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Prenatal Decision-Making Process of Patients in Three Cities in South Carolina

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Abstract

Purpose: Noninvasive prenatal testing (NIPT) has changed the landscape of prenatal genetic evaluation. This novel test can be performed as early as 10 weeks gestation without risk of pregnancy complication and has evoked questions about its applicability, appropriate use, and patient response. The purpose of this study was to evaluate patient decision-making processes about prenatal testing options as NIPT is integrated into the clinical realm. **Method:** Prenatal patients who were offered NIPT during genetic counseling (N = 105) in three cities in South Carolina completed a survey to address the goals of this study. **Results:** The top five factors most frequently rated as important by participants were as follows: (1) To be prepared if the baby had a disability (91%), (2) To avoid the risk of miscarriage (88%), (3) For reassurance the baby does not have a genetic condition (86%), (4) To obtain genetic information about the fetus as early as possible (81%), and (5) To have a test that provides more accurate information than other tests (77%). Three factors were found to be significantly more important to participants who selected NIPT than to participants who did not: (1) To obtain genetic information about the fetus as early as possible (p = .021), (2) To have a test that provides more accurate information than other tests (p = .025), and (3) To be prepared if the baby had a disability (p = .001). In addition, a majority of participants (74%) felt consideration of termination if the baby had a chromosome condition was irrelevant to their decision. This factor was not an NIPT-selection factor, meaning participants who selected NIPT were not significantly more

likely to consider termination of an affected pregnancy important to their decision than participants who did not select NIPT. **Conclusions:** Patients are faced with new decisions as NIPT is integrated into prenatal care. This study evaluated the top five factors most frequently rated important by participants about their prenatal testing decision and identified three NIPT-selection factors. While every patient should be counseled as a unique individual, the results from this study are observations that may help healthcare providers better understand patient perspective. This study reveals five factors important to patient decision-making regarding prenatal testing; of these, three factors (obtaining genetic information about the fetus as early as possible, having a test that provides more accurate information than other tests, and being prepared if the baby had a disability) were significantly influential in patient selection of NIPT.

Keywords: Noninvasive prenatal testing (NIPT), patient decision making, decision-making process, prenatal genetic testing

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List of Abbreviations

ACOG ..... American College of Obstetricians and Gynecologists

AFP ..... Alpha-Fetoprotein

AMA ..... Advanced Maternal Age

cffDNA ..... Cell-Free Fetal DNA

CVS ..... Chorionic Villus Sampling

DANSR ..... Digital Analysis of Selected Regions

DIA ..... Dimeric Inhibin-A

FTS ..... First Trimester Screening

FORTE ..... Fetal-Fraction Optimized Risk of Trisomy Evaluation

hCG ..... Human Chorionic Gonadotropin

ICSI ..... Intracytoplasmic Sperm Injection

ISPD ..... International Society for Prenatal Diagnosis

IVF ..... In Vitro Fertilization

LDT ..... Laboratory Developed Test

MMS ..... Multiple Marker Screening

MoM ..... Multiple of the Median

MPS ..... Massively Parallel Sequencing

MSAFP ..... Maternal Serum Alpha-Fetoprotein

NIPD ..... Noninvasive Prenatal Diagnosis

NIPT ..... Noninvasive Prenatal Testing

NSGC ..... National Society of Genetic Counselors

NT ..... Nuchal Translucency

ONTD ..... Open Neural Tube Defect

PAPP-A..... Pregnancy Associated Plasma Protein- A

uE3 ..... Unconjugated Estriol

Chapter 1: Background

Since 2011, noninvasive prenatal testing (NIPT) has been clinically available to obtain near-diagnostic results for aneuploidy as early as 10 weeks gestation without risk of pregnancy complication (Wilson et al., 2012). As this novel test integrates into the prenatal clinic, questions have been raised about its applicability, appropriate use, and how patients will respond. To address these questions, it is important to consult accepted practice guidelines, research, and ethical statements. An understanding of available prenatal testing and screening options is necessary to appreciate the conflict surrounding the role of NIPT in conjunction with or as a replacement for established prenatal tests. The following literature review attempts to provide an overview of prenatal testing and screening options currently available, the ethical implications of adding NIPT to these options as well as explore how patients make decisions about prenatal testing, and anticipatory patient response to NIPT.

1.1 Prenatal Diagnostic Testing

Prenatal diagnosis is typically offered by healthcare practitioners to patients whose pregnancies are at increased risk for chromosomal abnormalities or genetic disorders. Indications for diagnostic testing include: a woman age 35 or older at delivery, an abnormal result on a screening test, a family history of a hereditary condition, or fetal anomalies seen on ultrasound. While these indications prompt healthcare providers to discuss testing options with patients, diagnostic testing and ultrasound are available to all pregnant women (ACOG, 2007a). Current diagnostic procedures, such as

amniocentesis and chorionic villus sampling (CVS), use invasive methods to determine whether a fetus is affected with a genetic condition and provide highly sensitive results.

Chorionic villus sampling is used to detect chromosomal aneuploidy in the first trimester between weeks 10 and 13. Ultrasound guidance is required to remove trophoblastic tissue from the placenta with a catheter, either transcervically or transabdominally. CVS results are obtained with 98%-99% accuracy, with a <1% chance of mosaicism and a <1% chance for maternal cell contamination. Mosaicism in CVS cytogenetic analysis is often confined to the placenta, and amniocentesis is recommended for confirmation of the fetal karyotype (Collins & Impey, 2012). The CVS procedure-related chance of miscarriage approximates 0.5%-1% for both singleton and twin pregnancies (Wilson et al., 2012). Other complications after CVS can involve vaginal spotting or bleeding, which may occur in up to 32.2% of transcervical procedures, and less often in a transabdominal approach. The incidence of culture failure or amniotic fluid leakage after CVS is less than 0.5% (Milunsky, 2004). CVS procedures performed before 10 weeks have been shown to increase the risk of fetal limb defects (World Health Organization, 1992).

Amniocentesis is used to detect chromosomal aneuploidy in the second and third trimesters, starting at 15 weeks gestation. Ultrasound guidance is required to insert a needle transabdominally into the amniotic sac to withdraw 20-30 cc of amniotic fluid, which contains fetal cells. Amniocentesis results are obtained with 99.7%-99.9% accuracy. The procedure-related chance of miscarriage approximates 1/300-1/500 (ACOG, 2007b). Potential complications include a 1%-2% chance of vaginal spotting or amniotic fluid leakage and <0.1% chance of chorioamnionitis (Borgida, Mills, Feldman,

Rodis, & Egan, 2000). Needle injuries to the fetus are very rare but have been reported. Amniotic fluid cell culture failure occurs in 0.1% of samples (ACOG, 2007b).

While CVS and amniocentesis are most often used for chromosomal analysis by karyotyping, they can serve other functions. CVS may be used to test for biochemical abnormalities, single gene conditions, and collagen abnormalities, but cannot test for open neural tube defects (ONTDs). Amniocentesis can test for ONTDs, biochemical abnormalities, and single gene conditions (Wilson et al., 2012).

1.2 Prenatal Screening Procedures

Prenatal screening for aneuploidy is a standard of healthcare offered to all pregnant women. Screening procedures allow high-risk pregnancies to be identified; women with these pregnancies are then offered diagnostic testing. Two of the most common prenatal screening techniques are first trimester screening (FTS) and second trimester multiple marker screening (MMS). Screening tools are meant to be highly accessible and do not present risk to the pregnancy. Most laboratories target a 5% false positive rate for serum screening options (ACOG, 2007a).

First trimester screening identifies trisomy 21 with a sensitivity of 90% and trisomies 18 and 13 with a sensitivity of 95% (ACOG, 2007a). Nuchal translucency (NT) measurements are combined with maternal age and the levels of two proteins, human chorionic gonadotropin (hCG) and pregnancy plasma associated protein A (PAPP-A), to estimate the chance for aneuploidy unique to a pregnancy. PAPP-A and hCG are measured between 9w0d-13w6d, while the nuchal translucency (NT) measurement must be taken between 10w4d-13w6d. The patterns of the levels of the serum analytes change the chance for aneuploidy. For example, relative low hCG and low PAPP-A levels increases the chance for trisomy 18 or 13. Likewise relative increased hCG and low

PAPP-A increases the chance for trisomy 21 (Shamshirsaz, Benn, & Egan, 2010). A significantly elevated NT measurement (>3.0mm or the 95th percentile) is correlated with an increased chance of chromosomal aneuploidy, and it is appropriate to offer diagnostic testing whether the patient has a positive screening result or not. Elevated NT measurements above 3.5mm are associated with an increased chance of congenital heart defects; thus a fetal echocardiogram is appropriate. A late development or lack of a lymphatic system could also cause an elevated NT measurement. Even if a normal fetal karyotype is confirmed, the chance for an adverse pregnancy outcome remains elevated (ACOG, 2007a).

One recent study summarizing the results of first trimester screening performed at a single clinical center over a 10-year period found first trimester screening to be efficacious in identifying pregnancies with trisomies 13, 18, and 21. However, 29% of chromosomally abnormal fetuses identified to be at risk for these aneuploidies actually had a different chromosome complement. The authors suggest that prior to invasive diagnostic testing following a positive serum screen, patients should be counseled about the possible presence of a fetal aneuploidy other than trisomies 13, 18, and 21 (Alamillo, Krantz, Evans, Fiddler, & Pergament, 2013).

First trimester screening does not assess risk for ONTDs. Thus, a maternal serum alpha-fetoprotein (MSAFP) screen should be offered in the second trimester to patients who choose to undergo FTS (ACOG, 2007a).

There are three options for first trimester screening: (1) NT only with maternal age uses only the fetal NT measurement and maternal age, (2) First trimester analyte screening uses the levels of the analytes combined with maternal age, and (3) Combined

first trimester screening uses the NT measurement, the serum analytes, and maternal age. The last approach has been shown to have the highest detection rates (ACOG, 2007a).

Multiple marker screening is offered between weeks 15w0d-21w6d of gestation. This test assesses risk of trisomies 18 and 21 (not 13) and ONTDs by considering maternal age, weight, race, diabetic status, and protein analytes produced by pregnancy and found in the maternal bloodstream. Options include the "triple" screen and the "quad" screen. The triple screen measures the levels of maternal serum alpha-fetoprotein (AFP), hCG, and unconjugated estriol (uE3). The quad screen adds dimeric inhibin-A (DIA), which increases the detection rate for Down syndrome. The quad screen has a higher detection rate, with a sensitivity for Down syndrome of 75%-83% and a sensitivity for trisomy 18 of 60%-70% (ACOG, 2007a).

Similar to FTS, MMS identifies patterns that indicate an increased chance for trisomies 18 or 21. For example: elevated hCG and DIA in association with low AFP and uE3 indicate increased risk for trisomy 21; and low AFP, hCG, and uE3 levels indicate increased risk for trisomy 18. In addition, high levels of AFP (>2.5MoM) are an indication for an increased risk for an ONTD (Shamshirsaz et al., 2010).

Typically, patients opt for FTS aneuploidy screening *or* second trimester MMS, depending at what gestational age they present for prenatal care; however some practices utilize a combined approach. There are three options when combining FTS and MMS: integrated screening, stepwise sequential screening, and contingency screening. Using a combined approach increases detection rates and decreases false positive rates, but poses the difficulty of requiring multiple appointments to complete the process. All combined

screening approaches have similar detection rates. For example, integrated screening detects Down syndrome at 94%-96% and trisomy 18 at 91%-96% (Wilson et al., 2012).

Integrated screening combines the results from NT and PAPP-A measurements in the first trimester and serum analytes AFP, hCG, uE3, and DIA in the second trimester. No results are revealed until after the second step, when they are combined. Stepwise sequential screening begins with a first trimester calculation including an NT measurement, maternal age, and serum analytes PAPP-A and hCG. Results are disclosed to individuals at high risk for fetal aneuploidy, and these individuals are offered diagnostic testing. Individuals not in the high-risk group proceed to the second trimester blood draw, which uses serum analytes AFP, hCG, uE3, and DIA. Contingency screening adjusts maternal age-alone chance for aneuploidy based on serum analytes and fetal NT measurement. Patients are divided into low, medium, and high risk groups based on their results and are offered no further testing, the second trimester serum analyte screening step, or diagnostic testing, respectively. The medium risk group are then further sorted into a high risk group who are offered diagnostic testing and a low risk group who are not offered further testing by the results of the second screening step (ACOG, 2007a).

1.3 Noninvasive Prenatal Testing

As early as 1997, Lo et al. recognized that cell-free fetal DNA (cffDNA) accounts for 5%-10% of total free-floating DNA in the maternal bloodstream and is easier to isolate from maternal blood than cellular fetal DNA (Lo et al., 1997). This discovery prompted an effort to discover a reliable method for NIPT for fetal genetic conditions. Massively parallel sequencing (MPS) and selective analysis of cell-free fetal DNA in

maternal plasma are two methods that are highly sensitive and specific screening tools for common fetal chromosome aneuploidies (Wilson et al., 2012).

MPS allows large quantities of cffDNA to be read in a short amount of time with high through-put sequencing. Maternal and fetal DNA sequences are then assigned to the chromosome from which they originated and are quantified as a ratio. This results in a specific amount of genetic material read for a particular chromosome, which can be compared to the amount of genetic material that is present if the genotype is typical. An increase in detection of genetic material for chromosome 21, for example, would indicate trisomy 21 (Lo, 2012).

Massively parallel sequencing has been instrumental in detecting subtle quantitative differences between affected and unaffected pregnancies. Consider the example of detecting a pregnancy affected with trisomy 21: if 5% of cell free DNA in the maternal bloodstream originates in the fetus, the cffDNA from each copy of chromosome 21 of an unaffected fetus comprises 2.5% of the total cell free DNA for chromosome 21 in the maternal bloodstream. A pregnancy affected with trisomy 21 should have 2.5% more fetal chromosome 21 transcripts than an unaffected pregnancy. Because the mother supplies the majority (95%) of the cell free DNA, detecting a subtle 2.5% overall difference requires advanced technology and laboratory expertise (Simpson, Richards, Ontano, & Driscoll, 2012).

Identification of trisomies in twin gestations relies on a small incremental increase in the proportion of DNA fragments. Both monozygotic and dizygotic twin pregnancies have higher placental mass than singleton pregnancies; thus it is expected they contribute more fetal DNA to maternal circulation and consequently have higher fetal fraction.

Canick et al. (2012) found that on average multiple pregnancies contributed 35% more fetal DNA to the total free DNA in maternal plasma than singleton pregnancies. The largest study on MPS in twin gestations to date correctly classified seven pregnancies with trisomy 21, one with trisomy 13, and seventeen euploid pregnancies (two of which were triplets) with a detection rate of 100% and confidence interval of 95% (Canick et al., 2012). However, if NIPT is abnormal, which twin is affected is indiscernible. Confirmation by amniocentesis of each fetal sac is recommended when fetal trisomy is detected in twin pregnancies by NIPT (Canick et al., 2012).

Selective analysis sequences cell-free DNA from maternal plasma for selected loci from specific chromosomes of interest. Selective analysis and MPS both utilize sequencing technology, but unlike MPS, selective analysis only sequences DNA from chromosomes of interest and not the entire genome, which increases throughput. A novel selective analysis assay, digital analysis of selected regions (DANSR), generates sequencing templates from chromosome-specific assays and produces high mapping rates (Sparks et al., 2012). Thus, selective analysis has been proposed to be a more efficient and less expensive option for NIPT. Fetal-fraction optimized risk of trisomy evaluation (FORTE), a process of using fetal fraction of cffDNA results from sequencing cffDNA and generating a risk score, has been shown to estimate accurately the risk of aneuploidy (Sparks et al., 2012).

At least 5% of NIPT samples are yielding noninformative results due to insufficient cffDNA. Samples can be taken at 10 weeks gestation or any time after, but cffDNA levels do not increase with advancing gestational age (Simpson, 2013).

The newest advancements in NIPT focus on attaining diagnostic competency for aneuploidy detection, but this technology also provides access to RhD genotyping, fetal sex determination, paternity testing, and limited single gene testing. Although the proposed research project focuses on advancements in detecting fetal chromosomal aneuploidy, it should be recognized that NIPT has been used to fulfill these other purposes, which will be described briefly. Detection of RhD sequence in the bloodstream of an RhD-negative mother indicates the fetus is RhD-positive and warrants administration of Rh immune globulin. Using the same strategy, if Y-sequence is detected in the maternal bloodstream, one may deduce that the fetus is generating this genetic material and thus is a male (Simpson et al., 2012). Paternity is determined using informative single nucleotide polymorphisms (SNPs) (ie. occurring when the mother and one potential father are homozygous for the same allele while the other potential father is homozygous for the alternative allele) (Guo et al., 2012). Certain Mendelian disorders can be detected from cffDNA if they are paternally derived. For example, polycystic kidney disease, inherited as an autosomal dominant trait, may be detected in the fetus noninvasively if the presence of the paternal mutation is found in the blood of the unaffected mother (Simpson et al., 2012).

NIPT as a prenatal testing option is rapidly evolving yet has limitations. Conjecture has been put forth that NIPT will eventually reach diagnostic standards similar to CVS but not amniocentesis. This expectation recognizes that cffDNA are derived from trophoblasts, the same tissue studied in CVS. Other complications that can occur with CVS may potentially occur with NIPT as well, such as placental mosaicism. NIPT will not distinguish between trisomy and unbalanced translocation because the test

measures the *quantity* of each chromosome present in the fetus and does not provide a karyotype image (Benn, Cuckle, & Pergament, 2012). Despite current limitations, the technology supporting NIPT continues to advance and will likely have a considerable role in current and future prenatal assessment algorithms.

1.4 Noninvasive Prenatal Testing: Transitioning from Laboratory to Clinical Practice

The development of NIPT has been funded primarily by the private sector and is considered a Laboratory Developed Test (LDT). LDTs are developed, evaluated, and validated within one laboratory; unlike commercial tests, they are not manufactured and marketed to several labs. Consequently, LDTs are not regulated by the U.S. Food and Drug Administration. Multiple laboratories have developed processes for NIPT (Orton, 2012).

Three large-scale clinical trials have been published by two separate groups that used MPS of maternal plasma to detect an overrepresentation of chromosome material. An international study using MPS released two sets of analyzed data: one on trisomy 21 in 2011 and one on trisomies 18 and 13 in 2012. This multicenter study detected trisomy 21 with a sensitivity and specificity close to 99% (Palomaki et al., 2011). The follow-up study detected trisomy 18 with a sensitivity of 100% and a specificity of 99.7% and trisomy 13 with a sensitivity of 91.7% and a specificity of 99.1% (Palomaki et al., 2012).

Another group also used MPS to evaluate high-risk pregnancies for chromosome conditions. This study detected trisomy 21 with a sensitivity of 100%, trisomy 18 with a sensitivity of 97.2%, and trisomy 13 with a sensitivity of 78.6%. All three were detected with a specificity of 100%. In addition, this study found a 94% detection rate for

monosomy X and reported several cases of mosaicism for trisomy 21, trisomy 18 and monosomy X (Bianchi et al., 2012).

Other studies have validated NIPT through selective analysis. A multicenter cohort study performed chromosome-selective sequencing on chromosomes 21 and 18 in a population of women undergoing CVS or amniocentesis for any indication. The sensitivity and specificity for trisomy 21 were 100% and 99.97%. The sensitivity and specificity for trisomy 18 were 97.4% and 99.93% (Norton et al., 2012). Another study reported 80% sensitivity and 99.95% specificity for trisomy 13 (Ashoor, Syngelaki, Poon, Rezende, & Nicolaides, 2013).

NIPT first became clinically available in October of 2011 when Sequenom released *MaterniT21™*, a test for Down syndrome that uses MPS to detect cffDNA (Sequenom CMM, 2011). Sequenom has since included detection for chromosomes 13, 18, and Y in the more recent version of its test, *MaterniT21Plus™* (Palomaki et al., 2011). In 2012, Sequenom provided evidence that MPS could reliably detect Down syndrome in women with high-risk twin gestations and added this testing option (Canick et al., 2012). In February, 2013, Sequenom's *MaterniT21Plus™* included detection for sex chromosomal aneuploidies (PR Newswire, 2013).

LabCorp (Ariosa Diagnostics) and Verinata Health released similar tests in 2012, *Harmony™* and *verify™*, respectively. *Harmony™* uses MPS to detect cffDNA for chromosomes 21, 18, and 13. *Verifi™* uses MPS to detect chromosomes 21, 18, 13, X, and Y; thus sex chromosomal aneuploidies such as monosomy X, XXX, XXY, and XYY are reported (PR Newswire, 2012a; PR Newswire 2012b). Natera is undergoing a clinical

trial, *PreNATUS*, and once clinically validated will offer testing for trisomies 21, 13, and 18 and sex chromosomal aneuploidies (Biotechnology Industry Organization, 2012).

The clinical function of NIPT has been debated. The high sensitivity of the test has called to question whether it may be used for diagnostic purposes. In fact, NIPT is also known in current literature as noninvasive prenatal diagnosis (NIPD). However, guidelines and statements issued by professional organizations agree that NIPT should be considered a screening tool at this point in time, and only offered to high risk populations. A 2012 position statement by the National Society of Genetic Counselors (NSGC) stated that currently it "is recommended only as a highly specific screening measure for high-risk pregnancies, which requires follow-up diagnostic testing" (Devers et al., 2013). The International Society for Prenatal Diagnosis (ISPD) made a similar statement, which follows: "[T]his test is not fully diagnostic and therefore constitutes an advanced screening test. Accordingly, confirmation of MPS positive results through invasive testing would still be required" (Benn et al., 2011b, p.1). The American College of Obstetricians and Gynecologists (2012) reaffirmed this position in their committee opinion, stating, "A patient with a positive test result should be referred for genetic counseling and should be offered invasive prenatal diagnosis for confirmation of test results" (ACOG, 2012, p.1).

The NIPT clinical validation studies recruited only women who were otherwise pursuing invasive testing; thus the majority of pregnancies were high-risk for aneuploidy. Consequently, testing is currently offered to high-risk populations only. Current indications for NIPT include: advanced maternal age, an abnormal maternal serum

screen, personal or family history of aneuploidy, or an abnormal ultrasound (Wilson et al., 2012).

Clinical validation studies of the general population (i.e., low-risk patients) are in process. Preliminary evidence indicates NIPT should have similar sensitivity and specificity in a low-risk population (Nicolaides, Syngelaki, Ashoor, Birdir, & Touzet, 2012). Indeed, research has suggested that NIPT may be an effective screening method as a standard test for risk assessment of fetal trisomies 21, 18, and 13 in the general population (Fairbrother, Johnson, Musci, & Song, 2013). With further support, this advanced prenatal test may be offered to women with low-risk pregnancies (Norton et al., 2012).

1.5 Patients' Decision-making in Prenatal Testing

The number of prenatal testing options available to prospective parents has significantly increased during the past half-century. This presents prenatal patients with what can feel like a menu of confusing choices. The methods used to navigate these choices and reasons for making decisions are unique to each woman, and healthcare providers should be aware of the surrounding complexities in order to provide standard care (Pergament & Pergament, 2012).

Screening options are noninvasive, which make them attractive for patients who desire individualized risk assessment information about their pregnancy but do not want an associated risk of miscarriage, or for those who would like to use screening results to make a decision about whether or not to undergo more comprehensive diagnostic testing. The primary limitation of screening is that it does not provide a definitive diagnosis, potentially creating anxiety in women with unaffected pregnancies and falsely reassuring

women with affected pregnancies (ACOG, 2007b). Diagnostic tests offer a definitive result, but are associated with a risk of miscarriage (Collins & Impey, 2012).

Many women find NIPT appealing because it gains near-diagnostic genetic information about the fetus without an associated chance of miscarriage. In fact, when assessing pregnant women's level of future interest in NIPT, one study found pregnant women thought the most important feature of NIPT would be the safety of the fetus (75%), followed by accuracy (13%), and early availability of results (7%) (Tischler, Hudgins, Blumenfeld, Greely, & Ormond, 2011).

Reproductive decisions must be understood within the cultural context of the time period, as genetic testing is constantly evolving. Today in the United States, a strong emphasis is placed on personal choice, and individuals have unlimited access to information and external influences, such as the media, the internet, and social media (Pergament & Pergament, 2012). The uptake of prenatal testing has increased, which reflects the growing need in couples to seek further information genetic about their fetus (Pivetti, Montali, & Simonetti, 2012). Prospective parents have higher expectations than in the past of a successful reproductive outcome (Choolani & Biswas, 2012). This expectation could potentially stimulate a desire for reassurance about the pregnancy through prenatal testing.

There are a multitude of personal and social factors that directly and indirectly affect women's prenatal testing decisions. In general, it is accepted that "decision-making by prospective parents is based on rational assessment of risk, benefit, and choices, specifically: (1) the risk of a fetal abnormality compared with the loss of a normal pregnancy after invasive testing; (2) the benefit of gaining reassurance of a

healthy fetus; and (3) the options available if the fetus is identified as affected by a genetic, developmental disorder, or both" (Pergament & Pergament, 2012, p. 518). While these are useful guidelines, understanding specifically what is important to a patient has important implications in the delivery of service.

Factors that influence women's reproductive decisions following genetic counseling may include, for example: perceived pain of diagnostic testing, perceived risk of diagnostic testing, anxiety of health about the fetus, emotional and social burden of possible pregnancy termination, financial and social burden of a child with disabilities, access to prenatal services, past pregnancy history, socioeconomic status, personal philosophy, social and partner support, healthcare education and support, media, and uncertainty of genetic tests. Of course, the importance of each factor, how it interacts with other factors, and the influence it might have over a particular woman's decision varies. It is difficult to measure objectively the role each factor plays in a decision (Pergament & Pergament, 2012).

The overall most frequently reported sources of difficulty for decision-making in women in a systematic review of 32 unique studies regarding perceptions of Down syndrome prenatal testing were pressure from others, emotions, and lack of information. The same study found the most important sources of reassurance for women to be personal values, understanding, and confidence in the medical system (St-Jacques et al., 2008).

Prenatal patients often feel ambivalence towards screening and diagnosis of aneuploidy (Vassy, 2005). It has been postulated that for many women the miscarriage risk associated with invasive testing is a psychological barrier to diagnostic testing and

that if this risk were removed, women may feel more inclined to have a diagnostic test (Newson, 2008). Noninvasive prenatal testing may present an option for near-diagnostic information about fetal aneuploidy without an associated risk of miscarriage for these women.

However, some women prefer not to have genetic knowledge of their fetus if the knowledge does not alter their course of action. Because it is not possible to correct a chromosome condition cytogenetically, many women perceive termination as the only available option in light of a positive testing result. A meta-analysis of pregnant women's decision making processes with regard to prenatal screening for Down syndrome showed that some women consider genetic testing to be pointless, since they would not terminate the pregnancy even if the result were positive (Reid, Sinclair, Barr, Dobbs, & Crealey, 2009).

Other women consider genetic testing to be empowering, even if they would choose not to terminate an affected pregnancy. In fact, one study concluded that the introduction of NIPT is likely to cause a shift in decision-making that may be associated with an increase in the uptake of prenatal testing but a decrease in the decision to terminate pregnancies affected with Down syndrome (Verweij, Oepkes, & De Boer, 2013). Another study surveyed parents of children with Down syndrome: 75% were disinclined to terminate a future affected pregnancy, but only 33% would not have prenatal testing (Kuppermann et al., 2011). Learning of a fetus' diagnosis may provide the patient time to share the diagnosis with a support network and prepare emotionally.

Studies have been performed to evaluate uptake of invasive diagnostic testing following unexpected results. Women are more likely to undergo invasive diagnostic

testing when fetal anomalies are detected on ultrasound or a screening test result is positive, due to the increased chance for chromosomal aneuploidy (Pryde, Drugan, Johnson, Isada, & Evans, 1993). A more recent study evaluating factors determining uptake of invasive testing following first-trimester combined testing found that women opting for invasive testing are significantly younger and less likely to have had IVF/ICSI. Women less than 36 years old opt for invasive testing more frequently, regardless of their chance for Down syndrome, while women 36 years or older are more likely to let the magnitude of the chance estimate guide their decision (Lichtenbelt et al., 2013).

Research examining psychosocial determinants that influence women's intention to undergo prenatal genetic testing found women are more inclined to feel favorably about prenatal genetic testing if they: (1) are in favor of science and scientific progression, (2) possess a good knowledge of genetic testing, and (3) can count on the support of family members and friends. Women's attitudes about pregnancy termination are the most predictive indicators of intent to undergo prenatal testing (Pivetti et al., 2012).

Experience in previous pregnancies has been shown to play a role in women's prenatal testing decisions. Research demonstrates that women who had a previous miscarriage or termination are more likely to undergo testing than women who have already given birth to three or more children (Halliday, Lumley, & Watson, 1995).

Research has indicated that women's perceptions of chance of miscarriage or of having an affected fetus may form independent of empirical risk estimates. For example, women aged 35 years and older have a higher perceived chance of Down syndrome than younger women (this chance *is* higher in women 35 and over) but a lower perceived

chance of a procedure-related miscarriage (this chance is the *same* for both parties). Other correlations were made between race, socioeconomic status, education level, and perception of health. Interestingly, women who undergo diagnostic testing perceive a higher chance of having a baby with Down syndrome and a lower chance of a procedure-related miscarriage than women who choose not to have a diagnostic procedure (Caughey, Washington, & Kuppermann, 2008).

Some women are apprehensive about expected pain related to a procedure (Mujezinovic & Alfirevic, 2011). Research from Turkey reported that actual pain after amniocentesis was significantly lower compared with perceived pain before the procedure and anxiety before amniocentesis was significantly higher than anxiety after the procedure. Of particular interest, women who were informed about the procedure beforehand perceived the procedure to be less painful and expressed less anxiety before and after amniocentesis. The authors suggested that pre-amniocentesis counseling should emphasize that the actual pain and anxiety experienced during amniocentesis are often significantly lower than expected (Al, Yalvac, Altar, & Dolen, 2009).

Patients' own demographic characteristics play roles in their prenatal testing decision making. A meta-analysis of three national polls over a 14-year period, from 1990 to 2004 found married/separated/widowed individuals and those who attended church on a regular basis were less likely to want prenatal testing than individuals who were single and/or attended church less often. Catholics were significantly less likely, and Jewish individuals significantly more likely to opt for prenatal genetic testing (Singer, Couper, Raghunathan, Van Hoewyk, & Antonucci, 2008). Another study documented ethnic differences in the decision to undergo or not undergo prenatal

screening for aneuploidy, with women from minority groups and of non-Western ethnic origin less likely to participate (Fransen et al., 2010).

The attitudes of health professionals have been shown to impact the uptake of Down syndrome screening. In fact, in a study assessing pregnant women's interest in NIPT, one in five women said that they would do what their health professional recommended (Tischler et al., 2011).

Trends have been observed in differences between what women and healthcare providers consider most important when making a decision about prenatal testing. Choolani & Biswas (2012) point out that when it comes to risk and benefit of prenatal testing, what healthcare professionals feel is important, what patients feel is important, and what healthcare professionals believe patients feel to be important are often three completely separate things. Health professionals tend to place a higher value on tests that are conducted earlier in pregnancy than women, who prefer to wait for a result until later in pregnancy if the test is safer and more accurate. This discrepancy potentially could result in screening policies that overemphasize timing in the selection of a test to the relative neglect of tests associated with lower miscarriage rates and higher detection rates but conducted later in pregnancy (Bishop et al., 2004).

In another study, both women and health professionals preferred a test with greater accuracy, no risk of miscarriage, and one that provided as much information as possible. However, opinions between the two groups had statistically significant differences in the coefficients for accuracy, timing, and no risk of miscarriage. Women strongly preferred a test with no risk of miscarriage: they were prepared to wait more than twice as long and accept 12% lower accuracy for a test that had no risk of

miscarriage as compared with health professionals. In contrast, health professionals preferred to offer a more accurate test, even if it was associated with a small risk of miscarriage (Hill, Fisher, Chitty, & Morris, 2012).

Further subgroup comparisons in this discrete choice experiment indicated that women aged 35 years or more placed a greater emphasis on accuracy than younger women. Women who had undergone Down syndrome screening in their current pregnancy differed from those who had declined Down syndrome screening in the emphasis they placed on test timing and information. Of the 50 women who chose not to have screening for Down syndrome, only 12 indicated that they would not have any test presented to them on the questionnaire. The authors suggested many of the women who declined screening for Down syndrome may choose to undergo testing if there is no risk of miscarriage associated with the definitive diagnosis (Hill et al., 2012).

1.6 Clinical and Ethical Implications of Noninvasive Prenatal Testing

The extraordinary momentum with which the technology of NIPT has forged ahead is impressive. However, many feel hesitant to offer NIPT in a clinical setting without further consideration of ethical repercussions. It is the responsibility of those who provide and regulate healthcare to reflect on the benefits and risks of particular tests so that these are explained to patients, guidelines are established, and advancements in NIPT progress in a responsible manner.

NIPT presents many advantages to women. It is a noninvasive test without association of miscarriage that supplies highly sensitive results and imposes less time restrictions on gestational age than other prenatal tests. Eliminating the risk of miscarriage associated with invasive testing means women do not have to factor this

anxiety-producing prospect into their decision. Early detection of unaffected pregnancies could allow for parental reassurance and for bonding to occur sooner (Newson, 2008). Women with affected pregnancies have advantages in their options as well. Parents may use this time to prepare emotionally, make an appropriate delivery plan, and assemble a medical management team. If parents decide to terminate an affected pregnancy, this may be physically safer and psychologically less traumatic at an earlier gestational age (Benn & Chapman, 2010).

For some, the fact that a termination can occur early in gestation may make a morally relevant difference. De Jong et al. (2010) point out that the dominant opinion in most western countries, also reflected in legislation, is that the moral status of the fetus progressively increases with its development (De Jong, Dondorp, De Die-Smulders, Frints, & De Wert, 2010). Current guidelines recommend abnormal NIPT results be confirmed by CVS or amniocentesis prior to termination, so there may be additional delay after the results of the NIPT are received before the diagnosis is confirmed. This could present a stressful period of waiting. (Benn et al., 2012).

Some have expressed concern about potential negative repercussions of NIPT because there is no increased risk for miscarriage. The uptake of NIPT has been projected to increase detection of affected pregnancies and may in turn lead to an increased number of terminations (Newson, 2008). When understood from this perspective, the ease with which this test is undertaken and the fact that results are received early in pregnancy are seen by some as threatening conveniences that may promote termination of affected pregnancies. It has been suggested that receiving results of an affected fetus at an early gestational age, perhaps before parents have bonded with

the fetus or shared publicly the pregnancy encourages termination without thoughtful reflection (Skotko, 2009).

This concern has been further projected: NIPT may lead to fewer individuals with disabilities to be born, which may lead to reduced social acceptance and financial support for those who live with disabilities (Skotko, 2009). Some disability advocates contend that the implicit aim of prenatal genetic testing is to prevent the birth of disabled babies, which demeans and undermines the worth of individuals living with disabilities (Benn & Chapman, 2010). If this apprehension becomes reality, it has been suggested that societal pressures regarding individuals with disabilities may cause women to feel undue pressure to undergo NIPT and terminate an affected pregnancy (Tischler et al., 2011).

Advocates of the disability community are not alone in their concern about the potential negative effects of NIPT on the reproductive trends of the population. Many worry there could be unintended consequences. One such concern is that the risk-free and simple process of NIPT will lead to the routinization of the test. In other words, NIPT may become a standard test that most women uptake simply because other women uptake and thus it seems "normal". While this might increase efficiency and improve uptake, routinization could potentially undermine the decision-making process (Deans & Newson, 2011). Others feel alarmed by the reproductive power NIPT offers and wonder if in the future, a fetus might have to meet certain standards of desirable traits to qualify for birth. One ethicist suggested that potentially "every pregnancy becomes a 'tentative pregnancy' pending the results of prenatal screening" (Benn & Chapman, 2010, p. 131).

A primary cause for unease in this ethical quandary revolves around the concern that patients may not be afforded equal quality of pretest counseling as they would with

an amniocentesis or CVS. Obviously, women do not need to be counseled about risk of miscarriage associated with NIPT. To some extent, this lessens the gravity of the decision of prenatal testing, and indicates a difference in counseling between NIPT and invasive testing. However, the definitive nature of the information received and the significance of the decisions that might be made from this information necessitates pretest genetic counseling (Deans & Newson, 2011).

Because pretest informed consent is imperative for NIPT, there is an increased need for genetic counseling (Benn, Cuckle, & Pergament, 2012). The genetic counselor and the obstetrician serve to provide accurate and objective information about the implications, advantages, disadvantages, and consequences of any genetic testing (Pergament & Pergament, 2012). Patients have indicated mixed interest in pretest NIPT counseling but seem eager to meet with a genetic counselor to discuss results. A 2011 study assessing women's potential interests in NIPT demonstrated 50% of respondents indicated they would like pretest genetic counseling and 94.6% were interested in discussing test results with a genetic counselor (Tischler et al., 2011).

NIPT has invoked a variety of attitudes and opinions in healthcare and among the public about how most responsibly and ethically to implement this new option. Among attendees at a continuing medical education course on obstetrics and gynecology in 2011, enthusiasm, caution, discomfort, and uncertainty were among the feelings that surrounded the test. Genetic counseling and professional society approval were rated important to the implementation of NIPT. Respondents indicated a higher comfort level with the idea of offering testing for chromosomal abnormalities or single-gene disorders

than for sex determination or late-onset conditions (Sayres, Allyse, Norton, & Cho, 2011).

A similar study assayed public opinion on NIPT. The majority (63%) of respondents relayed a positive first impression of NIPT. Yet many expressed ambivalence, affirming the individual/medical rationale for NIPT but expressing unease concerning the public health rationale and societal implications. Subjects of concern included eugenic reasoning, too much reproductive control, commercial provision, information and support requirements for expanded testing, and limiting the use of testing. These results suggest that public preference is to regulate commercial provision of NIPT services and to monitor its introduction and clinical use (Kelly, 2012).

Noninvasive prenatal testing presents patients, genetic counselors, and physicians with exciting opportunities to gain accurate knowledge of a fetus early in gestation without increasing the risk of miscarriage. As this technology is integrated into prenatal practice, quality informed consent is imperative as well as thoughtful consideration of how best ethically and responsibly to employ NIPT. Despite the conflict surrounding NIPT, its presence in the prenatal setting is powerful and undeniable; it has major implications on reproductive health important to all (Tischler et al., 2011). It is essential that healthcare providers appreciate how NIPT changes the realm of prenatal testing from the perspective of a patient and complicates the decision-making process.

Chapter 2: Manuscript

Prenatal Decision-making Process of Patients in Three Cities in South Carolina [1]

[1] Hamann, K.H., Edwards, J.E., Shulman, L.P., & Gordon, B. To be submitted to *Journal of Genetic Counseling*

2.1 Abstract

Purpose: Noninvasive prenatal testing (NIPT) has changed the landscape of prenatal testing. This novel test, which can be performed as early as 10 weeks gestation without risk of pregnancy complication, has evoked questions about its applicability, appropriate use, and patient response. The purpose of this study was to evaluate patient decision-making processes about prenatal testing options as NIPT is integrated into the clinical realm. **Method:** Prenatal patients who were offered NIPT during genetic counseling (N = 105) in three cities in South Carolina completed a survey to address the goals of this study. **Results:** The top five factors most frequently rated as important to their decision-making about prenatal testing by participants were as follows: (1) To be prepared if the baby had a disability (91%), (2) To avoid the risk of miscarriage (88%), (3) For reassurance the baby does not have a genetic condition (86%), (4) To obtain genetic information about the fetus as early as possible (81%), and (5) To have a test that provides more accurate information than other tests (77%). Three factors were found to be significantly more important to participants who selected NIPT than to participants who did not: (1) To obtain genetic information about the fetus as early as possible (p = .021), (2) To have a test that provides more accurate information than other tests (p = .025), and (3) To be prepared if the baby had a disability (p = .001). In addition, a majority of participants (74%) felt consideration of termination if the baby had a chromosome condition was irrelevant to their decision. This factor was not an NIPT-selection factor, meaning participants who selected NIPT were not significantly more likely to find this factor important to their decision than participants who did not select NIPT. **Conclusions:** Patients are faced with new decisions as NIPT is integrated into prenatal testing options. This study evaluated the top five factors most frequently rated

as important by participants about their prenatal testing decision and identified three NIPT-selection factors. While every patient should be counseled as a unique individual, the results from this study are observations that may help healthcare providers better understand patient perspective This study reveals five factors important to patient decision-making regarding prenatal testing; of these, three factors (obtaining genetic information about the fetus as early as possible, having a test that provides more accurate information than other tests, and being prepared if the baby had a disability) were significantly influential in patient selection of NIPT.

Keywords: Noninvasive prenatal testing (NIPT), patient decision making, decision-making process, prenatal genetic testing

2.2 Introduction

Since 2011, noninvasive prenatal testing (NIPT) has been clinically available to obtain near-diagnostic results for aneuploidy as early as 10 weeks gestation without risk of pregnancy complication (Wilson et al., 2012). As this novel test integrates into the prenatal clinic, questions have been raised about its applicability, appropriate use, and how patients will respond.

Prenatal testing has traditionally been divided into screening and diagnostic tests. Prenatal screening for aneuploidy is a standard of healthcare offered to all pregnant women. Screening procedures allow high-risk pregnancies to be identified; women with these pregnancies are then offered diagnostic testing. Screening tools are meant to be highly accessible and do not present risk to the pregnancy (ACOG, 2007a). Conversely, prenatal diagnosis is typically offered by healthcare practitioners to patients whose pregnancies are at increased risk for chromosomal abnormalities or genetic disorders. These invasive methods provide sensitive results about genetic conditions but are

associated with procedure-related complications, such as a risk of miscarriage (Collins & Impey, 2012).

Noninvasive prenatal testing uses cell-free fetal DNA (cffDNA) from the maternal bloodstream to achieve near-diagnostic results for aneuploidy without an associated risk of miscarriage. Noninvasive prenatal testing is currently not available to all patient populations. The NIPT clinical validation studies recruited only women otherwise pursuing invasive testing; thus the majority of pregnancies were high-risk for aneuploidy. Consequently, testing is currently offered to high-risk populations only. Current indications for NIPT include: advanced maternal age, an abnormal maternal serum screen, personal or family history of aneuploidy, or an abnormal ultrasound (Wilson et al., 2012). Clinical validation studies of the general population (i.e., low-risk patients) are in process and may become a reality in the near future (Nicolaides, Syngelaki, Ashoor, Birdir, & Touzet, 2012; Fairbrother, Johnson, Musci, & Song, 2013; Norton et al., 2012).

Prenatal patients often feel ambivalence towards screening and diagnosis of aneuploidy (Vassy, 2005). The primary limitation of screening is that it does not provide a definitive diagnosis, potentially creating anxiety in women with unaffected pregnancies and falsely reassuring some women with affected pregnancies (ACOG, 2007b). Diagnostic tests offer a definitive result, but are associated with a risk of miscarriage (Collins & Impey, 2012). The high sensitivity of NIPT has called to question whether it may be used for diagnostic purposes. However, guidelines and statements issued by professional organizations agree that NIPT should be considered a screening tool at this

point in time, and recommend that positive results be followed up by invasive diagnostic procedures (ACOG, 2012; Benn et al., 2011a; Devers et al., 2013).

There are a multitude of personal and social factors that directly and indirectly affect women's prenatal testing decisions. Many women find NIPT appealing because it gains near-diagnostic genetic information about the fetus without an associated chance of miscarriage. In fact, when assessing pregnant women's level of future interest in NIPT, one study found pregnant women thought the most important feature of NIPT would be the safety of the fetus (75%), followed by accuracy (13%), and early availability of results (7%) (Tischler, Hudgins, Blumenfeld, Greely, & Ormond, 2011).

NIPT presents many advantages to women. However, some have expressed concern about potential negative repercussions of NIPT because there is no increased risk for miscarriage. The uptake of NIPT has been projected to increase detection of affected pregnancies and may in turn lead to an increased number of terminations (Newson, 2008). When understood from this perspective, the ease with which this test is undertaken and the fact that results are received early in pregnancy are seen by some as threatening conveniences that may promote termination of affected pregnancies (Skotko, 2009).

NIPT presents patients, genetic counselors, and physicians with exciting opportunities to gain accurate knowledge of a fetus early in gestation without increasing the risk of miscarriage. As this technology is integrated into prenatal practice, quality informed consent is imperative as well as thoughtful consideration of how best ethically and responsibly to employ NIPT. Despite the conflict surrounding NIPT, its presence in the prenatal setting is powerful and undeniable. It has major implications on reproductive

health important to all (Tischler et al., 2011). Healthcare providers need to appreciate how NIPT shifts the realm of prenatal testing and understand how to evaluate opinion of this change.

2.3 Materials and Methods

2.3.1 Participants. This study surveyed prenatal patients who were offered NIPT during genetic counseling about the motivations and reasons for their prenatal testing decision. Regardless of their prenatal testing decision, eligible patients were invited to participate by genetic counselors after the genetic counseling session ended. Interested patients were given the option to complete a survey at the prenatal office or to mail a response in a pre-paid envelope. For every patient who completed a survey, a genetic counselor completed a data collection form with basic information about the patient's indication for genetic counseling, testing offered, and testing decision. The patient surveys and genetic counselor data collection forms were numbered in sets such that data collection forms could be matched to respective patient surveys. Thus, patient confidentiality was maintained. Three South Carolina locations were sampled: University Specialty Clinics of University of South Carolina School of Medicine in Columbia, Medical University of South Carolina in Charleston, and the Greenville Hospital System in Greenville. This study was approved by the Institutional Review Board at the Medical University of South Carolina in December, 2012.

2.3.2 Research Methods. The patient survey consisted of a series of questions designed to assess factors most influential to patients in their prenatal testing decision. The format of the survey was primarily quantitative and utilized both Likert scale and multiple choice questions with the opportunity to specify other possible responses. The final question was open-ended and thus qualitative in nature. In total, the survey

consisted of thirty items. Questions were engineered to assess patient prenatal testing intentions pre- and post- genetic counseling. Patients were asked to rank the importance or relevance of specific factors to their decision, such as insurance covering testing or a recommendation by a physician. Demographic information was collected related to age, gestational age, annual household income, etc.

The genetic counselor data collection form was engineered to provide objective and accurate patient information about indication for genetic counseling, gestational age, testing offered during genetic counseling, and testing currently pursued. This form consisted of four quantitative questions, mostly multiple choice.

2.3.3. Statistical Analysis. Statistical Package for the Social Sciences (SPSS), version 21.0, was used to analyze quantitative data. Ordinal categorical data were reviewed using frequency, proportions, and percentages. Likert scale questions were reviewed item by item. In addition, an exploratory factor analysis was performed and reliability statistics calculated to determine if items were similar enough to create a "factor". These items were reviewed as categorical groups. Chi-square tests were used to compare responses of Likert scale questions. Multiple response questions were coded individually by response and analyzed using Chi-square test and Fisher's Exact Test. Open-ended responses were categorized into thematic groups and sub-groups for reporting.

2.4 Results

Data were collected from December, 2012, to March, 2013. A total of 105 patient surveys accompanied by genetic counselor data collection forms were collected: 51 from Columbia, SC, 32 from Charleston, SC, and 22 from Greenville, SC. Patient surveys were fully completed by 104 participants. Twenty-six genetic counselor data collection forms were received unaccompanied by patient surveys and thus were omitted from data analysis.

Results reported as "important" include "very important" and "somewhat important" responses; similarly, results reported as "unimportant" include "very unimportant" and "somewhat unimportant". Some results are still reported as "very important" or "very unimportant". Non-statistically significant results can be found in Appendix C.

2.4.1. Sample Demographics. All participants were female and pregnant. The plurality of participants presented during their first trimester, was between the ages of 35 and 39, possessed a high school/GED education, earned between $20,000 and $50,000, had private insurance, and received genetic counseling in Columbia, SC (Table 2.1).

Table 2.1 Personal Characteristics of Participants

Personal Characteristics	***n***	**%**
Location		
Greenville	22	21%
Charleston	32	30%
Columbia	51	49%
Estimated Household Income		
Less than $20,000	31	31%
$20,000-$50,000	28	28%
$50,000-$80,000	12	12%
$80,000-$110,000	12	12%
Greater than $110,000	17	17%
Highest Level of Education		
Less than High School	1	1%
High School / GED	39	38%
Associate's Degree	19	18%
Bachelor's Degree	27	26%
Advanced Degree	18	17%
Age at Due Date		
15-19	3	3%
20-24	4	4%
25-29	13	13%
30-34	12	12%
35-39	56	54%
40-45	16	15%
Pregnancy Trimester at Visit		
First	58	56%
Second	45	43%
Third	1	1%
Insurance		
Medicaid	37	36%
Private	60	59%
Both	5	5%

2.4.2 Participant Indications and Prenatal Testing Offered and Selected.

Participants were referred to genetic counseling for a variety of reasons, including advanced maternal age, a positive screening test, abnormal ultrasound findings, and a

family history of a genetic condition. The most common indication was advanced maternal age (Figure 2.1). This information was obtained from the genetic counselor data collection form.

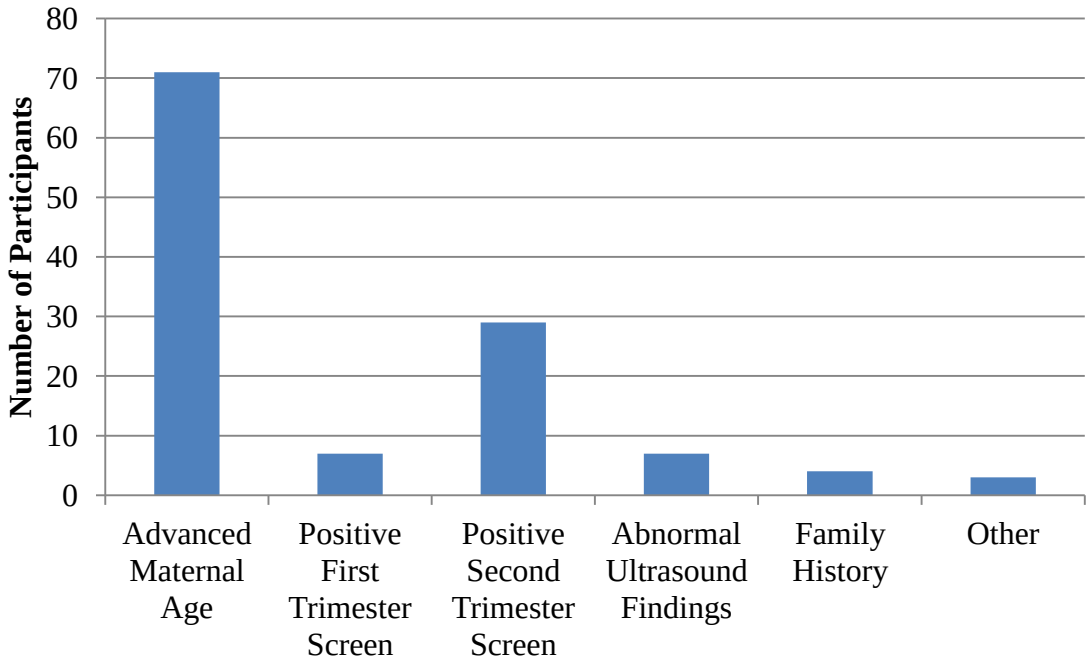

Figure 2.1 Participants' Indications for Referral to Genetic Counseling

As being offered NIPT during prenatal genetic counseling was a requisite for participation in the study, 100% of participants were offered this test. Other possible options included first trimester screening (FTS), chorionic villus sampling (CVS), multiple marker screening (MMS), amniocentesis, and other (notably, one center often wrote in "ultrasound only" for the other category). Noninvasive prenatal testing was the test most offered to participants, with amniocentesis offered second most often. Options for testing that were offered to participants are presented in Figure 2.2. This information

was obtained from the genetic counselor data collection form.

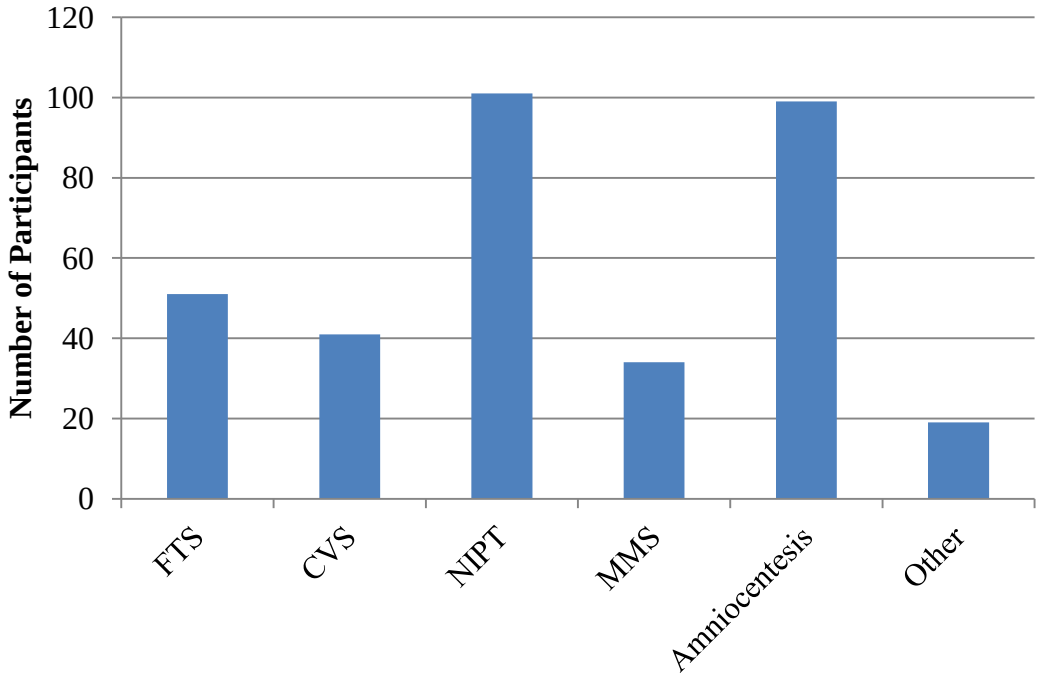

Figure 2.2 Procedures Offered to Participants during Genetic Counseling

All testing options were selected at least once, with NIPT being the most common choice (Figure 2.3). The "other" category primarily refers to participants who pursued ultrasound only. This information was obtained from the genetic counselor data collection form.

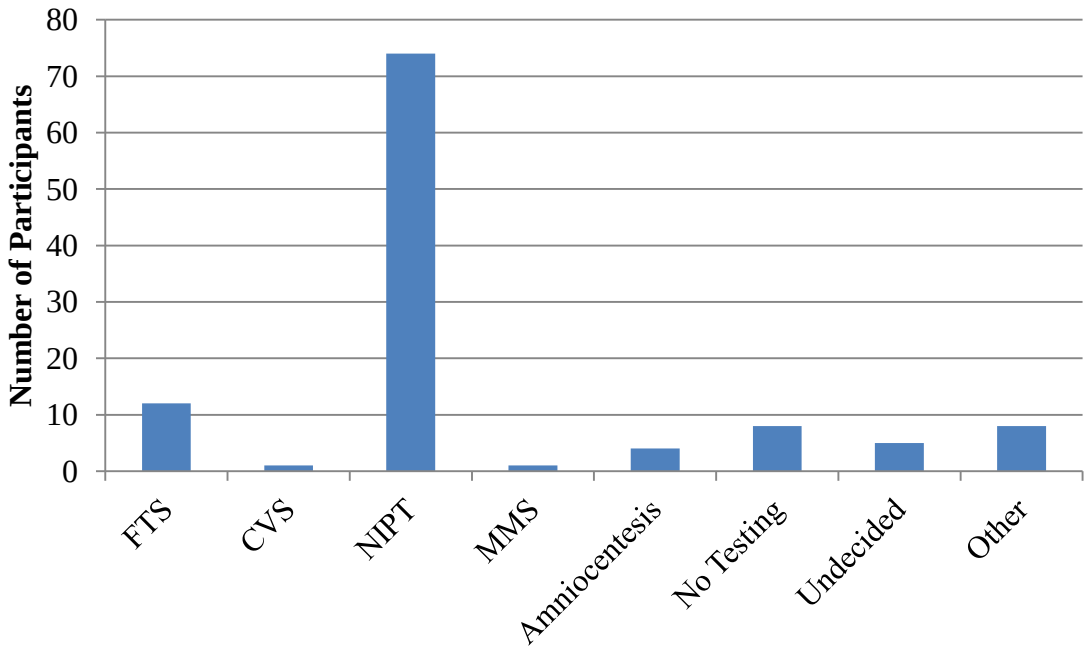

Figure 2.3 Participants' Prenatal Genetic Testing Decisions

A chi-square analysis was used to determine if participant demographic features influenced test selection. One significant relationship was found: participants who presented in second trimester were significantly more likely to opt not to have testing than participants who presented in first or third trimester, χ^2 (2, N = 104) = 11.363, p = .003. No significant relationship was found between participant test selection and location, estimated household income, level of education, age at due date, or insurance.

Possible differences in uptake of NIPT based on participant indication were evaluated. No differences were found for those studied, including: advanced maternal age, first trimester screen positive, second trimester screen positive, abnormal ultrasound results, family history of a genetic condition, and "other".

A chi-square analysis was performed to look for differences in the uptake of NIPT between participants in first, second, or third trimesters. No significant difference was noted, χ^2 (2, N = 104) = 2.68, p = .262. A similar analysis was performed to look for

differences in uptake of NIPT between the three study locations (Figure 2.4). Greenville was noted to have the lowest uptake of NIPT, and Charleston to have the highest uptake, but no significant differences were observed, χ^2 (2, N = 105) = 3.23, p = .198.

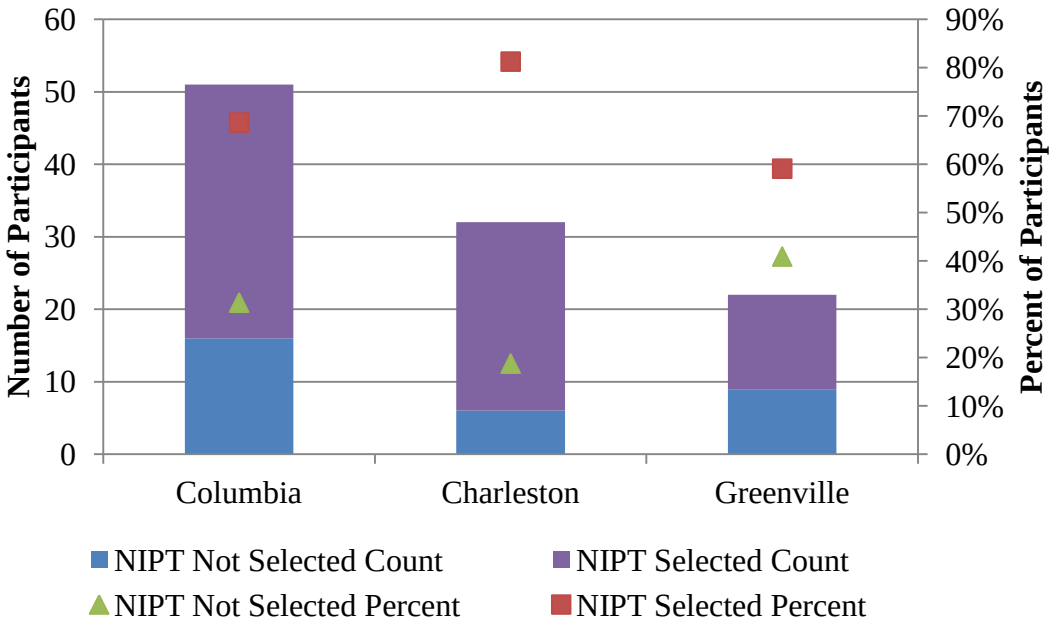

Figure 2.4 Uptake of NIPT by Study Location

Participants were asked what other testing options they considered other than their decision. Options included: FTS, CVS, NIPT, MMS, Amniocentesis, Other, and Not applicable. Using chi-square analysis, a significant difference was found between participants who chose NIPT and participants who did not in their consideration of CVS as a prenatal test, with participants who chose NIPT more likely to have considered this test, χ^2 (1, N = 95) = 4.16, p = .042. However, upon further examination with Fisher's Exact Test, no statistical significance was attributed to this factor (p = .054). In addition, the factors first trimester screening, NIPT, MMS, amniocentesis, "other", and "not applicable" were not noted to be significant.

2.4.3 Participant Resources used in Decision-making. In total, 73% of participants responded "yes" to the question, "Before you saw the genetic counselor, did you have an idea of what your decision would be?" When asked if their decision changed during the genetic counseling session, 82% of participants responded "no".

Participants were asked which of the following resources provided the most information to make their decision from the following: Internet, Genetic counselor, Family/friend, General physician, OB/GYN, Partner, Other, Not applicable. Some participants selected more than one answer, and these were included in analysis. Most notably, 61% of participants felt their genetic counselor provided the most information, and 19% of participants felt their OB/GYN provided the most information. A significant difference was not found between participants who selected NIPT and participants who did not select NIPT for the following: internet, genetic counselor, family/friend, general physician, OB/GYN, partner, "other", and "not applicable". A blank line was provided for participants to provide a response to the "other" option, and nine participants chose to do so. Their responses were classified into thematic groups, as follows: Healthcare resource (n = 2), Personal beliefs/values (n = 5), and Prior experience (n = 2).

Participants were asked which resources were most helpful in making their decision. Some participants selected more than one answer, and these were included in analysis. In total, 68% of participants found their genetic counselor to be most helpful in making their decision and 13% of participants found their OB/GYN to be most helpful. No significant difference was found between participants who chose NIPT and participants who did not for the following: internet, genetic counselor, family/friend, general physician, OB/GYN, partner, other, not applicable. A blank line was provided for

participants to provide a response to the "other" option, and five participants chose to do so. Their responses were classified into thematic groups, as follows: Prior experience (n = 1) and Personal beliefs/values (n = 4).

In general, most participants did not find test recommendations from their OB/GYN, general physician, partner, or "someone else" to be important to their decision-making process. Of these options, participants most often found recommendations from their OB/GYN to be important, with 43% designating this choice as very important or somewhat important. No significant difference was found between participants who selected NIPT and participants who did not select NIPT for the following: OB/GYN, general physician, and partner.

2.4.4 Factors that Influence NIPT Decision-making. When asked to consider the relevance to their decision of the statement, "I would consider pregnancy termination if a chromosome condition is present," the majority of participants (74%, n = 75) felt this was somewhat unimportant or very unimportant. One participant (1%, n = 1) expressed ambivalence by writing in and circling "2.5" between options "2" and "3" on a 1 through 4 Likert scale question (Figure 2.5). A chi-square analysis assessed the difference between participants who selected NIPT and participants who did not select NIPT, and no significant difference was noted, χ^2 (4, N =102) = 4.60, p = .330.

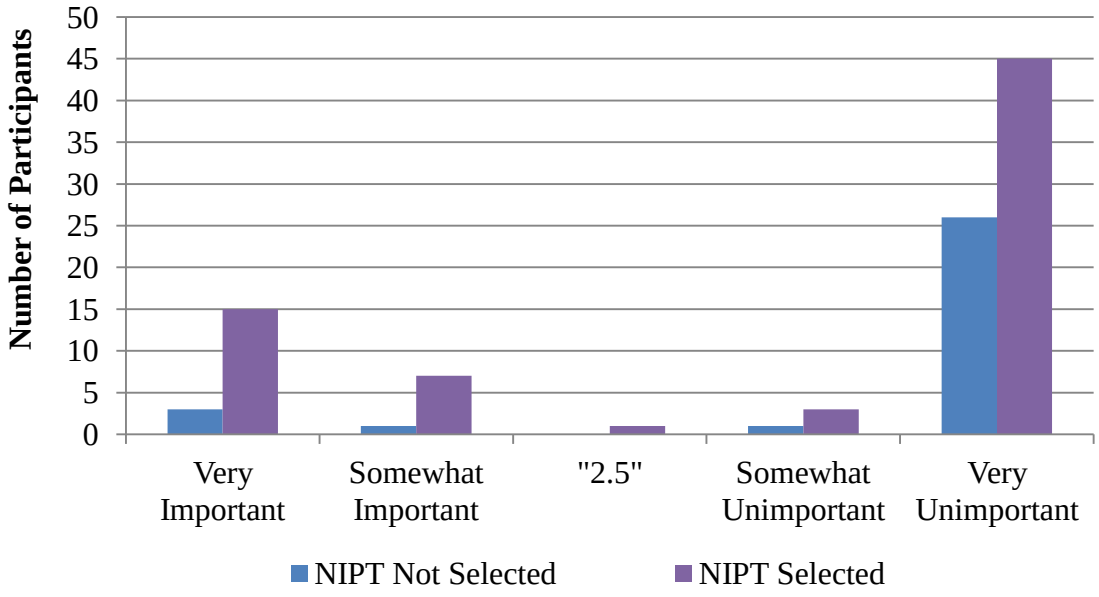

Figure 2.5 Participants' Response to "I would consider pregnancy termination if a chromosome condition is present".

The majority of participants (58%, $n = 58$) regarded the statement, "I would not consider a pregnancy termination regardless of the test results" as very relevant or somewhat relevant to their decision. One participant wrote in and circled "2.5" between options "2" and "3" on a 1 through 4 Likert scale question (Figure 2.6). No significant relationship was found between participants who selected NIPT and participants who did not, $\chi^2 (4, N = 100) = 3.54$, $p = .471$.

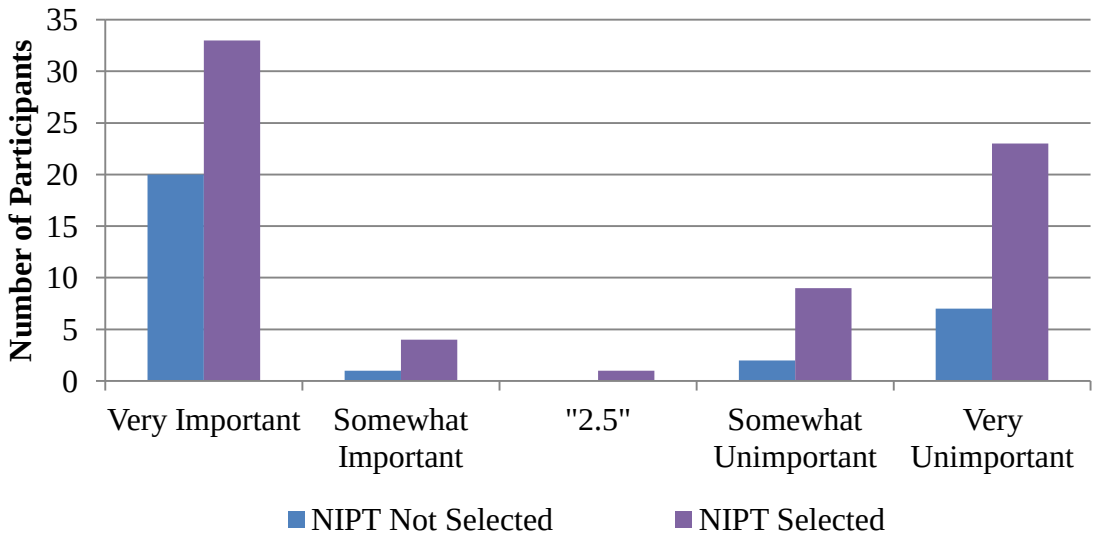

Figure 2.6 Participants' Response to "I would not consider a pregnancy termination regardless of the test results".

A majority (91%, $n = 95$) of participants found the statement, "I want to be prepared if the baby had a disability," to be either very important or somewhat important. A chi-square analysis was used to compare the response of participants who selected NIPT to participants who did not select NIPT, and a significant difference was observed, χ^2 (3, $N = 104$) = 16.2, $p = .001$. Participants who chose NIPT were 1.3 times more likely to feel this factor was important to their decision than participants who did not choose NIPT. Participants who did not choose NIPT were 8.2 times more likely than participants who chose NIPT to feel this factor was unimportant to their decision, though it should be noted that a small sample size was represented in this category (Figure 2.7).

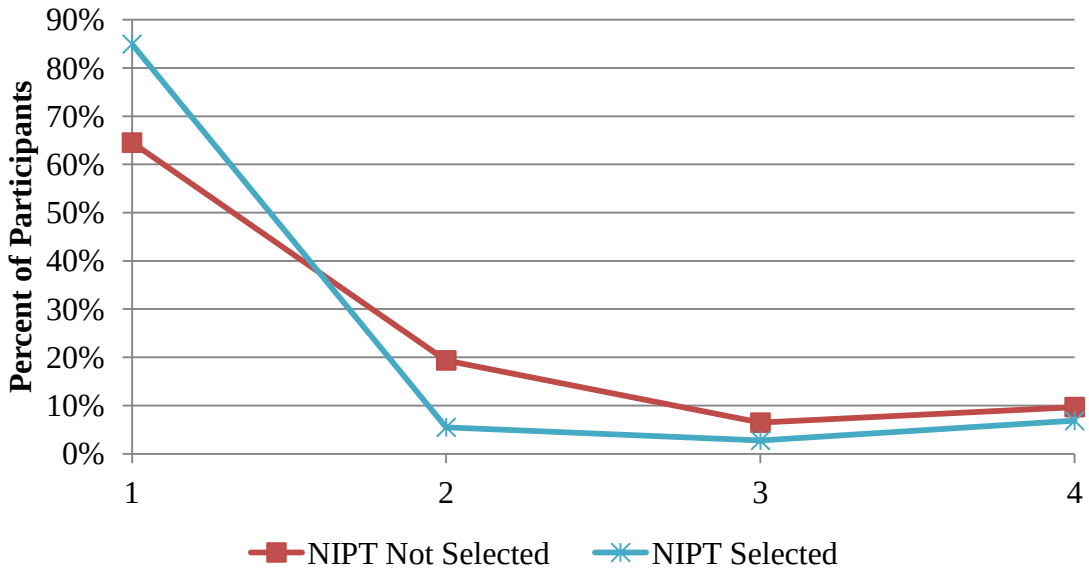

Figure 2.7 Participants' Responses to "I want to be prepared if the baby had a disability" (1=very important, 2=somewhat important, 3=somewhat unimportant, 4=very unimportant).

When asked to respond to the statement, "I want to avoid the risk of miscarriage associated with some tests, the majority (88 %, n = 92) of participants felt this was very important or somewhat important. A significant difference was not observed between participants who selected NIPT and participants who did not when chi-square analysis was performed, χ^2 (3, N = 104) = 6.51, p = .089.

A majority (81%, n = 83) of participants considered obtaining genetic information about the fetus as early as possible in the pregnancy to be a very important or somewhat important factor in their prenatal test decision-making. The differences between participants who selected NIPT and those who did not were assessed and a significant relationship was noted, χ^2 (3, N =103) = 11.0, p = .012, with participants who selected NIPT 1.5 times more likely than participants who did not select NIPT to feel obtaining genetic information about the fetus as early as possible was important. Conversely, participants who did not select NIPT were 3.5 times more likely than participants who

selected NIPT to feel obtaining genetic information about the fetus as early as possible was unimportant (Figure 2.8).

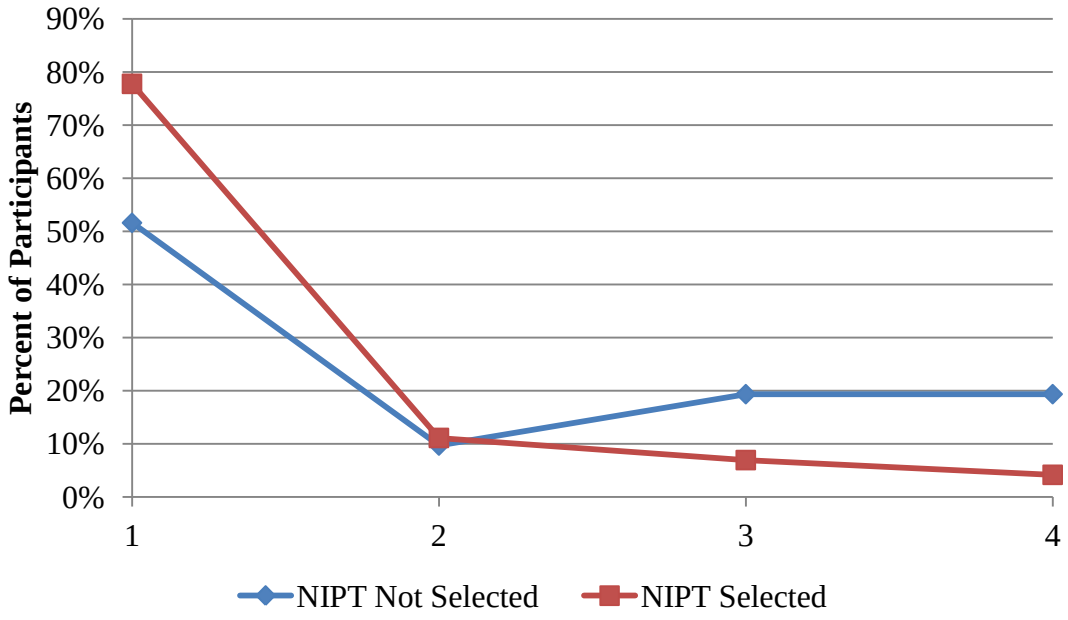

Figure 2.8 Participants' Responses to "I want to obtain genetic information about the fetus as early as possible" (1=very important, 2=somewhat important, 3=somewhat unimportant, 4=very unimportant).

When asked to reflect on the statement, "I hope to learn the baby does not have any genetic conditions", 86% (n = 87) of participants felt it was very relevant or somewhat relevant to their prenatal test decision. No significant difference was noted between participants who chose NIPT and participants who did not, χ^2 (3, N = 101) = 5.05, p = .168.

A significant difference was observed between participants who chose NIPT and participants who did not in their response to the statement, "I chose my decision because this test provides more accurate information than other tests", χ^2 (3, N = 102) = 9.32, p = .025. Participants who selected NIPT were 1.4 times more likely than participants who did not select NIPT to feel this factor was important. Conversely, participants who did

not select NIPT were 2.5 times more likely than participants who selected NIPT to feel this factor was unimportant (Figure 2.9). In total, 77% of participants felt this factor was very important or somewhat important.

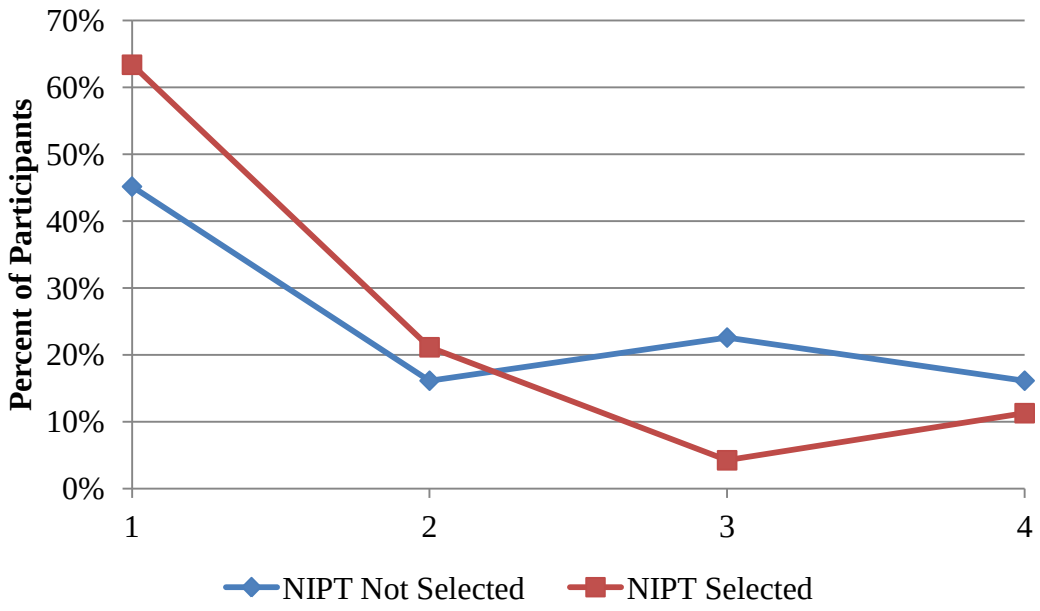

Figure 2.9 Participants' Response to "I chose my decision because this test provides more accurate information than other tests" (1=very important, 2=somewhat important, 3=somewhat unimportant, 4=very unimportant).

Participants were asked about other test characteristics as well. When presented the statement, "I chose my decision because this test provides results in a shorter time span than other tests" 54% (n = 55) of total participants felt this was very relevant or somewhat relevant to their prenatal test decision. No significant difference was found between participants who selected NIPT and participants who did not for the turnaround time of the test, χ^2 (3, N = 102) = 0.99, p = .802. When asked to rate the importance of the statement, "The cost of the test was an important consideration," 67% (n = 68) of participants found the statement to be either very unimportant or somewhat unimportant. In addition, 63% (n = 65) of participants found whether or not their insurance would pay

for the test to be very unimportant or somewhat unimportant. No significant difference was found between participants who selected NIPT and participants who did not for the cost of the test, χ^2 (3, N = 102) = 2.61, p = .456, or insurance paying for the test, χ^2 (3, N = 103) = 2.08, p = .555.

A blank line was provided for participants to provide factors they considered important; nine participants chose to do so. Their responses were classified into thematic groups, as follows: Concern about Down syndrome (3), Personal beliefs/values (1), Noninvasiveness/no risk of miscarriage (2), Accuracy of test (2), Gender (1), and Prior risk estimate (1).

In conclusion of this section, a graph was made to depict the factors that influenced the selection of NIPT (Figure 2.10). Three factors were found to be significantly more important to participants who selected NIPT than participants who did not. "Other" was also found to be a significant factor, but was not included in the graph, as responses to this factor were often unrelated to each other.

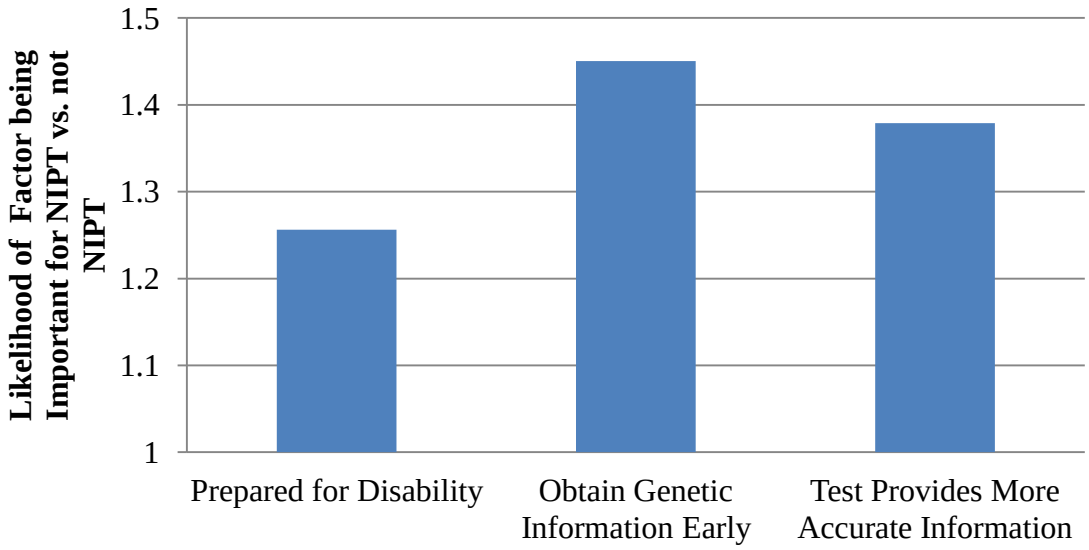

Figure 2.10 Factors Significantly More Important to Participants who Selected NIPT than Participants who did Not

Another graph was formulated to depict the top five factors of importance to total participants in the study (Figure 2.11). Participant response is reported as total participants (blue), participants who selected NIPT (red), and participants who did not select NIPT (green). Factors that were significantly more important to participants who selected NIPT than to participants who did not are designated with a white asterisk.

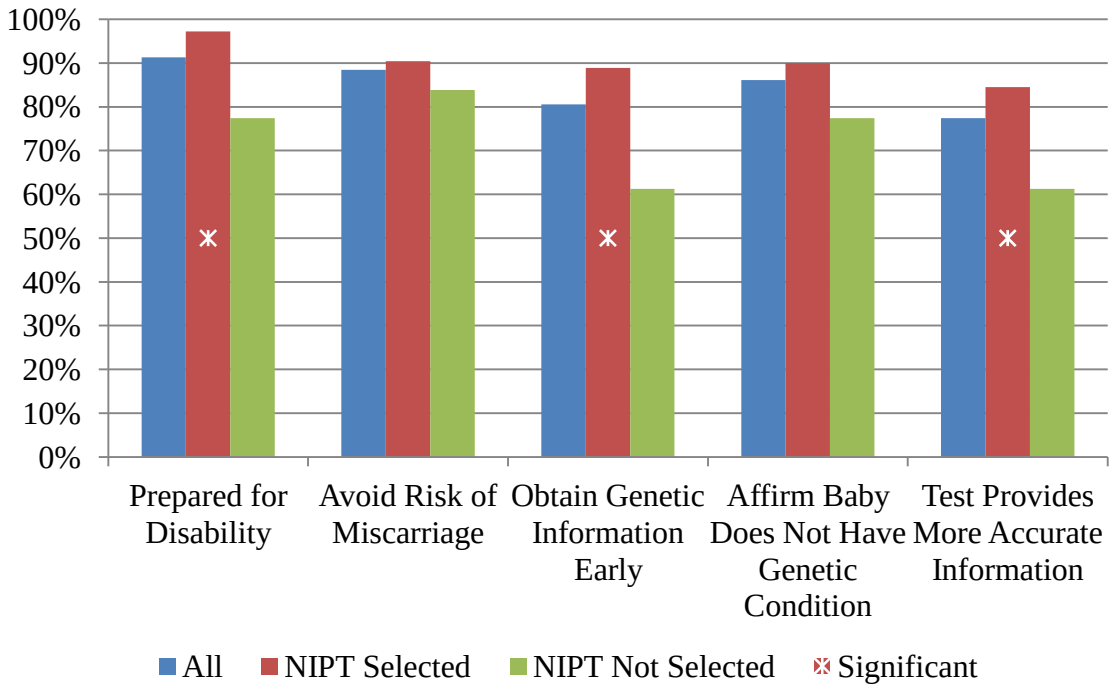

Figure 2.11 Top Five Factors Most Frequently Rated as Important by Participants

2.4.5 Open-ended Response. The final question of the survey tool was an open-ended response question asking participants if they had any thoughts or comments about their decision-making process that they would like to add. A total of ten participants responded to this question; seven responses were relevant to the decision-making process are depicted below in Table 2.2. One response is used in two thematic groups.

Table 2.2 Participant Responses to Open-response Question

Thematic Group	Sub-Group	Participant Responses
Information	Genetic Counselor	[Genetic Counselor] made all of this so easy. Information was explained so that we could understand everything
		Grateful for having to make my own decision and grateful for the informative information from the genetic counselor.
		I didn't know anything about a non-invasive prenatal test until today.
	Preparation	I want as much information as possible just in case my baby do have down syndrome but it will not change the outcome.
Personal Beliefs/ Values	Religious	God is in control!
		In the Book of Psalm: I
	Will Not Terminate	This child will be loved, regardless of the ultrasound results.
		I want as much information as possible just in case my baby do have down syndrome but it will not change the outcome.

2.5 Discussion

Since inclusion criteria for this study stated participants must be offered NIPT during genetic counseling, all participants were offered this test. Incidentally, this study consisted of a high-risk population. Indications for NIPT (and thus for participation in this study) currently include: advanced maternal age, an abnormal maternal serum screen, personal or family history of aneuploidy, or an abnormal ultrasound (Wilson et al., 2012).

However, not every testing option was offered during every genetic counseling session. This was not secondary to the study, but a function of appropriate clinical testing. Testing options were offered based on participant gestational age and indication. Amniocentesis was offered during almost every session. While amniocentesis can only be performed in second trimester, it is the most accurate diagnostic test available, so

patients were made aware of this test whether they presented during first or second trimester. Conversely, multiple marker screening (MMS) is less accurate than first trimester screening (FTS) and is performed later in gestation, so MMS was not usually discussed if patients presented in first trimester. Some tests, such as FTS and chorionic villus sampling (CVS) can only be performed during first trimester, and as such were not discussed if patients presented in second trimester.

Most participants indicated their genetic counselor provided the most information and was most helpful during their decision-making process. This suggests positive participant perception of prenatal genetic counseling and that genetic counselors played an integral role in participant selection of prenatal testing. Interestingly, a majority (73%) of patients had an idea of what their decision would be before genetic counseling, and of these, most (82%) did not change their decision during the genetic counseling session. As an overwhelming majority of participants elected to have NIPT, it seems unlikely that such a high percentage of participants were aware of the newest test before genetic counseling. However, it is likely they were familiar with the qualities they were seeking in prenatal testing, and had therefore formulated an idea of what type of testing (eg. noninvasive, screening, etc.) they would prefer, even if they were unaware of NIPT until genetic counseling. Some participants may have heard of NIPT from their OB/GYN. Almost half (43%) responded that a suggestion from their OB/GYN was important to their decision, which supports similar findings by the 2011 study of pregnant women's interest in NIPT and physician influence by Tischler et al.

Noninvasive prenatal testing was selected over six times more frequently than any other test. Interestingly, no difference in uptake of NIPT based on indication was noted.

One might have expected participants with abnormal ultrasound results to be less inclined to select NIPT, as NIPT detects aneuploidy only and is unable identify other potential causes for ultrasound anomalies. Invasive diagnostic procedures would supply more information about potential causes for ultrasound anomalies because testing for single gene conditions as well as chromosomal abnormalities is available. Yet participants with abnormal ultrasound results did not express particular interest in invasive diagnostic testing; of seven participants with ultrasound anomalies, one selected CVS and none selected amniocentesis.

2.5.1 Top Five Important Factors and Three NIPT-Selection Factors. The top five factors most frequently rated as important by participants were selected for discussion (Figure 2.11). Three factors were found to influence selection of NIPT, meaning these factors were significantly more important to participants who selected NIPT than to participants who did not (Figure 2.10).

The overall factor participants (91%) selected most often as important to test selection was the desire to be prepared if the baby had a disability. This was an NIPT-selection factor, as well. In the event of a positive test result, prospective parents may use this knowledge to prepare emotionally, make an appropriate delivery plan, and assemble a medical management team (Benn & Chapman, 2010).

Current literature suggests women consider genetic testing to be pointless if they would not terminate in light of a positive testing result (Reid, Sinclair, Barr, Dobbs, & Crealey, 2009). Yet other women consider genetic testing to be empowering, even if they would not terminate an affected pregnancy. For example, a study that surveyed parents of children with Down syndrome found 75% were disinclined to terminate a future

affected pregnancy, but only 33% would not have prenatal testing (Kuppermann et al., 2011). In our study, most participants who indicated termination of an affected fetus was irrelevant to their decision-making process opted to have prenatal genetic testing. Our participants valued having genetic knowledge of the fetus to prepare for a possible disability or health concern, even if they did not intend to use testing to alter the course of their pregnancy.

Participants (81%) indicated they wanted genetic information about the fetus as early as possible. This was both a top five factor and the most significant NIPT-selection factor. Early detection presents many advantages for women with affected or unaffected pregnancies. For example, early detection of unaffected pregnancies could allow for parental reassurance and for bonding to occur sooner (Newson, 2008). As discussed above, most participants regard a positive result as an opportunity to prepare to have a baby with a disability. If parents decide to terminate an affected pregnancy, the procedure may be both physically safer and psychologically less traumatic at an earlier gestational age (Benn & Chapman, 2010). Understandably, NIPT presents an attractive option to participants who value obtaining genetic information about the fetus early in gestation. With the capability of being performed as early as 10 weeks gestation, NIPT can provide genetic information earlier than most other prenatal tests. In addition, its availability is not restricted by a gestational time window like other prenatal testing options (Lo, 2012).

It has been suggested that NIPT may encourage termination of affected pregnancies without thoughtful reflection because the test provides results early in gestation, perhaps before parents have bonded with the fetus or publicly shared the

pregnancy (Skotko, 2009). Although participants in our study were unaware of the genetic status of their fetus, their pre-test response did not support this speculation. While the majority of participants who selected NIPT felt obtaining genetic information early in gestation was important, most indicated termination of an affected fetus was irrelevant to their decision. Furthermore, participants who selected NIPT were 1.3 times more likely to find being prepared if the baby had a disability important than participants who did not select NIPT.

A majority of participants (86%) indicated the desire to learn the baby did not have any genetic conditions was important. This factor was a top five factor but was not an NIPT-selection factor. As discussed above, patients may seek this affirmation because a negative test result can provide reassurance and guide expectations and planning (Newson 2008).

Many participants (77%) indicated they chose their test because it provided more accurate information than other tests. This factor was both a top five overall factor and an NIPT-selection factor. Of course, NIPT is not more accurate than amniocentesis or CVS, but it is more accurate than screening tests. Thus, because this factor was significantly important to participants who selected NIPT, we can infer its ability to provide more accurate information than screening tests increased its uptake in our study. A related question on the study tool asked participants which testing options they also considered when making their decision. We wondered whether participants who selected NIPT would more frequently consider invasive diagnostic testing (due to the increased accuracy of the test) or screening (no associated risk of pregnancy loss). However, no

specific test was considered significantly more often than any other by participants who selected NIPT.

The majority of participants (88%) indicated avoiding risk of miscarriage associated with invasive testing was important to their decision. This factor was one of the top five factors but, surprisingly, was not an NIPT-selection factor. It has been postulated that for many women the miscarriage risk associated with invasive testing is a psychological barrier to diagnostic testing and that if this risk were removed, women may feel more inclined to have a diagnostic test (Newson, 2008). To be clear, NIPT results are not considered diagnostic, but NIPT does remove the risk of miscarriage and gives near-diagnostic results. The majority of participants indicated learning genetic information about the fetus was important to them; thus, it would seem participants who wanted this information *and* to avoid risk of miscarriage would be motivated to pursue NIPT. However, avoiding risk of miscarriage was not significantly more important to participants who selected NIPT than participants who did not. We attempt to explain this phenomenon as follows: some participants who pursued invasive diagnostic testing indicated that 'avoiding risk of miscarriage' was an important factor in their decision-making process, even though they selected a test associated with risk of miscarriage. This suggests that although the desire to avoid risk of miscarriage influenced their decision, other factors were more important determinants.

This brings up an interesting point about the clinical utility of NIPT. The rapid advancements and high sensitivity of the test has called to question whether it may be used for diagnostic purposes. Current guidelines, however, maintain NIPT should be considered an advanced screening test (Devers et al., 2013). Thus, a relevant role

remains for invasive diagnostic tests. Our study indicates participants (at least some) perceive this difference and make decisions accordingly. They recognize that NIPT, while very advanced, does not provide as accurate nor as comprehensive information as CVS or amniocentesis and opted to have an invasive procedure associated with risk of miscarriage, although avoiding risk of miscarriage was important to them. Current literature has broached the possibility that the risk-free and simple process of NIPT will lead to the routinization of the test, but our study suggests this was not applicable to (at least some of our) participants' decision making processes (Deans & Newson, 2011). They saw value in the role of invasive diagnostic testing, despite the associated risk of miscarriage and invasive procedure.

2.5.2 Limitations. The sample size of our study was small and representative only of one geographic area. In general, women in South Carolina are much less likely to terminate a pregnancy than women across the nation (Centers for Disease Control and Prevention, 2011). This was supported by our study, as most participants indicated avoiding termination was an important factor, but it should be noted that this population is not representative of all women. Our survey did not address every possible factor that could influence participant decision-making. For example, we did not ask about expected pain related to invasive procedures or the influence of religious beliefs (although several patients commented on the importance of their beliefs/values in the open-ended response). Though we requested patient indication, we did not request specific risk estimates for advanced maternal age or screen positive results. A further limitation of our study was that we did not inquire what prenatal genetic testing participants had received

for their current pregnancy prior to genetic counseling, and whether they had ultrasound before or after genetic counseling.

2.5.3 Areas for Future Research. Our study surveyed pregnant women in three cities in South Carolina about their prenatal testing decisions. Future research may use a similar survey tool on participants in a different geographical area to observe the difference in prenatal test decision-making. Another future study could develop a survey to be completed by patients upon receiving NIPT results. It would be especially interesting to record invasive diagnostic procedure uptake and termination rates for patients with positive NIPT results.

It is predicted that NIPT may soon be offered to women with low risk pregnancies (Norton et al., 2012). If this becomes reality, an interesting follow-up would be to repeat this study using women of the general population, instead of women with high risk pregnancies only. The majority of participants in the current study were of advanced maternal age, meaning their pregnancies had increased chance for aneuploidy; however, the majority of pregnant women in a study of the general population would not be advanced maternal age or have this increased risk of aneuploidy. Not having this inherent elevated risk may affect their decision-making process.

Chapter 3. Conclusions

Patients are faced with new decisions as NIPT is integrated into prenatal testing. This study discussed the top five factors most frequently rated as important by participants about their prenatal testing decision and identified three NIPT-selection factors. Participants tended to want testing to be prepared if the baby had a disability, to avoid the risk of miscarriage, to be reassured the baby was unaffected, to obtain fetal genetic information as early as possible, and to have a test that provides more accurate results than other tests. Participants who selected NIPT were significantly more likely to want to obtain fetal genetic information as early as possible, to have a test that provides more accurate information than other tests, and to be prepared if the baby had a disability. While every patient should be counseled as a unique individual, the results from this study are observations that may help healthcare providers better understand patient perspective. This study reveals five factors important to patient decision-making regarding prenatal testing; of these, three factors (obtaining genetic information about the fetus as early as possible, having a test that provides more accurate information than other tests, and being prepared if the baby had a disability) were significantly influential in patient selection of NIPT.

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Appendices

Appendix A: Patient Survey

Dear patient,

Thank you for your interest in our research study. The purpose of our research is to examine how women make decisions regarding prenatal testing. This survey should take about 10 minutes to complete, and it may be returned to your genetic counselor or mailed in the return envelope provided. Any questions or concerns regarding this research may be directed to Kim Hamann, principle investigator, at (859) 803-3437 or Janice Edwards, project advisor, at (803) 545-5706. Questions about rights as a research participant may be directed to the Office of Research Compliance at the University of South Carolina at (803) 777-7095 or the Office of Research Integrity at the Medical University of South Carolina at (843) 792-4148.

Participation is voluntary and confidential. You may skip any questions you do not want to answer. Your genetic counselor will complete a short data collection form about your testing options and preferences.

The questions in this survey often reference "your decision". You might have decided:

- To have a specific prenatal test
- Not to have more prenatal testing
- Or, you might not have decided yet

Whatever choice you make is the right one for you and your genetic counselor supports your decision. Please reflect on your decision-making process in the following questions:

Reflecting on your decision…

1. Before you saw the genetic counselor, did you have an idea of what your decision would be?
    a. Yes
    b. No (If you answer no to Question #1, please skip to question #3.)

2. Did your decision change during genetic counseling?
    a. Yes
    b. No

3. Which resource provided the *most* information to make your decision?
    a. Internet
    b. Genetic counselor
    c. Family/friend
    d. General physician
    e. OB/GYN
    f. Partner
    g. Other_____
    h. Not applicable

4. Which resource was *most* helpful in making your decision?
    a. Internet
    b. Genetic counselor
    c. Family/friend
    d. General physician
    e. OB/GYN
    f. Partner
    g. Other_____
    h. Not applicable

5. When you were making your decision, did you consider any other options? If so, please circle all that apply.
    a. First trimester screening
    b. CVS
    c. Non-invasive prenatal testing
    d. Multiple marker screening
    e. Amniocentesis
    f. Other _____
    g. Not applicable

Considering your decision-making process…

Please consider the following statements and rate their importance to your decision as you were presented different testing options, where 1 is very important and 4 is very unimportant:

Very important			Very unimportant
1	2	3	4

6. Whether or not my insurance company would pay for the test was an important consideration
    1 2 3 4

7. The cost of the test was an important consideration
   1 2 3 4

8. I want to obtain test results before I tell others I am pregnant
   1 2 3 4

9. I wish to know nothing about the genetic makeup of the baby
   1 2 3 4

10. I want to be prepared if the baby had a disability
    1 2 3 4

11. I want to avoid the risk of miscarriage associated with some tests
    1 2 3 4

12. I want to obtain genetic information about the pregnancy as early as possible
    1 2 3 4

13. Other factors that were important to your decision may be listed below
    _____
    1 2 3 4

Please consider the following statements and rate their relevance to your decision as you were presented different testing options, where 1 is very relevant and 4 is very irrelevant:

Very relevant			Very irrelevant
1	2	3	4

14. I had a positive screening test and am concerned that a chromosome condition may be present
    1 2 3 4

15. I would consider pregnancy termination if a chromosome condition is present
    1 2 3 4

16. I chose my decision because this test provides more accurate information than other tests
    1 2 3 4

17. I chose my decision because this test provides results in a shorter time span than other tests
    1 2 3 4

18. My OB/GYN suggested this decision, which heavily influenced my decision
    1 2 3 4

19. My general physician suggested this decision, which heavily influenced my decision
    1 2 3 4

20. My partner suggested this decision, which heavily influenced my decision
    1 2 3 4

21. Someone else suggested this decision, which heavily influenced my decision
    1 2 3 4

22. I would not consider pregnancy termination regardless of test results
    1 2 3 4

23. I hope to learn the baby does not have any genetic conditions
    1 2 3 4

24. Other_____
    1 2 3 4

A couple more questions about you…

1. How old will you be at the expected due date? _____
2. How many weeks pregnant are you? _____
3. Please list your insurance provider. _____
4. Please estimate your annual household income
    a. Below $20,000
    b. $20,000-$50,000
    c. $50,000-$80,000
    d. $80,000-$110,000
    e. Above $110,000
5. What is your highest completed level of education?
    a. Less than high school
    b. High school/GED
    c. Associate's degree
    d. Master's degree
    e. Advanced degree

A Final Question

If there are any thoughts or comments about your decision-making process that you would like to add, please do so in the space below:

Appendix B: Genetic Counselor Data Collection Form

Please answer the following in regards to your patient…

1. Which of the following indications prompted the patient's visit to genetic counseling? (Circle all that apply.)
    a. Maternal age greater than 35
    b. First trimester screening was positive for trisomy 21, 18, or 13
    c. Second trimester screening was positive for trisomy 21 or 18
    d. Abnormal ultrasound findings
    e. Family history of
    _____
    f. Other
    _____

2. The gestational age of the patient was _____ weeks at the time of genetic counseling.

3. Which of the following procedures was offered to the patient during this session? (Circle all that apply.)
    a. First trimester screening
    b. CVS
    c. Non-invasive prenatal testing
    d. Multiple marker screening
    e. Amniocentesis
    f. Other
    _____

4. Which of the following has the patient chosen at this time? Only select the method she is *currently* pursuing. (Do not select a screening test if she has *already* had one for this pregnancy.)
    a. First trimester screening
    b. CVS
    c. Non-invasive prenatal testing
    d. Multiple marker screening
    e. Amniocentesis
    f. Has decided not to pursue any testing
    g. Has not decided
    h. Other _____

Appendix C: Statistical Analysis Results

Table C.1 Factors Influencing NIPT Selection

Indication	χ^2	**df**	**n**	***p-value***
Advanced Maternal Age	0.868	1	105	0.351
Positive First Trimester Screen	0.837	1	105	0.360
Positive Second Trimester Screen	0.072	1	105	0.788
Abnormal Ultrasound Results	0.003	1	105	0.954
Family History of Genetic Condition	0.041	1	105	0.840
Other	1.31	1	104	0.252
Testing Options	χ^2	**df**	**n**	***p-value***
First Trimester Screening	0.076	1	95	0.783
CVS	4.16	1	95	0.042
NIPT	0.022	1	95	0.883
MMS	2.68	1	95	0.102
Aminocentesis	2.99	1	95	0.084
Other	0.040	1	95	0.841
Not Applicable	0.455	1	95	0.500
Most Information	χ^2	**df**	**n**	***p-value***
Internet	0.207	1	102	0.649
Genetic Counselor	0.660	1	102	0.416
Family/Friend	0.119	1	102	0.730
General Physician	0.441	1	102	0.507
OB/GYN	0.016	1	102	0.901
Partner	1.16	1	102	0.282
Other	0.026	1	102	0.872
Not Applicable	0.013	1	102	0.910
Most Helpful	χ^2	**df**	**n**	***p-value***
Internet	0.030	1	102	0.863
Genetic Counselor	0.050	1	102	0.823
Family/Friend	0.062	1	102	0.803
General Physician	0.409	1	102	0.552
OB/GYN	0.669	1	102	0.413
Partner	0.007	1	102	0.932
Other	0.030	1	102	0.863

Not Applicable	2.46	1	102	0.117
Demographics	**χ^2**	**df**	**n**	***p-value***
Location	3.239	2	105	0.198
Estimated Annual Household Income	8.551	4	100	0.073
Level of Education	2.167	4	104	0.705
Trimester	2.682	2	104	0.262
Age at Due Date	35.767	36	102	0.480
Insurance	3.476	2	77	0.176
Suggested Decision	**χ^2**	**df**	**n**	***p-value***
OB/GYN	2.319	3	100	0.509
General Physician	2.247	3	95	0.523
Partner	2.306	3	98	0.511
Someone Else	1.937	3	99	0.586

Table C.2 Demographic Features Influencing Participant Decisions Not to have Testing

No Testing				
Demographics	**χ^2**	**df**	**n**	***p-value***
Trimester	11.363	2	104	0.003
Age at Due Date	17.474	25	104	0.864
Insurance	0.449	2	102	0.799
Estimated Annual Household Income	3.086	4	100	0.544
Level of Education	0.959	4	104	0.916