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# ATTITUDES TOWARD AND UTILIZATION OF NON-INVASIVE PRENATAL TESTING FOR CHROMOSOME ANEUPLOIDY AMONG OB/GYNS

Jessica Davis

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# ATTITUDES TOWARD AND UTILIZATION OF NON-INVASIVE PRENATAL TESTING FOR CHROMOSOME ANEUPLOIDY AMONG OB/GYNS

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Prenatal diagnosis is traditionally made via invasive procedures such as amniocentesis and chorionic villus sampling (CVS). However, both procedures carry a risk of complications, including miscarriage. Many groups have spent years searching for a way to diagnose a chromosome aneuploidy without putting the fetus or the mother at risk for complications. Non-invasive prenatal testing (NIPT) for chromosome aneuploidy became commercially available in the fall of 2011, with detection rates similar to those of invasive procedures for the common autosomal aneuploidies (Palomaki et al., 2011; Ashoor et al. 2012; Bianchi et al. 2012). Eventually NIPT may become the diagnostic standard of care and reduce invasive procedure-related losses (Palomaki et al., 2011). The integration of NIPT into clinical practice has potential to revolutionize prenatal diagnosis; however, it also raises some crucial issues for practitioners. Now that the test is clinically available, no studies have looked at the physicians that will be ordering the testing or referring patients to practitioners who do. This study aimed to evaluate the attitudes of OB/GYN's and how they are incorporating the test into clinical practice.

Our study shows that most physicians are offering this new, non-invasive technology to their patients, and that their practices were congruent with the literature and available professional society opinions. Those physicians who do not offer NIPT to their patients

would like more literature on the topic as well as instructive guidelines from their professional societies. Additionally, this study shows that the practices and attitudes of MFMs and OBs differ. Our population feels that the incorporation of NIPT will change their practices by lowering the amount of invasive procedures, possibly replacing maternal serum screening, and that it will simplify prenatal diagnosis. However, those physicians who do not offer NIPT to their patients are not quite sure how the test will affect their clinical practice.

From this study we are able to glean how physicians are incorporating this new technology into their practice and how they feel about the addition to their repertoire of tests. This knowledge gives insight as to how to best move forward with the quickly changing field of prenatal diagnosis.

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# BACKGROUND

## Introduction

There have been many advances in prenatal diagnosis in the last 50 years. Initially, chromosome abnormalities like Down syndrome were diagnosed using an invasive procedure, amniocentesis. An additional procedure, the chorionic villus sampling (CVS), was developed in order to diagnose abnormalities earlier in pregnancy. Since then, both tests have become the standard of care in the prenatal diagnosis of chromosome abnormalities. In an effort to identify affected pregnancies and decrease the amount of unnecessary invasive procedures, methods have been developed to evaluate a pregnancy utilizing the levels of certain analytes in maternal serum and ultrasound technology. More recently a new technology, non-invasive prenatal testing (NIPT), allows for the identification of affected pregnancies through cell-free fetal DNA isolated from maternal serum. This development has the potential to revolutionize the world of prenatal diagnosis. Our study aims to determine how obstetricians and gynecologists (OB/GYNs) are incorporating NIPT into their clinical practice as well as what their attitudes are regarding this new development.

## Prevalence

Aneuploidy is a common type of chromosome abnormality, defined as having an extra or missing chromosome(s). Down syndrome (Trisomy 21), Patau syndrome (Trisomy 13), Edwards syndrome (Trisomy 18), and Turner syndrome (Monosomy 45) are the most common live born aneuploidies. These chromosome abnormalities are compatible with life

but cause varying levels of morbidity and are identified in 0.65% of all newborns (Milunsky & Milunsky, 2009). Many sex chromosome aneuploidies are also compatible with life, but not as common as those listed above. Additionally, aneuploidies for the other autosomes have been identified in products of conception but are not compatible with life. Chromosome abnormalities have been identified in greater than 50% of clinically recognized early pregnancy losses (Gardner & Sutherland, 2004). Out of all stillbirths and neonatal deaths, 6-11% of these fetuses have an aneuploidy (Alberman & Creasy, 1977).

**Invasive Diagnostic Testing**

The first diagnosis of trisomy 21, or Down syndrome, was made via amniocentesis in 1968 (Valenti, Schutta, & Kehaty, 1968). Further developments allowed the utilization of the amniocentesis procedure to enable health care providers to test levels of alpha fetoprotein (AFP) to screen for neural tube defects, conduct metabolic studies, and perform chromosome analysis on fetuses during the second trimester of pregnancy. In the 1980's, some physicians began using CVS as an alternative to amniocentesis (Lippman et al., 1992). The amniocentesis detects fetal aneuploidy >99% of the time, and CVS detects the same anomalies at a detection rate of >98% but does so in the first trimester. However, both procedures are invasive and carry a risk of complications. These complications can include spotting and cramping, infection, fluid leakage, and miscarriage. According to the American Congress of Obstetricians and Gynecologists (ACOG), the rate of miscarriage following amniocentesis or CVS is 1/300-1/500 ("ACOG Practice Bulletin No. 77: Screening for fetal chromosomal abnormalities," 2007; Eddleman et al., 2006).

## Prenatal Screening

Due to the risks associated with amniocentesis and CVS, various screening methods were developed to identify women who have an increased risk to have a pregnancy with certain chromosome aneuploidies. Since there is a well-established association between advanced maternal age (AMA), i.e. being ≥35 years old, and Down syndrome, maternal age was the original "screening" tool (Hook, 1981). It was then noted that pregnancies affected with Down syndrome had decreased levels of maternal serum AFP during the second trimester (Merkatz et al., 1984). Additional markers have since been added and combined with maternal age to provide a risk assessment for certain conditions. Over the last 30 years, prenatal screening has expanded to provide a risk assessment for the common chromosome aneuploidies: trisomy 21, 18, and 13 and can be performed in both the first and second trimesters. The goal of prenatal screening is to identify the largest number of affected pregnancies (true positive screen) and minimize the amount of unaffected women told they are at risk (false positive screen); however, unaffected women are worried every day by positive screening tests (Ormond, 1997).

### *First Trimester Screening*

In the first trimester screen, the fetal nuchal translucency (NT) is measured and combined with the biochemical markers, pregnancy-associated plasma protein A (PAPP-A) and beta human chorionic gonadotropin (b-hCG), in order to provide a likelihood that the fetus has Down syndrome or Trisomy 18 and is performed between 9 and 14 weeks gestation (Wapner et al., 2003). Some labs will also provide a risk number for Trisomy 13. The detection rate for Down syndrome is 82-87% with a false positive rate of 5% (Malone et

al., 2005). The test detects 91-96% of cases of Trisomy 18/13, likely due to an increased nuchal translucency measurement (Malone et al., 2005; Spencer et al., 2000).

*Second Trimester Maternal Serum Screening*

Second trimester screening, most commonly called the "quadruple" screen, is performed between 15 and 22 weeks gestation and utilizes 4 analytes in maternal serum; AFP, hCG, unconjugated estriol (uE3), and dimeric inhibin A (DIA). Characteristic patterns of the analytes combined with maternal age enable the laboratories to assign a risk to the pregnancy for fetal aneuploidy. Levels of maternal serum AFP also assist in the detection of open neural tube defects like spina bifida. The test has a detection rate of 80% for Down syndrome, and 60-75% for Trisomy 18 with a false positive rate of 5% (Malone et al., 2005).

*Combined First and Second Trimester Maternal Serum Screening*

Some screening methods involve combining both first and second trimester serum analytes and ultrasound markers in order achieve higher detection rates and lower false positive rates. Depending on the method used, the detection rate for Down syndrome and Trisomy 18 is as high as 96% (Malone, 2005; Wald, 2004). However, since this method requires that the patient return for multiple visits, it may not be the best option for everyone.

*Second Trimester Ultrasound*

In addition to maternal serum markers, ultrasound is also used as a tool to screen pregnancies for possible chromosome aneuploidy. The full anatomy scan, or genetic sonogram in the second trimester can be used to support and/or adjust serum screening results, or on its own as a screening method (Bromley et al., 2002). This ultrasound is ideally performed between 18 and 21 weeks gestation. The scan can detect 59-87% of the

cases of Down syndrome, and 83-100% of the cases of Trisomy 13 and 18, (Breathnach, Fleming, & Malone, 2007).

## Non-invasive Prenatal Testing

For some women who are flagged as having a higher risk for an abnormality based on advanced maternal age or maternal serum screening, an ultrasound may be enough to allay their fears, but for others the only way to lower their anxiety is the assurance only an invasive diagnostic procedure can give. This choice, however, puts the pregnancy at risk for miscarriage. For some women the risk of miscarriage is worth the knowledge and/or comfort the information gained can provide, but for others no amount of risk is ever worth the chance of losing a pregnancy. For this reason, groups have spent years searching for an alternative; looking for a way to diagnose a chromosome aneuploidy without putting the fetus or the mother at risk for complications.

### *Cell-Free Fetal DNA*

It is traditionally taught that the placenta is an impermeable barrier between mother and fetus, but it is now known that intact fetal cells and cell-free fetal nucleic acids circulate in maternal blood. Studies have shown that it is possible to use intact fetal cells in maternal blood to identify genetic mutations or abnormalities; however intact cells have a long half-life and could be present from previous pregnancies, and the number of fetal cells in maternal circulation is too low to be clinically applied (Bianchi, 2004). Researchers then discovered that cell-free fetal DNA circulates in maternal blood and that these fragments can be amplified by polymerase chain reaction (PCR) to identify fetuses with abnormalities (Lo et al., 1997). Since it is estimated that the half-life of cell-free fetal DNA is 16.3 minutes, a

previous pregnancy would not affect the results of another (Lo et al. 1999). After this discovery, non-invasive tests were developed to determine fetal sex and Rh status (Bianchi, 2004). Now the focus has shifted to using the technology to identify fetuses with chromosome aneuploidy.

Methods have been developed to identify fetal DNA within maternal blood and assess chromosome dosage (Chiu et al., 2008). One of the main methods used is massively parallel shotgun sequencing (MPSS), which includes the sequencing of the first 36bp of DNA segments in maternal plasma and aligning these segments to their chromosome of origin. The sequences for each chromosome are then counted and expressed as a percentage of unique sequences mapped to that particular chromosome out of all unique sequences that were counted. A chromosome z-score is tabulated for each chromosome. If a fetus has an aneuploidy, the z-score will be higher for that chromosome than for a euploid fetus (Chiu et al., 2008). Due to the increase in the number of samples per run and potential to decrease costs, this new technology appears clinically practical.

*Available Commercial Testing*

The goal of non-invasive prenatal testing (NIPT) is to rival the sensitivity and specificity of current invasive diagnostic methods without the risk of complications intrinsic to those invasive procedures. NIPT for Down syndrome became commercially available in November 2011, and currently there are multiple laboratories offering the test. NIPT has been validated for use in detecting Down syndrome, Trisomy 18, Trisomy 13, Turner syndrome in the presence of a cystic hygroma on ultrasound between 10 and 22 weeks gestation (Palomaki et al., 2011; Palomaki et al., 2012; Ashoor et al. 2012; Bianchi et al. 2012; Norton et al., 2012). Most commercial labs quote detection rates of 99-100% for

Down syndrome, 97-100% for Trisomy 18, and 79-92% for Trisomy 13; FPR <1%. The use of NIPT has been studied in twin gestations; however the sample size was small (Canick et al., 2012).

It has been proposed that NIPT will become the diagnostic standard of care; however, the test is still considered a screen at this time. Palomaki et al. (2011) recommend confirmatory invasive diagnostic testing following a positive result. In addition, they estimate that the implementation of NIPT into the current screening practices will lower the cost of diagnostic testing and reduce procedure-related losses associated with invasive prenatal diagnosis by 96% (Palomaki et al., 2011).

## Current Guidelines

*National Society of Genetic Counselors Practice Guidelines, 2012*

Guidelines from the National Society of Genetic Counselors (NSGC) bring attention to the fact that the studies performed so far validate NIPT for use in high-risk populations including advanced maternal age, positive screening test, abnormal ultrasound suggestive of an aneuploidy, or prior pregnancy resulting in an aneuploidy. In addition, it is recommended that a positive NIPT result is followed by a diagnostic procedure in order to confirm the finding. If NIPT is performed, no further serum screening is necessary (Wilson et al., 2012).

*National Society of Genetic Counselors Position Statement, 2012*

NSGC supports NIPT as a screening test for those at increased risk to have a pregnancy affected by a chromosome aneuploidy as long as the test is offered with informed consent which includes appropriate testing and counseling about the benefits and limitations

of NIPT. It is also the recommendation of NSGC that women who receive a positive NIPT result be counseled and given the opportunity to pursue confirmatory diagnostic testing (NSGC, 2012).

*International Society for Prenatal Diagnosis Policy Statement, 2011*

The International Society for Prenatal Diagnosis (ISPD) acknowledges that the use of NIPT can be helpful for those women at increased risk to have a fetus affected by a chromosome abnormality as determined by previously recommended screening methods, but does not support utilizing NIPT in low risk pregnancies. The society also states that genetic counseling is needed to discuss benefits and limitations prior to informed consent (ISPD, 2011)

*American Congress of Obstetrics and Gynecologists Committee Opinion, 2012*

ACOG opinion states that patients at an increased risk for aneuploidy can be offered NIPT but that cell free fetal DNA testing should not be included in routine screening, nor should it be ordered without patient consent and appropriate pretest counseling. Additionally, patients with positive results should be referred for genetic counseling and offered invasive testing for confirmation (ACOG, 2012).

**Study Significance**

The integration of NIPT into clinical practice has the potential to revolutionize prenatal diagnosis; however, it also raises some crucial issues for prenatal healthcare providers and genetic counselors (GC) alike. A few studies have been published about public attitudes regarding NIPT. Kooij, Tymstra, and van den Berg (2009) found that women feel positively about the possibilities of NIPT, but may not fully understand its

impact on their individual pregnancies and the prenatal testing arena as a whole. Although studies are currently underway regarding the attitudes of genetic counselors, none have looked at the physicians that will be ordering the testing or referring patients to practitioners who do. Obstetricians and/or gynecologists (OB/GYNs) are in a position to identify those women who are at risk and might benefit from this new technology. It is important to know what physicians think of NIPT and how they are integrating this new technology into their practice.

*Objective*

Through this study, we aim to evaluate the attitudes of OB/GYNs and how they are incorporating the test into clinical practice.

# MATERIALS AND METHODS

## Study Design

This study was conducted by way of an online questionnaire in order to determine the attitudes toward and current utilization of NIPT in the practices of OB/GYNs. The aims of this study were to:

1. Determine if and how OB/GYNs are using the test in clinical practice.
2. Determine OB/GYNs attitudes about the test.

## Hypothesis

OB/GYNs are not utilizing NIPT for fetal chromosome aneuploidy in clinical practice, and are not comfortable with the testing.

## Study Approval

The study was approved on June 20, 2012 by the Institutional Review Board at the University of Texas Health Science Center at Houston Graduate School of Biomedical Sciences (IRB# HSC-MS-12-0330).

## Study Population

The study population consisted of 5,000 practicing OB/GYNs and maternal fetal medicine specialists (MFMs). The list of physician email addresses and other relevant practice information was compiled and verified by SK&A Information Services. Natera

purchased a nation-wide targeted list from SK&A which contains email addresses for 5,000 practicing OB/GYNs or MFMs who ordered CVS and/or amniocentesis in 2011-2012.

**Questionnaire**

A questionnaire (Appendix A) was created in order to assess a nation-wide sample of OB/GYN's. A review of the literature did not identify a questionnaire specifically evaluating the attitudes toward and utilization of NIPT in the practices of OB/GYN's. Therefore, an instrument was created and reviewed by the committee members through several phases to ensure that it was clearly worded and appropriately structured to gather the desired information. Experts within the fields relevant to the questionnaire reviewed the survey in order to assess content and validity.

A cover letter explaining the nature of the study was included in each survey. This letter served as the consent document (Appendix B). Through the cover letter, physicians were informed of the incentive for the study; a $1 donation would be made to the March of Dimes for every completed survey received. Participation in the survey served as consent.

The questionnaire consisted of 22-28 questions (depending on the clinician's prior experience with NIPT) and took less than 15 minutes to complete. The instrument was composed of multiple-choice, yes or no, Likert scale, and short answer questions, as well as statement agreements. There were three main sections: (1) demographics, (2) utilization of NIPT in clinical practice, and (3) attitude toward NIPT.

1. Demographics: This section consisted of 11 questions to ascertain gender, areas of certification, years since completing residency, area of practice, practice setting, and

number of increased-risk patients seen per week among the respondents. Questions in this section were multiple choice and free response where applicable.

2. Utilization of NIPT in clinical practice: This section was divided based on the utilization of NIPT in clinical practice. The first question evaluated whether or not the participant currently uses NIPT in their practice. If so, the participant answered 11 questions evaluating which patients are offered NIPT, what factors play a role in offering the test, and how the physician responds to the results of the test. If the participant does not offer NIPT in their practice, he/she answered 4 questions regarding what factors influence the decision not to offer the test, how the physician would respond if a patient requested NIPT, and if he/she plans on incorporating NIPT into their practice in the future. Questions in this section were multiple choice (some limited to one response while others were open to several responses), and free response were applicable.
3. Attitude toward NIPT: This section consisted of 5 questions regarding the overall comfort in explaining NIPT to patients, and views on how this new technology might change the way we screen for prenatal genetic conditions. Questions in this section were multiple choice, agree/disagree statements, and five point Likert scale to assess comfort (very comfortable, somewhat comfortable, neutral, somewhat uncomfortable, and very uncomfortable) where applicable.

At the conclusion of the survey, there was a free response box designed for any comments regarding the survey or NIPT in general. Additionally, after notifying participants that their participation in the current study had ended, there was space to leave contact information should they wish to be contacted in the future for a follow up study.

The final questionnaire was created in Survey Monkey and included a logistic flow allowing for those physicians who do and do not utilize NIPT to follow different paths through the survey.

**Data Collection**

An email was sent to all 5,000 physicians on Natera's purchased list inviting them to participate in the study. The invitation explained the purpose of the study and what was involved in participation. A direct link to the survey was embedded in the body of the message and directed the participant to the questionnaire on Survey Monkey. The email invitation was sent from Natera but was linked to the PI's email address so as to protect privacy of the study population. The survey was sent out in 4 waves, each two weeks apart. Data collection began on August 14, 2012 and ended on October 3, 2012.

**Statistical Analysis**

Data collected from the questionnaires was downloaded from Survey Monkey to a Microsoft Excel file and analyzed using statistical analysis software program, STATA (v.11, College Station, TX). For our primary analysis, we performed a descriptive analysis to describe the population and evaluate the attitudes toward and clinical utilization of NIPT. A secondary analysis of the data was performed after stratifying by various demographic factors, current use of the test, and attitudes regarding the test. A comparison between groups was performed using contingency tests (Fisher's exact test, Chi-squared analysis), Mann-Whitney sign-rank, Wilcoxon signed rank, and Kruskal-Wallis tests where appropriate. Linear and logistic regression models were used to assess any linear trends

over a series of ordinal categories. Spearman's correlation tests were utilized to assess the degree of correlation between two continuous variables. Results with a p-value of less than 0.05 were considered statistically significant. The null hypothesis used for all statistical analysis was that there was no difference between groups.

# RESULTS

## Survey Response

The survey was distributed in four waves; each wave was two weeks apart and reached out to the same 5,000 physicians. After each wave, about 1% of the surveys were returned immediately due to invalid email addresses or out-of-office replies. There were a total of 175 responses. Sixteen participants were not included in data analysis for the following reasons: 1) nine participants did not complete more than the demographic information of the survey, 2) two participants had IP addresses that matched two other respondents and had answered questions similarly to those other respondents indicating that he/she was likely the same person, and 3) five additional participants were dropped because they were not certified as an OB/GYN. Of the 175 responses, 159 were used in statistical analysis, which resulted in an overall 3.2% response rate.

## Part I: Demographics

The first set of questions aimed to describe the study population. Out of 159 participant physicians, 84 (53%) were female, 79 (50%) were boarded in a subspecialty, 77 (48%) practiced as an MFM, 140 (88%) practiced in an urban area, and 109 (69%) saw less than 25 increased-risk patients per week. The mean number of years since a physician's residency training was 19.3 with a standard deviation of 8.8. On average among all respondents, 55% of their patient population have private insurance, 35% Medicaid, 1% military, and 5% uninsured. Overall, 67% (n=103) of the participants predominantly had a

privately insured population, while 29% (n=44) had a patient population that was predominantly insured by Medicaid.

Correlations between demographic variables and whether or not the physician currently offers NIPT to his/her patients were evaluated, as well as correlations between demographic variables and whether or not the physician is a OB/GYN or MFM (Tables 1 and 2). "General OB/GYN," "GYN only," and "OB only" were combined to make up the group "OBs" when compared to MFMs for analysis. Proportionately more physicians who offer NIPT are boarded in a subspecialty ($p=0.006$). Of the respondents that are certified in a subspecialty, only 3 were not certified as MFMs ($p<0.001$). "MFM" was the most commonly reported practice area among physicians offering NIPT compared to "General OB/GYN" which was the most commonly reported practice area among physicians not offering NIPT ($p=0.006$). A predominantly privately insured patient population is more common among OBs, whereas MFMs see a higher proportion of predominantly Medicaid patients ($p<0.001$). Compared to MFMs, OBs see a lower volume of increased-risk patients per week ($p<0.001$).

| | | | Offered vs. Did not Offer | MFM vs. OB |
|---|---|---|---|---|
| | | n (%) | p-value | p-value |
| Gender | | | 0.202 | 0.950 |
| | Female | 84 (53) | | |
| | Male | 72 (45) | | |
| | Missing | 3 (2) | | |
| Boarded in Subspecialty | | | 0.006 | <0.001 |
| | Yes | 79 (50) | | |
| | No | 80 (50) | | |
| Practice Area | | | 0.006 | <0.001 |
| | General OB/GYN | 72 (45) | | |
| | GYN only | 3 (2) | | |
| | OB only | 2 (1) | | |
| | MFM | 77 (48) | | |
| | Reproductive Endocrinology | 1 (1) | | |
| | Other | 4 (3) | | |
| Practice Location | | | 0.121 | 0.143 |
| | Urban | 140 (88) | | |
| | Rural | 15 (9) | | |
| | Missing | 4 (3) | | |

**Table 1: Demographic Background of Physicians with analysis by whether or not NIPT is offered and practice area.**

| | | | Offered vs. Did not Offer | MFM vs. OB |
|---|---|---|---|---|
| | | n (%) | p-value | p-value |
| Patient Insurance by Practice | | | 0.533 | <0.001 |
| | Predominantly Private | 103 (67) | | |
| | Predominantly Medicaid | 44 (29) | | |
| | Equally Private or Medicaid | 7 (4) | | |
| Increased Risk Patients Per Week | | | 0.187 | <0.001 |
| | Less than 25 | 109 (69) | | |
| | 25-50 | 45 (28) | | |
| | 50-75 | 2 (1) | | |
| | More than 75 | 3 (2) | | |

**Table 2: Demographic Background of Patient Populations with analysis by whether or not NIPT is offered and practice area.**

**Part II: Knowledge**

Participants were given five different patient scenarios and asked to identify which scenario represented a patient at an increased-risk for having a pregnancy affected by Down syndrome. One hundred fifty-five (97%) correctly identified an AMA patient as increased-risk, 158 (99%) correctly identified a patient with a positive quadruple screen as being increased-risk, 147 (92%) correctly marked that a patient with an abnormal ultrasound is at an increased-risk, and 146 (92%) correctly answered that a patient with a second cousin with Down syndrome is not at an increased-risk. Only 90 (57%) participants correctly identified that a patient with a karyotype indicating she is 46, XX t(11:22) is not at an increased risk

for having a child with Down syndrome. In summary, participants were able to identify who is at an increased-risk.

**Part III: Clinical Practice**

Each participant was asked whether or not they currently offer NIPT to patients in their practice. This question served as a gateway in the survey; physicians that answered "yes" answered a different set of questions than those who answered "no". Both sets of questions aimed to describe the clinical practices of the physicians in each category. The majority (n=127, 80%) of physicians reported that they currently offer NIPT in their clinical practice. Compared to OB/GYNs, proportionately more MFMs are ordering NIPT for their patients (p=0.004).

*Physicians Who Offer NIPT*

The first group of questions aimed to determine which patients are being offered NIPT as well as what factors influence a physician's decision not to offer the test. Most physicians who offer NIPT will offer the test to their patients who are at increased-risk (73%), not sure about invasive testing such as CVS or amniocentesis (72%), or refuse invasive testing (69%). Compared with OBs, MFMs offer NIPT significantly more to these subset of patients (p=0.014, 0.002, <0.001, respectively). OBs are more likely to offer NIPT to all pregnant patients as compared to MFMs (p<0.001). Physicians offering NIPT are doing so to over 75% of their increased-risk patients (84%). Compared to MFMs, OBs reported that they offered the test to a higher proportion of their increased-risk patients (p=0.044). Participants were then asked which factor(s) influence their decision not to offer NIPT to a patient. Fifty-seven (45%) indicated they do not offer it when their patient shows

a lack of interest, 54 (43%) when the patient cannot afford it or when the test is not covered by insurance, 13 (10%) when the physician does not feel it is in the patient's best interest, and three (2%) when they run out of time to discuss it with the patient. Fifty (39%) respondents reported that there was another reason for not offering the test. These individuals indicated that they would not order the test if the patient did not have a risk factor, there is concern for another genetic condition for which NIPT does not detect, or a patient declines.

The next question asked physicians at what point do they order NIPT for their AMA patients. Participants were able to check all of the options that apply to their practice. Fifty-four (43%) reported they offer NIPT instead of maternal serum screening if the patient is AMA. Sixty-seven (53%) order NIPT after maternal serum screening results are positive. Compared to OBs, MFMs are twice as likely to order NIPT after screening results are positive ($p<0.001$). Seventy-four (58%) offer NIPT to AMA patients if she declines invasive testing. Compared to OBs, MFMs are also twice as likely to order NIPT if a patient declines invasive testing ($p<0.001$). Seventy-six (60%) offer NIPT in order to help a patient decide if they want to pursue invasive testing. Physicians were then asked what detection rate they quote their patients when discussing the option of NIPT. Most physicians quote the accuracy of NIPT in detecting Down syndrome as greater than 89%; 71 (45%) quote 99-100%, and 42 (26%) quote 90-98%.

The next group of clinical practice questions for participants who offer NIPT was aimed to describe what physicians do with a positive NIPT result. Most participants indicated that their first recommendation after a positive NIPT result is invasive testing. MFMs are more likely than OBs to offer invasive testing, whereas OBs are more likely to

refer patients to a specialist following a positive result ($p<0.001$). When asked if the physician offers a CVS/amniocentesis to confirm the NIPT result, most physicians answered yes; however, MFMs are more likely to offer an invasive procedure following a positive result compared to OBs ($p=0.029$). Of note, physician participants offer invasive testing to the majority of their increased-risk patients even without a positive NIPT. Eighteen participants answered that whether or not they would offer invasive testing after a positive NIPT result would depend on factors such as ultrasound findings and patient preferences. Three of the 18 indicated that they would refer to an MFM at that point. MFMs are more likely to refer to a GC prior to ordering the test, whereas OBs are more likely to refer after a receiving a positive result ($p<0.001$).

The last two questions for physicians that offer NIPT to their patients asked what they do with the two populations for whom the testing is not currently validated, women who are pregnant with multiples, and low-risk women. Fifty-nine (37%) physicians reported that they do offer NIPT to patients who are pregnant with multiples, fifty-three (33%) reported that they would not, and forty-seven (30%) did not answer this question. Physicians that would not offer the test to this type of patient indicated their concern about the accuracy and validity of the test and the need for more data, as well as the fact that the affected fetus cannot be identified using this method. Forty-five percent of participants would order NIPT on a low-risk patient if she requested it. Compared to MFMs, OBs are more likely to order NIPT if a low-risk patient asked for it ($p<0.001$). Twenty-nine (23%) physicians reported that their decision to offer the test for a low-risk patient would depend on her understanding the benefits and limitations of the testing in a low-risk population, what her other options are, and what the test will cost.

*Physicians Who Do Not Offer NIPT*

The questions for physicians who do not currently offer NIPT to their patients were aimed to determine what factor(s) influence their decision not to offer the test, what the physician would do if a patient requested the test, and whether or not the physician plans on incorporating NIPT into their practice in the future. Fourteen (23%) do not feel there is enough published data on NIPT, 14 (23%) identify that there were no published practice guidelines at the time from their professional society, 12 (19%) identify cost and/or lack of insurance coverage as a factor, six (10%) report that their institution and/or colleagues are not utilizing this test, three (5%) note a lack of interest from their patients, three (5%) express that the test is not convenient, and one (2%) participant felt that there is not enough time to discuss this new option with patients. Nine (15%) chose "other." These physicians indicated that they prefer to start with maternal serum screening, rely on others such as MFMs to offer this testing, or that the population of patients they see would not benefit from this test. If an increased-risk patient requested NIPT, 18 (56%) would order it, one (3%) would not, and 13 (41%) would refer the patient to an MFM or genetic counselor. Significantly more MFMs are willing to order NIPT if requested by an increased-risk patient than OBs ($p=0.009$). If a low-risk patient requested NIPT, 10 (32%) physicians would order it, 7 (23%) would not, and 14 (45%) would refer to an MFM or genetic counselor. MFMs are more likely to not order NIPT if requested by a low-risk patient compared to OBs, whereas OBs are more likely to refer those patients to an MFM and/or genetic counselor ($p=0.002$). When asked if the physician plans to incorporate NIPT into his/her practice in the future, 22 (69%) answered yes and 10 (31%) answered no. Those participants that

answered no did so because they would refer their patients to an MFM or genetic counselor, it is not standard of care, or there is not enough data for low-risk populations.

**Part IV: Attitudes**

When asked how comfortable they are explaining NIPT to patients, most physicians indicated that they were very comfortable (43%) or somewhat comfortable (31%). Responses show that physicians that offer NIPT are more comfortable explaining the test to their patients than those who do not order it ($p<0.001$). Additionally, physicians who could correctly identify that women with an abnormal ultrasound were at an increased-risk to have a child with Down syndrome were more comfortable explaining NIPT to patients than those physicians who could not ($p=0.010$).

All participants answered the following series of questions by indicating whether they agree or disagree with the following statements (Table 3). When asked to evaluate the statement about NIPT making prenatal diagnosis more complicated, more OBs disagreed with this statement than MFMs (71% vs. 49%, $p=0.001$). Proportionately more OBs think NIPT will replace invasive procedures than MFMs (67% vs. 54%, $p=0.018$). Physicians that do not offer NIPT disagreed more with the statement about more studies being needed to establish the clinical validity and utility of NIPT than physicians that do offer it (88% vs. 66%, $p=0.046$). When asked to evaluate whether NIPT is going to simplify prenatal diagnosis, proportionately more OBs agree with this statement than MFMs (63% vs. 44%, $p=0.011$). More MFMs disagreed with the statement saying NIPT should currently be offered to low-risk patients than OBs (75% vs. 36%, $p<0.001$). When asked whether they think NIPT will replace maternal serum screening in the future, proportionately more MFMs disagree with this statement than OBs (29% vs. 13%, $p=0.017$).

| Statement | Agree, n (%) |
|---|---|
| I think NIPT is pointless. | 0 (0) |
| NIPT is leading us down a slippery slope. | 16 (10) |
| I feel NIPT is just a way for labs to make money. | 3 (2) |
| NIPT is going to make prenatal diagnosis more complicated. | 49 (31) ** |
| I think NIPT will replace invasive procedures. | 95 (60) ** |
| As practitioners, we need more information/education about the test/technology. | 125 (79) |
| More studies are needed to establish clinical validity and utility. | 112 (70) * |
| NIPT is going to revolutionize prenatal diagnosis. | 115 (72) |
| NIPT is going to simplify prenatal diagnosis. | 85 (53) ** |
| NIPT should currently be offered to patients not at increased risk. | 54 (34) ** |
| I think NIPT will replace maternal serum screening in the future. | 112 (70) ** |

* Significant difference between physicians that offer NIPT and those who do not

** Significant difference between MFMs and OBs

**Table 3: Attitude Statements with analysis by whether or not NIPT is offered and practice area.**

When asked whether the physicians consider NIPT to be a screening test or diagnostic test, 86 (54%) consider it a screen, 33 (21%) consider it a diagnostic test, 15 (9%) consider it to be neither a screening nor a diagnostic test, and 13 (8%) are not sure how to classify it. Compared to MFMs, OBs are more likely to consider NIPT a diagnostic test ($p=0.024$).

The aim of the last two questions was to determine how the participants viewed the future of NIPT. When asked how the introduction of NIPT will affect their clinical practice,

121 (76%) participants felt it would reduce the number of invasive procedures performed, 21 (13%) were not sure how it would affect their practice, and 4 (8%) reported that they did not think NIPT would affect their practice. Proportionately more physicians that do not offer NIPT are unsure as to how the introduction of the test will affect their practice as compared to those who do offer NIPT to their patients (p=0.038). One hundred (63%) physicians reported that they think NIPT will eventually become the standard of care when evaluating a pregnancy for chromosome aneuploidy, 14 (9%) do not think it will be standard of care, and 33 (21%) are unsure. Proportionately more physicians that do not offer NIPT are unsure as to whether or not NIPT will become the standard of care for the evaluation of chromosome aneuploidy as compared to those who do offer NIPT to their patients (p=0.007).

# DISCUSSION

The use of invasive prenatal testing (NIPT) has grown since it became clinically available in the fall of 2011. Additional laboratories have introduced their own version, costs have decreased, insurance coverage has improved, and public awareness has increased. In the absence of professional society guidelines, the purpose of this study was to determine if and how OB/GYNs are utilizing this new technology in detecting chromosome aneuploidy in their patients as well as how the physicians view the introduction of this new test. This is the first nation-wide study looking at the utilization of and attitudes toward NIPT among OB/GYNs and MFMs in the detection of fetal aneuploidy.

## Demographics

The study cohort consisted of physicians who had ordered a CVS or amniocentesis in 2011-2012 and self-identified as being certified as OB/GYNs. Fifty-three percent of our respondents were females. Our study population reported a mean number of 19.3 years since completion of residency. Forty-eight percent of our physicians practice primarily as MFMs and 45% practice in a general OB/GYN capacity. Nine percent of our physicians reported practicing in an area other than general OB/GYN or MFM, including GYN only, OB only, gynecologic oncology, reproductive endocrinology, reproductive genetics, prenatal genetics, and urologic gynecology. According When compared to the demographic distributions reported in the 2008 Socioeconomic Survey of ACOG Fellows (2008), our study sample is not representative of the current ACOG membership with regards to gender, years in practice, and specialty. However, since our participants were pulled from a likely

biased population of physicians who had recently ordered invasive testing, differences between this study's population and the ACOG Fellows are not surprising.

**Knowledge**

ACOG, NSGC, and ISPD recommend that NIPT be offered only to those women whose pregnancy is at an increased-risk for chromosome aneuploidy (ACOG, 2012; NSGC, 2012; ISPD, 2011). One goal of the study was to determine if physicians could correctly identify patients who were at an increased-risk to have a pregnancy affected by a chromosome aneuploidy. Participants were given five patient descriptions and instructed to mark those who were at an increased risk to have a child with Down syndrome. One of the patient descriptions indicates that the woman has a second cousin with Down syndrome. For some labs offering NIPT, a "family history" of Down syndrome is sufficient to classify a pregnancy as "increased-risk"; however, having one distant relative, like a second cousin, with Down syndrome does not increase a couple's risk for having a child with Down syndrome nor any other chromosome aneuploidy. Ninety-two percent of our physician participants correctly identified that this description is not enough to put the patient in the increased-risk category. The final patient description required physicians to indicate whether or not a woman with a balanced translocation between chromosomes 11 and 22 was at an increased risk to have a baby with Down syndrome. Since this translocation does not involve the 21$^{st}$ chromosome which is the one responsible for causing Down syndrome, a woman who is 46, XX t(11:22) is not at an increased risk to have a pregnancy affected by Down syndrome. However, 10% of our participants considered this patient at an increased-

risk. It could be that the physicians do not understand the genetic etiology of Down syndrome and/or how balanced translocations can cause genetic abnormalities in offspring.

Overall, the majority of our participants were able to correctly identify which women were at an increased-risk to have a child with Down syndrome. Based on this finding, most physicians are capable of identifying those women who could benefit from NIPT. Sayres et al. (2011) showed that 85% of their physician respondents did not report having a high level of knowledge about cell-free fetal DNA testing. Although our study did not address this question directly, our results indicate that physicians could indeed have a sufficient level of knowledge to order the testing for their patients. Whether or not participants interpret test results correctly, is not addressed by this study. The discrepancy between the results from the Sayers study and ours could be explained by the time lapse between the two. Sayers et al. (2011) collected their data in October of 2010, one year before the launch of NIPT for the detection of chromosome aneuploidy. In 2010, cell-free fetal DNA testing was available only for Rh group blood group typing and fetal sex determination.

**Clinical Practice**

One aim of the current study was to determine if and how OB/GYNs are utilizing non-invasive prenatal testing (NIPT) in their clinical practice. To address the first part of the study aim, physician participants were asked whether or not they currently offer NIPT to their patients. Most physicians reported that they do offer NIPT to their patients. In order to address the second part of the study aim, physicians were asked a different set of questions depending on whether or not they currently offer NIPT to their patients. The participants who offer NIPT were asked questions about how they use the testing in their practice,

whereas the participants who do not offer NIPT were asked questions about their reasoning for not offering the test and intention to incorporate it into their practice in the future.

*Factors Influencing Decisions*

At the time of this study, the use of NIPT for the detection of chromosome aneuploidy had been validated for the increased-risk population (Palomaki et al., 2012; Sparks et al., 2012). Published statements from NSGC and ISPD further supported the utilization of NIPT for women at an increased risk for chromosome aneuploidy (NSGC, 2012; ISPD, 2011). A study by Sayres et al. (2011) suggests that providers of healthcare in obstetrics will follow the guidance of their professional societies when deciding whether or not to offer NIPT. Our study shows that physician practices regarding NIPT are congruent with the literature and professional society opinions available at the time of data collection. Physicians are ordering NIPT for their increased-risk patients and are doing so for those patients who are undecided about or have refused invasive testing options. Patients refuse may refuse invasive testing due to the fact that they are not comfortable with the risk of miscarriage; however some patients refuse testing because they do not want more information about the genetic condition of their unborn child. It is important that physicians enquire further about a patient's reason for declining invasive testing before offering NIPT as an alternative. For those physicians who are offering NIPT to their patients, the most common factors influencing them to not offer NIPT were a lack of interest from the patient and an inability of the patient to afford it. The list price for the test when first launched was nearly $2,000. Over time, more competition and acceptance by insurance companies has decreased the patient's out-of-pocket cost significantly. It may be that as time passes, this factor will hold less importance in decision making.

Although physicians who do not offer NIPT also indicated that cost and/or lack of insurance coverage plays a role in their decision not to offer the testing, the most common factors influencing their decision were that there is not enough published data on NIPT and that there are no published practice guidelines from their professional society. Even though there have been several studies published about the effectiveness of NIPT in detecting chromosome aneuploidy, the technology is new and not well established. Furthermore, many of the studies have been conducted with assistance from the laboratories offering the testing, which may lessen the effect of their findings for some physicians. Additionally, the group of physicians that do not offer NIPT might have been waiting for a specific ACOG guideline before making a change in their practice. Our findings also show that MFMs who do not currently offer NIPT to patients are more likely to order it if an increased-risk patient requests it compared to OBs, indicating that they recognize the test's utility but do not see the need to offer it to their patients at this time. Since the completion of data collection, ACOG has released a committee opinion about NIPT. The document supports the use of NIPT for increased-risk women who receive adequate pretest counseling, and recommends that women with a positive result should be referred for genetic counseling and confirmatory invasive testing (ACOG, 2012). This ACOG guideline is likely to affect the practices of OBs and MFMs alike with physicians modifying their current practices and/or attitudes about testing. Some physicians/institutions will likely begin offering the test with this additional support.

*Detection and Diagnosis*

The literature, as well as the two laboratories offering NIPT at the time of data collection, quoted the detection rate for Down syndrome as being above 99% (Palomaki et

al., 2012; Sparks et al., 2012). Seventy-one percent of our physician respondents tell their patients the detection rate of NIPT for Down syndrome is greater than 89%. Forty-five percent tell their patients the detection rate is at least 99%. For Down syndrome, the detection rate of NIPT is very similar to that of the available invasive procedures. It may be that they are not comfortable quoting such a high detection rate for such a new test being marketed as a screening tool. The literature, the laboratories offering testing at the time of this study, and NSGC practice guidelines recommend confirming a positive NIPT result with a diagnostic invasive procedure such as a CVS or amniocentesis (NSGC, 2012; Palomaki et al., 2011). Most of our respondents reported that they offer an invasive procedure to confirm a positive NIPT result. In fact, confirmation via invasive diagnostic testing is the first recommendation for 59% of our respondents when the NIPT indicates an affected fetus. This is not surprising given that the majority of our respondents offer invasive procedures to a high percentage of their increased-risk patients in general. For those participants that do not always offer an invasive procedure to their patients following a positive result, many reported that their decision to offer a diagnostic procedure would depend on ultrasound findings. It seems that if ultrasound findings supported the NIPT result, physicians would feel comfortable enough to not follow up with an invasive procedure prior to discussing pregnancy options with the patient.

*Additional Patient Populations*

At the time of data collection for this study, NIPT testing was validated, recommended, and marketed only for women who were at an increased-risk of having a baby with a chromosome aneuploidy; however, 45% of our participants who currently offer NIPT to patients would order it for a low-risk woman if she requested the testing compared

to 32% of physicians who do not currently offer NIPT. Regardless of whether or not they currently offer NIPT to their patients, MFMs in our study were more likely to say no to a low-risk patient requesting NIPT, indicating that they are more selective than OBs when ordering the testing. Yotsumato et al. (2012) surveyed healthcare professionals in Japan and reported that 36% of their participants felt that all women should be allowed to undergo the test if they desire. Our study participants emphasized that when a low-risk woman requests NIPT, she should have a good understanding of the benefits and limitations, what all of her options are, and what the test might cost her financially. Many physicians, especially OBs, indicate that a patient should be referred to an MFM and/or genetic counselor to address these issues.

During the data collection of this study, Canick et al. (2012) published a paper showing that the MPSS technology utilized in NIPT can reliably detect Down syndrome in women with high-risk twin gestations; however only 25 twin and two triplet pregnancies were evaluated. It is unclear as to whether or not this study population is enough to validate NIPT usage in multiple gestations. The issue is further complicated in that NIPT in multiple gestation pregnancies is limited, as is maternal serum screening, because the affected fetus cannot be identified by this method alone. Without significant ultrasound findings, an invasive procedure would be necessary to confirm which baby was the affected one. At the time of this study, the ISPD was the only professional society to mention multiple gestation pregnancies in their position statement. The society noted that more studies were needed to validate its use in this population (International Society of Prenatal Diagnosis, 2011). Our study showed that about one-third of physicians would not order NIPT on a patient who was pregnant with multiples, about one-third would, and about one-third of our participants did

not answer this question. The authors wonder if so many participants did not answer this question because they were not sure if they should offer NIPT to multiples, or if they had not come across this situation at the time of this study.

*MFMs vs. OBs*

Among the physician participants who offer NIPT to their patients, this study found differences between the clinical practices of MFMs and general OBs regarding NIPT. First, although most of our physician participants offer NIPT to their patients, more MFMs are offering the test compared to OBs. When the test is offered, MFMs offer it specifically to help increased-risk patients decide whether or not to pursue invasive testing. However, most OBs in our population felt that NIPT should be offered to low-risk patients. MFMs also report that they primarily order the test after maternal serum screening results come back positive. This finding could be due to the fact that many patients are not referred to an MFM until after the results of a patient's maternal serum screen, drawn by the OB, are positive. MFMs tend to turn more to invasive testing after a positive result, whereas OBs tend to refer their patients to an MFM and/or genetic counselor to discuss the results and available options. When referring patients to genetic counselors, MFMs generally do so before ordering NIPT whereas OBs primarily refer to specialists after the results are positive. MFMs are certified primarily as OB/GYNs but have completed more focused training in high-risk pregnancy situations, including women suspected of being at an increased-risk for having a baby with a chromosome aneuploidy. For this reason, it is not surprising that their practices would differ from that of OBs regarding the utilization of NIPT. For example, some OBs may feel comfortable managing a pregnancy at increased-risk for aneuploidy, whereas others may not. Others may prefer to not perform invasive

procedures and refer their patients to specialists. Due to the nature of their practice, MFMs are usually somewhat familiar with genetic testing; they may be in a position to better understand the technology including its benefits and limitations, and therefore are likely to be more selective when ordering the test.

## Attitudes

### *Comfort*

Our physician participants, especially those who offer NIPT, report that they are comfortable explaining NIPT to their patients. This finding is supported by the fact that respondents who do not offer NIPT identified a need for more information about the testing as a major factor in their decision to not offer it, as well as a need for more studies to establish clinical validity and utility. The ability to identify increased-risk patients is also associated with a high level of comfort explaining the test to patients. Specifically, physicians that associate an abnormal ultrasound with an increased-risk for Down syndrome are more comfortable explaining the testing to their patients. This implies that physicians with a higher level of knowledge about NIPT could be more comfortable explaining the testing to patients, and possibly more likely to order the testing. However, more knowledge measures would be needed in order to verify this possibility.

### *Screening or Diagnostic Test?*

NIPT has been validated and marketed as a new technology in order to screen pregnancies at increased-risk for chromosome aneuploidy; however, the test's detection rate for Down syndrome is greater than 99%, which approaches the accuracy of current invasive diagnostic procedures. About half of our study participants classified NIPT as a screening

test; however 17% consider NIPT to be neither a screen nor diagnostic, or are unsure as to how to classify it. OBs more often identified NIPT as a diagnostic tool. These findings indicate that physicians do not know how to classify the test. Additionally, some physicians may not consider NIPT as a diagnostic tool due to the fact that it only tests for a limited number of conditions. Those OBs that are considering NIPT a diagnostic test may be doing so more hastily than other physicians. NIPT may be considered a diagnostic test in the future; however at this time there are not enough studies to classify it as such.

Although NIPT is a new method for screening AMA women to aid providers in personalizing risk, when considering their AMA patients, more of our participants indicated they offer NIPT after a positive maternal serum screening result as opposed to using the test as a replacement for first or second trimester screening. NIPT was developed in order to provide a new means of prenatal diagnosis without the risk of miscarriage, but at the time of this study NIPT is not considered diagnostic but rather a screening tool. However, it appears that when physicians are utilizing this technology, they are doing so as a way of getting more detailed information after less reliable screening methods rather than replacing them.

*Future*

Palomaki et al, (2011) proposed that complete uptake of NIPT by high-risk women would decrease the amount of invasive procedure-related losses due to the fact that less invasive procedures would be necessary to detect almost all cases of Down syndrome. Our participants agree that NIPT will affect their practice by reducing the number of invasive procedures performed. Within our study population, more OBs felt that NIPT would replace invasive procedures compared to MFMs. A reduction in invasive procedures may decrease the amount billed by physicians for those procedures which could impact clinic income.

MFMs care for more increased-risk patients than OBs and also follow women whose pregnancies at increased-risk of complications for a variety of reasons. Overall, NIPT may replace invasive procedures, but MFMs are likely to still have a reason to perform them than general OBs, due to the nature of their patient population. Of note, both MFMs and OBs felt that NIPT would eventually replace maternal serum screening; however, OBs agreed more strongly with this idea. OBs seem to feel that NIPT covers both maternal serum screening and invasive procedures at the same time. Additionally, study respondents feel that NIPT will simplify the world of prenatal diagnosis rather than make it more complicated; however, OBs agreed with this idea more than MFMs. Since more MFMs are ordering the testing than OBs, it may be that MFMs see how NIPT might affect the bigger picture of prenatal diagnosis. For example, MFMs might be thinking ahead to how the technology might expand to other genetic conditions and what affect that may have on their practice.

The physicians who did not offer NIPT at the time of this study were unsure as to how the test might affect their practice. It is reasonable to assume that this feeling could be influencing their decision not to offer the testing to their patients. The majority of the physicians who do not currently offer NIPT reported that they plan to do so in the future. It may be that the published opinion from ACOG as well as more research about the testing and potential effects on prenatal diagnosis would increase comfort with offering NIPT. Physicians who do not plan to incorporate NIPT into their clinical practice report that they refer their patients to an MFM and/or genetic counselor. These respondents would likely continue to do so despite additional information and publications on NIPT.

Currently, maternal serum screening and CVS/amniocentesis are the standard of care for evaluating for chromosome aneuploidy. However, the majority of the study population

feels that NIPT will eventually become the standard of care. Physicians that do not offer NIPT are most likely to be unsure as to whether or not NIPT will become the standard of care for evaluating a pregnancy for chromosome aneuploidy. This is likely related to the finding that physicians that do not offer NIPT are also unsure as to how NIPT will affect their practice. Overall, those that don't offer NIPT are unsure about how the test might affect them, which is likely influencing their choice not to offer the testing at this time, and is supported by their desire for more validation and recommendations from their professional societies.

**Additional Factors to Consider**

Since NIPT became clinically available in November 2011, much has changed. Prior to data collection for this study, NIPT for trisomies 21, 18, and 13 was offered by three clinical laboratories, one of which reported the presence or absence of Y chromosome material, another accepted patients with Medicaid and/or CHIP insurance. Additionally, ISPD and NSGC had published position statements on the testing and its utilization in detecting fetal chromosome aneuploidy. During the period of data collection, one more lab began reporting on the presence or absence of Y material. After data collection was complete for this study, a fourth laboratory began offering the test utilizing a different method, two labs began testing for sex chromosome abnormalities, and an additional lab began reporting on the presence of Y material. Additionally, NSGC published a white paper on the clinical use of NIPT and the American College of Obstetricians and Gynecologists (ACOG) published a committee opinion on NIPT for fetal aneuploidy (ACOG, 2012). It is unclear how these changes might affect the results of this study; however, the authors

suspect that ACOG's committee opinion is likely to have an impact, especially on physicians who were previously not offering the testing.

**Strengths and Limitations**

There have a been few studies examining attitudes of physicians regarding the future incorporation of NIPT (Sayres et al., 2011; Yotsumato et al., 2012). However, since NIPT became clinically available in the fall of 2012, there have been no studies, to our knowledge, addressing the utilization of and attitudes toward this new technology among physicians who could order the testing for their patients. Through the clinical practice portion of this study, we were able to describe how OB/GYNs and MFMs are incorporating NIPT into their clinical practice. Additionally this section enabled us to better understand why physicians may not utilize this testing with their patient populations. This study evaluated the attitudes of OB/GYNs and MFMs regarding NIPT as well as the attitudes of physicians who do and do not offer the test to their patients.

Although this study queried physicians across the United States, our response rate was only 3.18%. This response rate is lower than similar studies examined for this project; however, the total number of respondents is higher making our study the largest, most comprehensive study on the topic of NIPT to date.

Due to the low response rate and small sample size, there was not an adequate amount of respondents to stratify by multiple variables. For example, outside of the general OB and MFM sub-specialties, there were very few participants in order to determine if their clinical practice and attitudes differed from other groups. In addition, the study sample may not be representative of the greater ACOG fellowship, especially in practice area. This

difference may be due to the way this study population was selected from a group of physicians that had ordered an invasive procedure in 2011-2012. In general, MFMs order more invasive procedures due to the nature of their practice, and therefore would be more highly represented in our study population than that of ACOG's fellowship. Furthermore, all of the variables measured in this study were based on self-reported information and may not represent actual practice. This study is limited by a selection bias in that the questionnaire was emailed to a select group and may not represent the target population as a whole. Physicians that knew more about NIPT and/or utilized the test in their clinical practice might have been more likely to participate in the study. Another limitation to this study is that the questionnaire was not adapted from an established tool; it was created by the authors and piloted to committee members. There was no reliability or internal validity tests performed on the questionnaire prior to its utilization in the study population.

**Final Conclusions and Future Studies**

This study shows that most physicians are offering this new, non-invasive technology to their patients, and that at the time of data collection their practices were congruent with the literature and available professional society opinions. Physicians did indicate, however, that they would deviate from these guidelines if a patient fully understood the benefits and limitations of the testing. Those physicians who do not offer NIPT to their patients indicated that they needed more literature on the topic as well as instructive guidelines from their professional societies. Since then, ACOG has published a committee opinion on the matter, likely providing this group with what they needed to feel comfortable offering the test as an option to their patients. Additionally, our study shows that the

practices and attitudes of MFMs and OBs differ somewhat, which may be a result of their differing patient populations and area of expertise. The respondents feel that the incorporation of NIPT will change their practices by lowering the amount of invasive procedures, possibly replacing maternal serum screening, and that it will simplify prenatal diagnosis. However, those physicians who do not offer NIPT to their patients are not quite sure how the test will affect their clinical practice. This may be an underlying reason as to why they are not offering it.

From this study we learned much about how physicians are incorporating this new technology into their practice and how they feel about the addition to the plethora of available prenatal tests. This knowledge gives us insight as to how to best move forward with the quickly changing field of prenatal diagnosis. It is likely that in the future we will be able to diagnose single-gene disorders in a similar fashion. Genetic professionals need to be aware of what the ordering physicians are doing as we encounter more and more of their patients. This study also gives us an idea of how we can better serve our patients by properly supporting and educating their physicians.

Although this study adds to the current literature about the utilization of NIPT, there is much to be learned about implementing this technology. The environment surrounding NIPT will continue to evolve with additional literature, improvements of technology, and the inclusion of more laboratories offering the test. Our study captured physician attitudes and practices at one moment in time, but this may have changed since the publication of ACOG's committee opinion. Additional studies may address these changes by examining whether or not the abundance of choices in testing labs and methodology affects their practice as well as their preferences. It would also be beneficial to replicate our study with a

larger sample size. Since there were many differences between OBs and MFMs, a focused study on OBs may add much to the literature as well. Our study did not focus on the knowledge of physicians regarding NIPT. A future study might examine what they understand about the technology, and whether or not physicians truly understand the benefits and limitations of NIPT.

## Appendix A

**Part I: Demographics**

What is your gender?

Male
Female

How many years has it been since the completion of your primary residency?

_____

Are you board certified in Obstetrics and Gynecology?

Yes
No

Are you boarded in any sub-specialty?

No
Yes. Please indicate which one(s) below:

i. Gynecologic Oncology
ii. Maternal Fetal Medicine
iii. Medical Genetics
iv. Reproductive Endocrinology
v. Urogynecology
vi. Other: _____

Which of the following best describes your area of practice? (check one)

General Obstetrics and Gynecology
Gynecology only
Obstetrics only
Gynecologic Oncology
Maternal fetal Medicine
Reproductive Endocrinology
Urogynecology
Other: _____

What is your primary practice setting? (choose all that apply)

Private Practice
Hospital-based
Academic Institution/University Medical Center
Other _____

Where is your practice located?

STATE

Is your practice mostly:

Urban
Rural

Regarding insurance coverage, what proportion of your patients are:

___ Privately insured
___ Medicaid
___ Military (Tricare)
___ Uninsured (Self-pay)

In your practice, who do you consider at increased risk for Down syndrome? (check all that apply)

a. A patient who is advanced maternal age (≥35)
b. A patient with an abnormal quad screen for Down syndrome
c. A patient whose fetus has a heart defect on ultrasound
d. A patient whose second cousin has Down syndrome
e. A patient who is 46, XX t(11:22)

On average, how many patients do you see per week with an increased risk for a chromosome aneuploidy?

a. Less than 25
b. 25-50
c. 50-75
d. More than 75

**Part II: Clinical Practice**

1. Do you offer non-invasive prenatal diagnosis (NIPT) with patients in your practice?
   Y____ N____
   If yes, answer questions 2-12. If no, answer questions 13-16. (The answer to this question determines the track of questioning the participant will answer. Survey Monkey allows for this set up.)

2. To which patients do you offer NIPT: (check all that apply)
   a. Patients at increased risk
   b. Patients who request it
   c. Patients who have an indication for invasive prenatal diagnosis but are not sure they want to do it
   d. Patients who have an indication for invasive prenatal diagnosis but refuse invasive testing
   e. All pregnant patients
   f. Other: (please list)_____

3. To what percentage of your increased risk patients do you offer NIPT?
   a. 90-100%
   b. 75-90%
   c. 50-75%
   d. 25-50%
   e. 10-25%
   f. <10%

g. None

4. For those patients that you do not order NIPT, what factors influence your decision not to offer it? (check all that apply)
    a. Lack of interest from my patient
    b. My patient cannot afford it/it is not covered by their insurance
    c. I run out of time discussing options with my patient
    d. I feel it is not in my patient's best interest
    e. Other (please elaborate)_____

5. To what percentage of your increased risk patients do you offer invasive testing (CVS, amniocentesis)?
    a. 90-100%
    b. 75-90%
    c. 50-75%
    d. 25-50%
    e. 10-25%
    f. <10%
    g. None

6. If a patient is advanced maternal age, do you order NIPT: (check all that apply)
    a. Instead of first trimester or quad screens
    b. After serum screen results are positive
    c. If a patient declines CVS/amniocentesis
    d. To help a patient decide if they want to pursue CVS/amniocentesis

7. What do you tell your patients the accuracy is for NIPT in detecting Down syndrome?
    a. 99-100%
    b. 90-98%
    c. 80-89%
    d. 70-79%
    e. <70%

8. Do you offer invasive diagnostic testing (CVS, amnio) to confirm abnormal NIPT results?
    a. Yes
    b. No
    c. It depends Comments:

9. Do you order NIPT on multiple gestations?
    a. Yes
    b. No Why not? _____

10. If a patient has a positive NIPT result, what is your first recommendation? (Choose the best answer)

a. I offer CVS/amniocentesis.
b. I perform a targeted ultrasound.
c. I refer the patient to a specialist, such as an MFM or genetic counselor.

11. With regards to NIPT, when do you refer patients to a genetic counselor?
    a. Prior to ordering the test.
    b. Only when patients have a positive result.
    c. I do not refer to genetic counselors for NIPT.

12. If a low-risk patient asks for NIPT, would you order it? Yes_____ No_____ Depends_____ Comments:

13. What factors influence your decision to not use NIPT (check all that apply)?
    a. Not enough published data regarding detection rates, effectiveness, etc.
    b. Lack of interest from my patients
    c. My colleagues and/or institution are not supportive of this test and/or are not using it
    d. No published position papers or practice guidelines from my professional society(ies) about this testing
    e. Not convenient (i.e. not enough local blood draw sites for my patients to access this testing)
    f. Cost and/or lack of insurance coverage for my patients
    g. Not enough time to discuss NIPT with the patient
    h. Other (please elaborate)_____

14. If an increased-risk patient asks for NIPT, would you order it?
    a. Yes
    b. No
    c. I would refer them to an MFM or genetic counselor.

15. If a low-risk patient asks for NIPT, would you order it?
    a. Yes
    b. No
    c. I would refer them to an MFM or genetic counselor.

16. Do you plan on incorporating NIPT into your practice in the future?
    a. Yes
    b. No Why not? _____

**Part III: Attitudes**

1. How comfortable are you explaining NIPT to your patients?

| 5 | 4 | 3 | 2 | 1 |
|---|---|---|---|---|
| Very comfortable | Somewhat comfortable | Neutral | Somewhat uncomfortable | Very uncomfortable |

2. Check whether you agree or disagree with the following statements:

| | Agree | Disagree |
|---|---|---|
| I think NIPT is pointless. | | |
| NIPT is leading us down a slippery slope. | | |
| I feel NIPT is just a way for labs to make money. | | |
| NIPT is going to make prenatal diagnosis more complicated. | | |
| I think NIPT will replace invasive procedures. | | |
| As practitioners, we need more information/education about the test/technology. | | |
| More studies are needed to establish clinical validity and utility. | | |
| NIPT is going to revolutionize prenatal diagnosis. | | |
| NIPT is going to simplify prenatal diagnosis. | | |
| NIPT should currently be offered to patients not at increased risk. | | |
| I think NIPT will replace maternal serum screening in the future. | | |

3. Which do you consider NIPT to be?
    a. A screen
    b. A diagnostic test
    c. Neither
    d. Unsure

4. Introduction of this technology will:
    a. Reduce the number of invasive procedures performed.
    b. I am not sure how it will affect my practice.
    c. Not affect my practice.

5. Do you think NIPT will eventually be the standard of care for evaluation of chromosome aneuploidy?
    a. Yes
    b. No
    c. Unsure

Please provide us with any comments regarding this survey or NIPT:

_____

_____

Thank you for your time! This completes your participation in this study. A donation will be made to the March of Dimes.

If you would like to be contacted in the future to possibly participate in a follow up study, please enter your contact information below. If you do not wish to be contacted, please leave this field blank.

Name: _____

Phone: _____

E-mail: _____

# Appendix B

**Research study (Survey) Regarding Obstetricians and Gynecologists attitudes toward and utilization of NIPT testing for chromosome aneuploidy**

You are invited to take part in a research project called, "Attitudes Toward and Utilization of Non-Invasive Prenatal Testing for Chromosome Aneuploidy Among OB/GYNs," conducted by Jessica Davis, of the University of Texas Health Science Center. For this research project, she will be called the Principal Investigator or PI.

The purpose of this research study is to determine the attitudes of obstetricians and gynecologists' regarding non-invasive prenatal testing (NIPT) for chromosome aneuploidy and how they are incorporating the test into their clinical practice.

NIPT is a newly commercialized technology that utilizes cell-free fetal DNA present in maternal serum in order to screen a pregnancy for a chromosome aneuploidy. Chromosome aneuploidy refers to an abnormal number of chromosomes (1 or 3 instead of the normal pair). The most well known diagnosed chromosome aneuploidy is Trisomy 21 or Down syndrome. Other chromosome aneuploidies include Trisomies 13 and 18, and Klinefelter syndrome. NIPT is currently validated in women who are at increased risk for an aneulpoidy. Women at increased risk are traditionally defined as women with a 1/270 chance or higher for Down syndrome, and 1/100 chance or higher for Trisomy 18 and 13.

Non-invasive technology is used for other purposes, but for the sake of this survey, please refer to its detection of fetal chromosome aneuploidy.

This study is composed of multiple-choice, yes or no, likert scale, and short answer questions, as well as statement agreements, which will allow us to better understand current practice regarding this topic. Space is available for additional comments should you find this necessary. There are no other alternative ways to participate in this study without filling out the survey below. There are no known risks for your participation in this study.

Completion of this anonymous survey is voluntary and for research purposes only. It should take less than 15 minutes to complete this survey. All responses are completely confidential, and you will not be personally identified in any reports or publications of this study. Data will be summarized and presented as part of a thesis project at The University of Texas Graduate School of Biomedical Sciences at Houston and part of a session at the National Society of Genetic Counselor's Annual Education Conference. By completing and submitting the questionnaire, you are implying consent to have your answers used and shared among collaborators for this study. You will not receive any financial compensation for completing the survey, however, for every survey completed a donation will be made to the March of Dimes.

Although the results of this study will be useful for physicians and other health professionals, there may be no direct benefit to you for participating in this study. You can refuse to answer or skip any questions or stop taking the survey at any time. Refusing to take part or stopping at any point during the survey will involve no penalty. If you decide to participate in the study, it is very important that you answer the questions as honestly as you can.

If you have any questions or concerns, please contact Jessica Davis or Kate Wilson, MS, CGC at (713) 486-2291. Thank you very much for your input regarding this important issue.

Survey link: http://www.surveymonkey.com/s/NIPT_Survey

Sincerely,

Jessica Davis
Genetic Counseling Student
UT Health Science Center at Houston
Graduate School of Biomedical Sciences
Principal Investigator

Kate Wilson, MS, CGC
Genetic Counselor/Clinical Instructor
UT Health Science Center at Houston
Department of Obstetrics, Gynecology and Reproductive Sciences
Committee Chair

Survey link: http://www.surveymonkey.com/s/NIPT_Survey

# BIBLIOGRAPHY

American Congress of Obstetricians and Gynecologists (2012). Noninvasive prenatal testing for fetal aneuploidy. *Obstetrics and Gynecology, 120*, 1532-1534.

American Congress of Obstetricians and Gynecologists (2007). Invasive prenatal testing for aneuploidy. *Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists, 88*.

A.C.o.O.a. Gynecologists, 2008 Socioeconomic Survey of ACOG Fellows, 2008.

Bianchi, D. W. (2004). Circulating fetal DNA: its origin and diagnostic potential – a review. *Placenta, 25*, S93-S101. doi:10.1016/j.placenta.2004.01.005

Bianchi, D. W., Platt, L. D., Goldberg, J. D., Abuhamad, A. Z., Sehnert, A. J., Rava, R. P., & MatErnal Blood IS Source to Accurately diagnose fetal aneuploidy (MELISSA) Study Group (2012). Genome-wide fetal aneuploidy detection by maternal plasma DNA sequencing. *Obstetrics and Gynecology*.

Breathnach, F.M., Fleming, A., & Malone, F.D. (2007). The second trimester genetic sonogram. *American Journal of Medical Genetics, 145C*, 62-72.

Bromley, B., Lieberman, E., Shipp, T. D., & Benacerraf, B. R. (2002). The genetic sonogram: a method of risk assessment for Down syndrome in the second trimester. *Journal of Ultrasound Medicine, 21*, 1087-1096.

Canick, J. A., Kloza, E. M., Lambert-Messerlian, G. M., Haddow, J. E., Ehrich, M., van den Boom, D., Bombard, A. T., Deciu, C., & Palomaki, G. E. (2012). DNA sequencing of maternal plasma to identify Down syndrome and other trisomies in multiple gestations. *Prenatal Diagnosis, 32*, 1-5. doi:10.1002/pd.3892

Chiu, R., Chan, K., Gao, Y., Lau, V., Zheng, W., Leung, T. Y., Foo C. H., Xie, B., Tsui, N. B., Lun, F. M., Zee, B. C., Lau, T. K., Cantor, C. R., & Lo, Y. (2008). Noninvasive prenatal diagnosis of fetal chromosomal aneuploidy by massively parallel genomic sequencing of DNA in maternal plasma. *Proceedings of the National Academy of Sciences, 105*, 20458-20463.

Eddleman, K. A., Malone, F. D., Sullivan, L., Dukes, K., Berkowitz, R. L., Kharbutli, Y., Porter, T. F., Luthy, D. A., Comstock, C. H., Saade, G. R., Klugman, S., Dugoff, L., Craigo, S. D., Timor-Tritsch, I. E., Carr, S. R., Wolfe, H. M., & D'Alton, M. E. (2006). Pregnancy Loss Rates After Midtrimester Amniocentesis. *Obstetrics & Gynecology, 108*, 1067-1072.

Gardner, R.J. M., & Sutherland, G. R. (2004). *Chromosome abnormalities and genetic counseling* (3rd ed.). New York, NY: Oxford University Press.

Hook, E. B. (1981). Rates of chromosome abnormalities at different maternal ages. *Obstetrics &Gynecology, 58*, 282-285.

International Society of Prenatal Diagnosis (2011). Prenatal detection of Down syndrome using massively parallel sequencing (MPS): a rapid response statement from a c ommittee on behalf of the Board of theInternational Society for Prenatal Diagnosis.

Kooij, L., Tymstra, T., & van den Berg, P. (2009). The attitude of women toward current and future possibilities of diagnostic testing in maternal blood using fetal DNA. *Prenatal Diagnosis, 29*, 164-168. doi:10.1002/pd.2205

Lippman, A., Tomkins, D. J., Shime, J., & Hamerton, J. L. (1992). Canadian multicentre randomized clinical trial of chorion villus sampling and amniocentesis: final report. *Prenatal Diagnosis, 12*, 385-408.

Lo, Y., Corbetta, N., Chamberlain, P. F., Rai, V., Sargent, I. L., Redman, C., & Wainscoat, J. S. (1997). Presence of fetal DNA in maternal plasma and serum. *Lancet, 350*, 485-487.

Lo, Y., Zhang, J., Leung, T. N., Lau, T. K., Chang, A. M., & Hjelm, N. M. (1999). Rapid clearance of fetal DNA from maternal plasma. *American Journal of Human Genetics, 64*, 218-224.

Malone F.D., Canick J.A., Ball R.H., Nyberg D.A., Comstock C.H., Bukowski R., Berkowitz, R. L., Gross, S. J., Dugoff, L., Craigo, S. D., Timor-Tritsch, I. E., Carr, S. R., Wolfe, H. M., Dukes, K., Bianchi, D. W., Rudnicka, A. R., Hackshaw, A. K., Lambert-Messerlian, G., Wald, N. J., D'Alton, M. E., & First- and Second-Trimester Evaluation of Risk (FASTER) Research Consortium (2005). First-trimester or second-trimester screening, or both, for Down's syndrome. *New England Journal of Medicine, 353*, 2001–11.

Merkatz, I. R., Nitowsk, H. M., Macri, J. N., & Johnson, W. E. (1984). An association between low maternal serum alpha-fetoprotein and fetal chromosomal abnormalities. *American Journal of Obstetrics & Gynecology, 148*, 886-894.

Milunsky, A., & Milunsky, J. (2009). *Genetic Disorders and the Fetus*. Oxford: Wiley Blackwell. Print.

Norton, M. E., Brar, H., Weiss, J., Karimi, A., Laurent, L. C., Caughey, A. B., Rodriguez, M. H., Williams, J. 3rd, Mitchell, M. E., Adair, C. D., Lee, H., Jacobsson, B., Tomlinson, M. W., Oepkes, D., Hollemon, D., Sparks, A. B., Oliphant, A., & Song, K. (2012). Non-invasive chromosomal evaluation (NICE): results of a multicenter

prospective cohort study for detection of fetal trisomy 21 and trisomy 18. *American Journal of Obstetrics and Gynecology, 207*, 137.e1-137.e8.

Ormond, K. E. (1997). Update and review: maternal serum screening. *Journal of Genetic Counseling, 6*, 395-417.

National Society of Genetic Counselors Public Policy Committee (2012). Noninvasive prenatal testing/noninvasive prenatal diagnosis: the position of the National Society of Genetic Counselors.

Palomaki, G. E., Deciu, C., Kloza, E. M., Lambert-Messerlian, G. M., Haddow, J. E., Neveux, L. M., Ehrich, M., van den Boom, D., Bombard, A. T., Grody, W. W., Nelson, S. F., & Canick, J. A. (2012). DNA sequencing of maternal plasma reliably identifies trisomy 18 and trisomy 13 as well as Down syndrome: an international collaborative study. *Genetics in Medicine*, 14, 296-305. doi:10.1038/gim.2011.73

Palomaki, G. E., Kloza, E. M., Lambert-Messerlian, G. M., Haddow, J. E., Neveux, L. M., Ehrich, M., van den Boom, D., Bombard, A. T., Deciu, C., Grody, W. W., Nelson, S. F., & Canick, J. A. (2011). DNA sequencing of maternal plasma to detect Down syndrome: an international clinical validation study. *Genetics in Medicine*, 13, 913-920. doi:10.1097/GIM.0b013e3182368a0e

Sayers, L. C., Allyse, M., Norton, M. E., & Cho, M. K. (2011). Cell-free fetal DNA testing: A pilot study of obstetric healthcare provider attitudes toward clinical implementation. *Prenatal Diagnosis*. doi:10.1002/pd.2835.

Sparks, A. B., Struble, C. A., Wang, E. T., Song, K., & Oliphant, A. (2012). Non-invasive

prenatal detection and selective analysis of cell-free DNA obtained from maternal blood: evaluation for trisomy 21 and trisomy 18. *American Journal of Obstetrics and Gynecology*. doi:10.1016/j.ajog.2012.01.030.

Spencer, K., Ong, C., Skentou, H., Liao, A. W., & Nicolaides, K. H. (2000). Screening for trisomy 13 by fetal nuchal translucency and maternal serum free beta-hCG and PAPP-A at 10–14 weeks of gestation. *Prenatal Diagnosis, 20*, 411–416.

Valenti, C., Shutta, E. J., & Kehaty, T. (1968). Prenatal diagnosis of Down's syndrome. *Lancet, 2*, 220.

Wald, N. J., Rodeck, C., Hackshaw, A. K., & Rudnicka, A. (2004). SURUSS in perspective. *British Journal of Obstetrics and Gynaecology, 111*, 521-531.

Wapner, R., Thom, E., Simpson, J. L., Pergament, E., Silver, R., Filkins, K., Platt, L., Mahoney, M., Johnson, A., Hogge, W. A., Wilson, R. D., Mohide, P., Hershey, D., Krantz, D., Zachary, J., Snijders, R., Greene, N., Sabbagha, R., MacGregor, S., Hill, L., Gagnon, A., Hallahan, T., Jackson, L., & First Trimester Maternal Serum Biochemistry and Fetal Nuchal Translucency Screening (BUN) Study Group (2003). First-trimester screening for trisomies 21 and 18. *New England Journal of Medicine, 349*, 1405-1413.

Wilson, K. L., Czerwinski, J. L., Hoskovec, J. M., Noblin, S, J., Sullivan, C. M., Harbison, A., Campion, M. W., Devary, K., Devers, P., & Singletary, C. N. (2012). NSGC practice guideline: prenatal screening and diagnostic testing options for chromosome aneuploidy. *Journal of Genetic Counseling*. doi: 10.1007/s10897-012-9545-3.

Yotosumato, J., Sekizawa, A., Koide, K., Purwosunu, Y., Ichizuka, K., Matsuoka, R.,

Kawame, H., & Okai, T. (2012). Attitudes toward non-invasive prenatal diagnosis among pregnant women and health care professionals in Japan. *Prenatal Diagnosis*. doi:10.1002/pd.3886.

# VITA

Jessica Madge Davis was born in San Diego, California on February 9, 1987. She is the daughter of Gene and Madge Davis. After completing her work at Palm Harbor University High School, Palm Harbor, Florida in 2005, she entered Stetson University in DeLand, Florida. She received the degree of Bachelor of Science with a major in psychology from Stetson in May, 2009. For the next three years, she worked as a research technician in the Department of Cell Biology at Baylor College of Medicine. In the Fall of 2011 she entered The University of Texas Genetic Counseling Program and graduated with a Master of Science in Genetic Counseling in May, 2013.