OBSTETRICS

# Impact of noninvasive prenatal testing in regionally dispersed medical centers in the United States

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**OBJECTIVE:** Noninvasive prenatal testing using cell-free DNA is a new alternative to screen for common fetal aneuploidies. It is not known what impact regional location may play on noninvasive prenatal testing implementation and downstream invasive prenatal procedure use in the United States.

**STUDY DESIGN:** Six different regionally based centers collected data on noninvasive prenatal testing indication and results between February and November 2012, as well as their invasive prenatal procedure rates before and after offering noninvasive prenatal testing. Statistical analyses were performed using the 2-proportion Z-test.

**RESULTS:** Of 1477 patients who underwent noninvasive prenatal testing; 693 (47%) were from centers in the West; 522 (35.3%) from centers in the East; and 262 (17.7%) from 1 center in the Midwest. Statistically significant differences were observed between West Coast and nonWest Coast sites for gestational age (14.1 weeks; $P \leq .0001$). Advanced maternal age (AMA-only) was the most frequent indication in 5 of 6 sites (range, 21.8—62.9%) A total of 98 invasive prenatal procedures performed on 94 (6.4%) patients of which 64 (65.3%) were performed at centers in the West. More invasive procedures were performed following negative noninvasive prenatal testing results (n = 61) than abnormal noninvasive prenatal testing results (n = 30). The overall rate of patients undergoing invasive procedure after an abnormal noninvasive prenatal testing result was 32.6% (30 of 92). All 6 centers reported a decrease in invasive procedure volume after noninvasive prenatal testing introduction.

**CONCLUSION:** This study demonstrates differences in clinical implementation of noninvasive prenatal testing across regionally dispersed centers in the United States, suggesting patient demographics and views toward prenatal testing influence use as well as downstream management.

**Key words:** noninvasive prenatal test, regional implementation

**Cite this article as: Platt LD, Janicki MB, Prosen T, et al. Impact of noninvasive prenatal testing in regionally dispersed medical centers in the United States. Am J Obstet Gynecol 2014;211:368.e1-7.**

For many years, amniocentesis and chorionic villus sampling (CVS) have been offered to women at increased risk for fetal aneuploidy, in particular, those of advanced maternal age (AMA, ≥35 years at delivery). The paradigm of prenatal screening for fetal trisomy 21 (T21) and trisomy 18 (T18) has shifted over the past few decades with the combination of maternal serum analyte screening in conjunction with measurement of the fetal nuchal translucency (NT) thickness in the late 1990s as ultrasound resolution improved.[1] These advancements in aneuploidy screening options have been shown to cause a reduction in rates of invasive prenatal testing.[2-5]

In October 2011, noninvasive prenatal testing (NIPT) using cell-free DNA (cfDNA) became clinically available for the detection of T21[6] and subsequently expanded to include analysis of chromosomes 13, 18, X and Y.[7-10] Statements from professional medical organizations supporting the use of NIPT for patients at increased risk of aneuploidy rapidly

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Received Oct. 23, 2013; revised Jan. 17, 2014; accepted March 31, 2014.

L.D.P. received an honorarium for his role on the Illumina Clinical Advisory Board. M.B.J., T.P., and J.A. are reimbursed for their activities on the IlluminaSpeakers Bureau. A.J.S. and H.L.S. are employees of and W.L. is a consultant of Illumina. The remaining authors report no conflict of interest.

This investigator-initiated work was funded by Illumina (formerly Verinata Health); project grant number IS-VER-0001.

Reprints will not be available from the authors.

0002-9378/$36.00 •  • http://dx.doi.org/10.1016/j.ajog.2014.03.065

followed.[11-15] By late 2012, NIPT was regarded as the "most effective aneuploidy screening method for pregnant women" in a Committee Opinion by the American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine.[14] Indications for NIPT cited in the ACOG opinion and other statements include AMA, fetal ultrasonographic findings associated with increased risk of aneuploidy, history of prior pregnancy with trisomy, positive result for aneuploidy by conventional screening methods, or parental balanced robertsonian translocation. All statements also recommend pre- and posttest counseling as well as diagnostic confirmation of positive results.[11-15]

Simultaneous with development of these initial recommendations, early adopters, including general obstetricians and maternal-fetal sub-specialists made clinical decisions for their own practices exactly how and for whom to offer NIPT. The impact of these decisions has not been widely studied. One study to assess the impact of NIPT introduction on uptake of first trimester screening and invasive prenatal testing, at the University of Texas Health Center, Houston, TX, witnessed statistically significant decreases of 33% and 50%, respectively, in patients referred between 14-22 weeks' gestation.[16] Another study at Stanford University, Palo Alto, CA, of patients with a positive aneuploidy screen who were offered NIPT also found a significant decrease in diagnostic testing of 17%.[17] The current study aimed to evaluate and compare the indications for NIPT and impact of results on downstream management as well as invasive procedure rates across 6 regionally dispersed US locations.

## Materials and Methods

Retrospective, deidentified clinical data from pregnant women who underwent NIPT through Illumina Laboratory (formerly Verinata Health) from Feb. 15, 2012, through Nov. 15, 2012, at 6 US medical centers (3 of which have multiple clinic locations) was collected by trained study coordinators on a standardized case report form. Participating centers were early adopters of NIPT from various locations (California [n = 2], Nevada, Minnesota, Virginia, and Connecticut). Before the introduction of NIPT into practice, all centers used standard forms of first and/or second trimester prenatal screening (eg, first trimester combined, integrated or sequential screening) as recommended by the 2007 ACOG guideline.[14] Trained genetic counselors and/or maternal-fetal medicine specialists presented NIPT as an additional screening option and provided pre- and posttest counseling to their patients. The study protocol was approved by Chesapeake Institutional Review Board and a waiver for collection of informed consent and authorization for use and release of deidentified clinical information from patient charts was granted. Three of 6 centers obtained an additional approval from their local institutional institutional review board.

Study-site coordinators reviewed relevant clinical records for specific data elements pertaining to the study. Completed case report forms were returned to the central clinical research team at Illumina for double data entry into a custom study database (Microsoft Access, Redmond, WA). The following data was collected: maternal age and gestational age at time of NIPT, pretest indications, prenatal screening results (biochemical screening with or without NT measurement), medical history relevant to the pregnancy (eg, maternal diabetes, hypertension, thrombophilia), NIPT test results, prenatal invasive procedure indications, and cytogenetic results, if performed, and pregnancy outcome if known. Finalized datasets were exported into a Microsoft Excel file for further analysis and generation of tables. Each site was also asked to collect overall rates of CVS and amniocentesis procedures for their practice for 1 year before the introduction of NIPT and for the year following its introduction. Data was provided by centers in 1 of 3 ways: billing statistics (n = 3), laboratory accessioning (n = 1), or an internal physician database (n = 2).

All tests had been processed at the College of American Pathologists–accredited, Clinical Laboratory Improvements Amendments–licensed, Illumina clinical laboratory in Redwood City, CA. NIPT by massively parallel sequencing of cfDNA was performed and results reported as described by Futch, et al.[18] Samples received before July 2, 2012, were classified for aneuploidy status of chromosomes 21, 18, and 13. For chromosomes 21, 18, and 13, the sequencing laboratory classified the sample in 1 of 3 ways: aneuploidy detected, no aneuploidy detected, or unclassifiable (borderline value). On or after July 2, 2012, an additional testing option for Monosomy X (MX) became available for indication of cystic hygroma. For the MX option, the classification was either MX detected or MX not detected. Unclassified was not a result option for MX. Laboratory cancellations of tests were due to either administrative reasons or technical reasons. Providers were notified if a result was cancelled and offered the option to submit a second sample.

The 3 sites located in the west were grouped together as were the 2 sites in the east. Both groups were compared with each other and with the site located in the Midwest. Summary statistics were used for demographic variables. Data comparisons between the 3 groups were performed using the 2-proportion Z-test to calculate *P* values.

## Results

Data forms for 1490 patients were returned of which 1477 comprised the analysis cohort for this study. Thirteen cases were excluded because they were marked twin gestation for which the test was not indicated during the time of testing. NIPT results were reported by the laboratory for 1455 (98.5%) patients, of which 51 (3.5%) showed aneuploidy detected for chromosome 21 (n = 26), 18 (n = 10), 13 (n = 9), or MX (n = 6). An unclassifiable result was reported in 41 (2.8%). There were 10 (0.7%) tests cancelled because of administrative reasons (insufficient quantity [n = 6], duplicate order [n = 1], patient or physician request [n = 1], compromised sample in transit [n = 1] and improper labeling [n = 1]). Twelve samples (0.8%) were cancelled because of technical reasons; excessive DNA