villus sampling or amniocentesis) if the procedures were performed at least 2 weeks before plasma samples were obtained for cfDNA testing.

Study inclusion required accessibility to pregnancy and delivery records, such as reports from laboratory screening, fetal ultrasonography, cytogenetic testing, and newborn physical examinations. Site research personnel entered all clinical data in the electronic case-report form; clinical monitors verified the data through a review of source documents.

CLINICAL OUTCOMES

All patients were followed for pregnancy outcomes and categorized as having had a live birth or a nonlive birth or as having been lost to follow-up. For live births, a single, independent, board-certified pediatrician reviewed the medical record of the newborn physical examination that was performed at the hospital where the infant was delivered. The pediatrician then completed a standardized study form and recorded the outcome as affected or not affected for trisomies 21, 18, and 13. In the case of nonlive births for which cytogenetic testing of the products of conception was performed, the cytogenetic report was obtained. For all cytogenetic reports that were generated in accredited laboratories and associated with an invasive procedure or neonatal or products-of-conception testing, an independent, board-certified cytogeneticist reviewed the results and classified each fetus as being affected or not affected for trisomies 21, 18, and 13. These reports were used as the reference standard when available. Otherwise, classification was based on the newborn physical examination.

SAMPLE COLLECTION, SEQUENCING, AND ANEUPLOIDY CLASSIFICATION

At enrollment, study personnel obtained a peripheral venous blood sample (10 ml) in a cfDNA blood-collection tube (Streck); each tube was de-identified and labeled only with a unique bar-code number. Site research personnel entered the study number, date, and time of blood collection in a secure electronic case-report form. Whole-blood samples were shipped from enrollment sites to the Illumina research laboratory (formerly Verinata Health, Redwood City, CA). On receipt, samples were inspected, and cell-free plasma was prepared according to methods that have been described previously. All plasma samples were frozen at −80°C in two aliquots and stored until the time of sequencing. A sample was eligible for analysis if it was received within 5 days after the sample was obtained and contained at least 7 ml of blood. The accessioned sample list was reconciled with the clinical database on an ongoing basis throughout enrollment.

Research personnel at Illumina processed and analyzed all samples according to procedures that have been described previously. All personnel were unaware of clinical data and outcomes. In this study, sequencing libraries were prepared with the use of the Illumina TruSeq DNA Sample Prep Kit, version 2.5, and sequencing (eight samples per lane) was performed with the use of an Illumina HiSeq 2000 instrument that obtained single-end, 25-bp reads. The sequence mapping, tag counting, and methods for estimating the fetal fraction have been described previously. For autosomal aneuploidy of chromosomes 21, 18, or 13, samples with a normalized chromosome value of 4.0 or more were classified as affected, and samples with a normalized chromosome value of 3.0 or less were classified as unaffected. A total of 12 samples with a normalized chromosome value between 3.0 and 4.0 were resequenced with the use of one sample per lane and classified as affected if deeper sequencing showed a normalized chromosome value of 4.0 or more.

ANEUPLOIDY CLASSIFICATION ON STANDARD SCREENING

We used the results of standard prenatal aneuploidy screening with individual risk scores and interpretations produced by accredited clinical laboratories for comparison with the results of cfDNA testing. First-trimester serum markers included pregnancy-associated plasma protein A (PAPP-A) and free beta subunit or total human chorionic gonadotropin (hCG). Second-trimester serum markers included maternal serum alpha-fetoprotein (MSAFP), hCG, unconjugated estriol, and inhibin A. First-trimester serum markers were used in combination with sonographic measurement of fetal nuchal translucency (which was termed “first-trimester combined”) to formulate the risk score. Second-trimester serum values could
be evaluated alone (which was termed “quadruple screening” for all four markers) or in combination with first-trimester results (which was termed “fully integrated” if the first-trimester screening included measurement of serum markers and nuchal translucency, “serum integrated” if the first-trimester screening included only serum markers, or “sequential” if the results of the first-trimester screening were reported before the final report in the second trimester).

Certified genetic counselors who were unaware of the results of cfDNA testing and clinical outcomes reviewed all laboratory reports and entered the data in a separate screening database. Trisomies 21 and 18 were classified as positive or negative for individual risk scores that were higher or lower, respectively, than the cutoff values used by the individual laboratories; results were classified as uninterpretable if they were so designated on the clinical laboratory report. Depending on the type of screening that was performed, the risk classification was determined on the basis of a first-trimester result (first-trimester combined) or a second-trimester result (quadruple, serum integrated, fully integrated, or sequential).

STUDY CONDUCT
The first author wrote the first draft of the manuscript, and all the authors vouched for the accuracy of the data and the fidelity of the study to the protocol and statistical analysis plan (available with the full text of this article at NEJM.org). Clinical and sequencing data were gathered and generated as described below. Two clinical research organizations (SynteractHCR and InClin) were retained for clinical data management and biostatistics services, and all analyses were performed by InClin. All the authors made the decision to submit the manuscript for publication and approved the content.

STATISTICAL ANALYSIS
To be eligible for the primary analysis, each patient was required to have a clinical outcome, the results of cfDNA testing, and an interpretation of the fetal aneuploidy risk from standard screening. Since the primary objective was to compare the false positive rates, the primary analysis excluded all cases of true aneuploidy for each condition tested.

Summary data were reported as frequencies and percentages for categorical data, as frequencies and medians for ordinal data, and as frequencies, means, standard deviations, and median, minimum, and maximum values for quantitative data. We used McNemar’s test to evaluate the statistical significance of the comparison of false positive rates; a P value of less than 0.05 was considered to indicate statistical significance. We used the Clopper–Pearson method to calculate the performance characteristics of the test (sensitivity, specificity, and positive and negative predictive values) and exact 95% confidence intervals. The SAS statistical software package (version 9.2 or higher) was used to provide all summaries, listings, graphs, and statistical analyses.

RESULTS

STUDY PATIENTS
A total of 2052 women with singleton pregnancies were enrolled. Of these, 2042 had an eligible blood sample for sequencing analysis. Ten samples were ineligible because of an insufficient blood volume (seven samples), late receipt (one sample), maternal age younger than 18 years (one sample), or withdrawn consent (one sample) (Fig. 1).

Table 1 shows the demographic characteristics of the study patients. Results from standard aneuploidy screening were incomplete for 39 patients, a deficiency that was discovered during data monitoring. For example, 18 patients had only second-trimester samples of maternal serum alphafetoprotein for assessment of neural-tube defects. The slight difference in the size of the primary series for analyses of trisomy 21 (1909 patients) and trisomy 18 (1905 patients) was due to censoring of data regarding true positive results for each chromosome and uninterprable or missing results on standard screening (Fig. 1). The use of cfDNA testing did not provide a result in 18 of 2042 samples (0.9%); for approximately half these samples, testing failure occurred during cfDNA extraction, and for the other half, failure occurred during sequencing. There were no clear biologic reasons for these testing failures.

In the primary analysis population of 1914 patients, the outcome was determined on the basis of the newborn physical examination in 1857 patients (97.0%) and on the basis of karyotype in 57 patients (3.0%). In the latter group, the karyotype was identified by means of chorionic villus sampling in 10 patients, amniocentesis in 38, testing of the products of conception in 3, and postnatal evaluation in 6.
DNA Sequencing vs. Standard Aneuploidy Screening

Primary Analysis

Results of the primary outcome analysis are shown in Table 2. For trisomies 21 and 18, the false positive rates on cfDNA testing were significantly lower than the rates on standard screening, with false positive results in 6 versus 69 of 1909 patients (0.3% vs. 3.6%, P<0.001) for trisomy 21 and in 3 versus 11 of 1905 patients (0.2% vs. 0.6%, P=0.03) for trisomy 18. These results did not change significantly when the analysis was limited to the subgroup of patients whose blood samples were obtained during the first or second trimester (<27 weeks of gestational age). There was no overlap in the patients who had false positive results with the use of the two methods. The 6 patients who had positive results for trisomy 21 and the 3 patients who had positive results for trisomy 18 on cfDNA testing had negative results on standard screening, and all had live births with normal physical examinations.

A comparison of overall test performance results and 95% confidence intervals is shown in Table 3. The two methods detected all cases of true aneuploidy (5 cases of trisomy 21, 2 cases of trisomy 18, and 1 case of trisomy 13), for an overall negative predictive value of 100% (95% confidence interval [CI], 99.8 to 100). However, specificity was higher with cfDNA testing. The positive predictive values for trisomy 21 were 45.5% (95% CI, 16.7 to 76.6) with cfDNA testing and 4.2% (95% CI, 0.9 to 11.7) with standard screening; for trisomy 18, the positive predictive values were 40.0% (95% CI, 5.3 to 85.3) with cfDNA testing and 8.3% (95% CI, 0.2 to 38.5) with standard screening.

Figure 1. Enrollment and Outcomes for Primary Analysis of False Positive Rates.

Among the 39 patients who did not have a result on standard screening, 2 had fetuses with true trisomy 21 and 1 had a fetus with true trisomy 18. One patient did not have results on either cfDNA testing or standard screening but is counted only once. Of the 1914 patients with samples that underwent primary analysis, 5 were excluded from the trisomy 21 analysis; these patients included 3 with true positivity and 2 with uninterpretable results on standard screening. In the primary analysis for trisomy 18, 9 patients were excluded, including 1 with true positivity, 2 with uninterpretable results on standard screening, and 6 without results on standard screening. The abbreviation cfDNA denotes cell-free DNA, used in massively parallel sequencing of maternal plasma.
SECONDARY ANALYSIS

The secondary analysis of the comparison of false positive results for trisomy 13 showed a trend toward significance (P = 0.059) among 899 patients in whom the standard screening results included a risk assessment for trisomy 13. There was one false positive result for trisomy 13 on cfDNA testing, as compared with six false positive results on standard screening. All the results on standard screening were generated by one clinical laboratory that calculates a combination risk result for trisomies 18 and 13. Among the remaining 1015 patients for whom standard-screening results for trisomy 13 were unavailable, there were two false positive results on cfDNA testing.

In addition to 17 patients with positive results on standard screening who underwent invasive prenatal procedures, 27 patients with negative results on standard screening also elected to undergo an invasive prenatal procedure (chorionic villus sampling in 5 and amniocentesis in 22). All fetal karyotypes were normal, and all results of cfDNA testing were negative for trisomies 21, 18, and 13.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Maternal age — yr</td>
<td>29.6±5.54</td>
</tr>
<tr>
<td>Range</td>
<td>18.0–48.6</td>
</tr>
<tr>
<td>Ethnic group — no. (%)†</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>213 (11.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Race — no. (%)†</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1252 (65.4)</td>
</tr>
<tr>
<td>Black</td>
<td>427 (22.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>140 (7.3)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>16 (0.8)</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>16 (0.8)</td>
</tr>
<tr>
<td>Multiracial or other</td>
<td>63 (3.3)</td>
</tr>
<tr>
<td>Body-mass index‡</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>28.7±6.96</td>
</tr>
<tr>
<td>Median</td>
<td>27.4</td>
</tr>
<tr>
<td>Range</td>
<td>15.5–59.0</td>
</tr>
<tr>
<td>Maternal medical history — no. (%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>38 (2.0)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>72 (3.8)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>9 (0.5)</td>
</tr>
<tr>
<td>Other autoimmune disorder</td>
<td>19 (1.0)</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>23 (1.2)</td>
</tr>
<tr>
<td>First pregnancy — no. (%)</td>
<td>1299 (67.9)</td>
</tr>
<tr>
<td>Pregnancy by assisted reproductive techniques — no. (%)</td>
<td>66 (3.4)</td>
</tr>
<tr>
<td>Gestational age at time of testing — wk</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>20.3±8.6</td>
</tr>
<tr>
<td>Median</td>
<td>17.4</td>
</tr>
<tr>
<td>Range</td>
<td>8.0–39.4</td>
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</tbody>
</table>
For samples drawn in the first and second trimesters, the estimated mean fetal fraction (the mean percentage of free fetal DNA in maternal plasma) in patients who were 35 years of age or older, who had positive results on standard screening, or both (putative high-risk features, accounting for 20% of the samples) was almost identical to that for patients who were younger than 35 years of age, who had negative results on standard screening, or both (putative low-risk features), with rates of 11.3% and 11.6%, respectively. The fetal fraction was increased (mean, 24.6%) among patients who provided a blood sample in the third trimester, a finding that was consistent with study results that have been reported previously.\(^{21}\)

**DISCUSSION**

We found that the performance of noninvasive prenatal testing with cfDNA in a general obstetric population that was representative of women seen in contemporary clinical practice in the United States was equivalent to its previously demonstrated performance in high-risk pregnant women. The patients in our study were mostly at low risk for aneuploidy; the mean maternal age was 29.6 years, and for most of the women, it was a first pregnancy and a spontaneous conception. In the primary analysis comparing cfDNA testing with standard aneuploidy screening for trisomies 21 and 18, the results showed a significant reduction in the false positive rates with cfDNA testing. Furthermore, the positive predictive value for cfDNA testing was significantly higher than that for standard screening, for both trisomy 21 (45.5% vs. 4.2%) and trisomy 18 (40.0% vs. 8.3%), within confidence limits determined by the sample size. These findings are consistent with performance expectations for screening in a population with a reduced prevalence of fetal aneuploidy. They may represent a worst case scenario, because the false positive rate for trisomy 21 in our study was slightly higher than that reported by the Illumina clinical laboratory previously.\(^{19}\) Furthermore, the similarity of the fetal-fraction distribu-
discordant cases, findings that are undergoing confined placental mosaicism) in six of the nine explanations (maternal copy-number variation or laboratory showed evidence of potential biologic sequent bioinformatics analysis of the sequencing mother cannot be absolutely confirmed. Sub-
somy 21 are not detected by standard screening, tive results detected by either method. However, the number of truly affected fetuses in this cohort prevented an accurate assessment of the sensitiv-
tive screening result.
reduction of 89% in the number of diagnostic invasive procedures required to confirm a posi-
tive result.
Our study was not designed to compare the sensitivities of the different approaches. The small numbers of truly affected fetuses in this cohort prevented an accurate assessment of the sensitiv-
ity of the two methods. There were no false negative results detected by either method. However, the literature suggests that 4 to 19% of cases of tri-
somy 21 are not detected by standard screening,22 and there have been case reports describing false negative results obtained on cfDNA testing.15,23
For the nine false positive results obtained on cfDNA testing in our cohort, no follow-up studies of placental cytogenetic features, cord-blood karyotypes, or maternal karyotypes were performed, so the presence of confined placental mosaicism24,25 or mosaicism in the newborn or the mother cannot be absolutely confirmed. Sub-
sequent bioinformatics analysis of the sequencing data at higher resolution than is currently used in the Clinical Laboratory Improvement Amendments laboratory showed evidence of potential biologic explanations (maternal copy-number variation or confined placental mosaicism) in six of the nine discordant cases, findings that are undergoing additional analyses. The positive predictive values of cfDNA testing (45.5% for trisomy 21 and 40.0% for trisomy 18) underscore the need for follow-up diagnostic testing to confirm true positive results before decisions are made about irre-
vocable clinical intervention and to resolve discordant results.
The strengths of this study include its pros-
ppective, blinded design, the collection of samples from 21 different U.S. sites, the racial and ethnic diversity of the patients, the availability of complete clinical follow-up, the inclusion of standard screening methods performed in a va-
riety of ways that reflect current U.S. practice, and the performance of the analysis by an independent biostatistician. The weaknesses include a relatively small number of true positive results for determining test sensitivity and the need to base the outcome data mainly on clinical exami-
nations. In addition, 28.5% of the results of cfDNA testing were obtained in the third trimester. Since the fetal fraction increases with gesta-
tional age,21 this factor may have contributed to the improved performance of cfDNA testing. How-
ever, exclusion of the samples drawn in the third trimester did not have a significant effect on the false positive rates. Finally, 0.9% of cfDNA tests did not provide results. Although this rate of failure is lower than rates in other studies of DNA testing, the possibility of test failure should be discussed during pretest counseling.
In conclusion, our head-to-head comparison showed that noninvasive prenatal cfDNA testing performed better than standard screening meth-
ods, with an improvement by a factor of 10 in the positive predictive value for trisomy 21 in our predominantly low-risk patient population. The major advantage of using cfDNA testing was the reduction in rates of false positive results. A con-

<table>
<thead>
<tr>
<th>Screening Method</th>
<th>Primary Analysis for All Trimesters (N = 1909)</th>
<th>Analysis for First and Second Trimesters Only (N = 1365)</th>
<th>Secondary Analysis for All Trimesters (N = 899)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cfDNA testing — no. (%)</td>
<td>6 (0.3) 3 (0.2) 4 (0.3) 2 (0.1) 1 (0.1)</td>
<td>69 (3.6) 11 (0.6) 51 (3.7) 11 (0.8) 6 (0.7)</td>
<td>&lt;0.001 0.03 -0.001 0.01 0.06</td>
</tr>
</tbody>
</table>

* The abbreviation cfDNA denotes cell-free DNA used in massively parallel sequencing of maternal plasma.
consideration of cost-effective ways to incorporate cfDNA testing into general obstetrical practice.26 Is beyond the scope of this study. Our findings, however, suggest that cfDNA testing merits serious consideration as a primary screening method for fetal autosomal aneuploidy.

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Dr. Bianchi reports receiving fees for serving on an advisory board from Illumina; Dr. Das, receiving consulting fees from Illumina through her employer, InClin; and Dr. Chudova, Ms. Devers, Dr. Jones, Ms. Oliver, Dr. Rava, and Dr. Sehnert, being employees of Illumina. Dr. Chudova reports holding a pending patent related to normalizing chromosomal abnormalities by massively parallel DNA sequencing of cell-free fetal DNA from maternal blood: a study in a clinical setting. Am J Obstet Gynecol 2011;204(3):e1-205.


References


DNA SEQUENCING VS. STANDARD ANEUPLOIDY SCREENING


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