PROVIDER KNOWLEDGE OF NON-INVASIVE PRENATAL TESTING: A SURVEY OF OBSTETRICIANS

by

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ABSTRACT

Following its introduction to clinical use, noninvasive prenatal testing (NIPT) has dramatically altered the landscape of prenatal screening. Due to its high detection rate of trisomies 21, 18, and 13, along with sex chromosome aneuploidies, many patients are choosing NIPT over traditional screening and diagnostic methods. Previously, this testing was offered to women whose pregnancies were at an increased risk for aneuploidies. Now, guidelines from professional organizations recommend that NIPT should be included as a screening option for all pregnant women. Additionally, laboratories have started to expand NIPT to include microdeletions and microduplications, and are investigating the detection of monogenic disorders as well.

With the rapid introduction of NIPT, surveying health care providers can help to determine how screening guidelines are being implemented in the clinical setting, an important aspect of two of the core public health functions: policy development and assurance. This project assessed obstetricians' knowledge of NIPT, their readiness for offering NIPT to all women during pregnancy, and the expansion of NIPT testing options through an online survey conducted from February 3, 2017 to March 20, 2017. The survey was distributed to 4,770 ACOG members via their professional list serve and was completed by 238 participants. Results found that most participants demonstrated accurate knowledge of NIPT, but there was a discordance between

clinical practice and current guidelines about offering NIPT to the general obstetric population as 45.72% indicted not offering NIPT to low-risk patients. Additionally, when asked about expanded NIPT options, 54.08% indicated that they were not confident in test interpretation and 54.54% were not confident in their explanation of results to patients. This coincided with respondents expressing a preference for choosing what, if any, expanded testing should be offered to patients. Overall, participant confidence and comfort declined with expanded testing. Informational material and educational support regarding expanded NIPT testing should be developed for obstetricians.

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PREFACE

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1.0 INTRODUCTION

Prenatal genetic testing is utilized by healthcare professionals for care of their patients throughout pregnancy. The purpose of prenatal testing is to screen for and diagnose medical conditions in the developing fetus. The identification of medical conditions prenatally can allow for medical management decision-making to occur prior to birth. This may include coordinating lifesaving surgery, giving anticipatory guidance to parents about what to expect of their child's condition, or a discussion of pregnancy termination.

Chromosome abnormalities, including aneuploidy, occur in approximately 0.65% of live born children and more than half of clinically recognized early pregnancy losses.[1–3] Instances of aneuploidy are associated with increased maternal age. In the United States, women aged 35 and older at the time of delivery are considered to be of advanced maternal age and are at an increased risk of having a baby with a chromosome abnormaility.[3,4]

Prenatal tests are classified as either screening or diagnostic tests. A screening test is designed to identify women whose pregnancies are at an increased risk for chromosome abnormalities or birth defects such as neural tube defects. Screening tests cannot confirm abnormalities. Such screening tests include imaging with ultrasonography and/or analysis of serum proteins and hormones in a multiple marker screen. A diagnostic test yields nearly definitive answers since it allows for genetic analysis of placental tissue or fetal cells present in

amniotic fluid.[2] However, diagnostic tests are also associated with an increased risk for miscarriage.

In 2011, the development and clinical availability of a new method of prenatal screening emerged: non-invasive prenatal testing (NIPT). NIPT is a screening test that is based on detecting cell free fetal DNA (cffDNA) in a maternal blood sample. The test has been promoted for its increased accuracy in detecting common fetal aneuploidies.[5] Initially, NIPT was recommended for women considered to be at high-risk for aneuploidies. In 2016, the American College of Obstetricians and Gynecologists (ACOG) released a practice bulletin which indicated that all women, regardless of age, should be offered the option of screening or diagnostic testing for aneuploidies and NIPT was included as one of the screening options.[6]

The uptake of NIPT has been rapid and is beginning to take the place of conventional screening methods. Within a year of introducing NIPT, one center experienced a 48.7% decrease in first trimester screening.[57] In conjunction with the recent changes to practice recommendations by professional organizations, it is therefore important to examine healthcare providers' knowledge, opinions, and practices surrounding NIPT.

The purpose of this project was to survey currently practicing, US –based obstetricians of ACOG regarding their knowledge of NIPT, elicit their current clinical practices of presently available expanded NIPT testing, and assess readiness for future expansions of NIPT. Assessing these specific aims will help in identifying gaps in provider knowledge, differences in recommendations and practice, and how providers are planning to use expanded testing. Confirming providers' knowledge ensures the accuracy of information that patients receive. As technological growth surrounding this test continues to evolve rapidly, and professional

organizations attempt to update their recommendations to include policies regarding new developments, it is imperative to know if providers can remain up-to-date.

2.0 LITERATURE REVIEW

2.1 BACKGROUND

2.1.1 Aneuploidy

Aneuploidy is defined as an abnormal number of chromosomes in a cell, most often occurring by nondisjunction. Aneuploidy is estimated to occur at an incidence of 10-30% of all pregnancies and can result in miscarriage, stillbirth, and congenital anomalies.[10]

The most common aneuploidies in liveborn children are the major trisomies, trisomy 21, trisomy 18, and trisomy 13, as well as sex chromosome aneuploidies: XXX, XXY, XYY, and 45,X.[3,11] According to the CDC, trisomy 21, more commonly known as Down syndrome, occurs in 1 in 691 livebirths in the United States.[12] The incidences of trisomy 18 and 13 are 1 in 3,762 and 1 in 7,906, respectively.[12] Sex chromosome aneuploidy incidences are estimated to range between 1 in 400 and 1 in 1,000 in the general population.[13]

One of the risk factors for aneuploidy is advanced maternal age. Numerous studies have modeled the predicted prevalence of aneuploidy as maternal age increases.[4,14] Advanced maternal age (AMA) is defined as the age of 35 years at delivery. The age of 35 years or older has been used as a criterion to designate high-risk pregnancies that should be offered additional testing options for aneuploidy screening. Currently, advanced maternal age is not the only

criteria to indicate a high-risk pregnancy. Family history, abnormal ultrasound results, and positive prenatal screening results can also place women into a high-risk population for aneuploidy.[15]

2.1.2 Prenatal Screening and Diagnosis of Genetic Conditions

2.1.2.1 A Brief History of Prenatal Diagnosis and Screening

Prenatal screening and diagnosis aim to strike a balance between accuracy of information gathered and corresponding risk involved. Traditionally, screening methods carry no risk to the pregnancy, but have lower accuracy. Conversely, diagnostic testing is exceptionally accurate, but confers a risk due to the nature of the procedures. As described by laboratories that provide NIPT, the promise of NIPT is superior screening accuracy compared to traditional screening methods without the risk associated with a diagnostic test.[16–21]

There are currently two methods by which aneuploidy is diagnosed prenatally: chorionic villus sampling and amniocentesis. These procedures allow for samples to be acquired and cultured for analysis. Karyotyping cultured cells is 97.5- 99.8% accurate.[5,22,23] Other types of analyses including fluorescence *in situ* hybridization (FISH) and microarray are more than 99% accurate.[24–26]

Amniocentesis was first performed in 1952 and by the mid-1970s was the standard procedure for obtaining fetal karyotypes.[27] It is offered to women after 15 weeks gestation. The procedure allows access to the amniotic fluid, which contains fetal cells that have been shed. The fetal cells are then cultured for analysis. Amniocentesis has the added benefit of allowing for the measurement of alpha-fetoprotein (AFP) and acetylcholinesterase (AChE). Elevated levels can indicate birth defects such as abdominal wall defects and neural tube defects.[2,27,28]

Chorionic villus sampling (CVS) was clinically introduced in the 1970s and 1980s.[27] It is offered to women during weeks 10-12 of gestation. The procedure involves obtaining a placental villi sample. The villi are typically genetically representative of the fetus since they both arise from the same totipotent stem cells.[2,27,28]

Due to the methods by which samples are acquired, both procedures are considered invasive and are associated with an increased risk for miscarriage. Previous studies indicated a 1% and a 1-2% risk of miscarriage for amniocentesis and CVS, respectively.[28,29] A recent meta-analysis concluded that miscarriage rates are lower than currently quoted to patients.[11,12] The pooled risks were 0.11% for amniocentesis and 0.22% for CVS.[32] In the past, CVS was also correlated with fetal limb anomalies.[33] However, a large review showed no difference in limb anomalies between the general population and CVS when the procedure was performed between 9-12 weeks gestation.[34]

There are several prenatal screening methods available to women during pregnancy. These screening tests help to identify pregnancies that are at an increased risk for aneuploidy by modifying the mother's age-related risk with personal information about her current pregnancy. Although all women, regardless of age, are at risk to have a child with aneuploidy, this risk increases with age.

The first screening method used to identify pregnancies at increased risk for aneuploidy and other birth defects is ultrasonography, which is routinely performed throughout pregnancies to assess development and growth. Anatomic ultrasounds, typically offered to all women, are usually performed between 18-20 weeks gestation. These ultrasounds can identify physical anomalies, or markers, some of which are associated with aneuploidy. For example, common markers that are associated with Down syndrome include: heart defects, thickened nuchal fold,

shortened long bones, hyperechogenic bowel, echogenic intracardiac focus and pylectasis.[35] Each isolated marker has a likelihood ratio associated with it, with the likelihood ratio increasing when additional markers are present. Conversely, the absence of markers decreases the risk.[36] Ultrasounds are generally offered to all women, making it an important screening tool for the general population.[35] The anatomic ultrasound alone detects 73% of Down syndrome cases, and has a 4% false positive rate.[35,37] Other aneuploidies can be suspected based on ultrasound findings: cystic hygromas are associated with monosomy X, choroid plexus cysts and omphalocle with trisomy 18, and holoprosencephaly with trisomy 13.[38,39]

Second trimester biochemical screening, also referred to as multiple marker screening, is traditionally performed between 16-20 weeks gestation. These tests combine maternal age, weight, race, diabetic status, pregnancy history, and gestational age along with the level of several biochemical markers to assess risk. The test is known as a multiple marker screening (MMS). Although the number of makers used is dependent on the lab, typically three (a triple screen) or four (a quad screen) are used, although a pentascreen is also available.[40] The triple screen analyzes levels of maternal serum alpha-fetoprotein, unconjugated estriol, and human chorionic gonadotrophin. The quad screen incorporates inhibin A, as well.[27] This screening can identify pregnancies with an increased risk of Down syndrome, trisomy 18, and open neural tube defects. The triple screen detects 70% and the quad screen detects 75% of Down syndrome. They have a false positive rate of 5%.[35,41] Table 1 compares detection and false positive rates of the common trisomies across various screening methods.

First trimester screening (FTS) is offered between 11-14 weeks gestation. It relies on a combination of maternal serum marker levels and a specific fetal measurement. The maternal serum markers are pregnancy associated plasma protein A (PAPP-A) and free beta human

chorionic gonadotrophin. The fetal measurement is an evaluation of thickness of the nuchal translucency, which is visualized by ultrasound during the first trimester. A thickened nuchal translucency is associated with fetal aneuploidy.[42] In addition to Down syndrome, FTS has the added benefit of screening for trisomies 18, and in some cases trisomy 13, as well.[43] The detection rate for each of these trisomies is 90% with a 5% false positive rate.[14,44] Notably, FTS does not specifically test for open neural tube defects.

To further improve detection, a combination first and second trimester screening, known as an integrated screen has been developed. Integrated screening uses PAPP-A levels and NT thickness from the FTS and combines it with the second trimester quad screen. Only the combined result is disclosed to the patient. Integrated screening detects 85-87% of Down syndrome with a false positive rate of 0.8%-1.5%.[41,43] The availability of integrated screening is often dependent on the healthcare institution**.** Due to the challenge of not disclosing FTS screening results to patients, alternatives to integrated screening are also available: sequential and contingent screening. Sequential screening takes a step-wise approach. Women with high-risk FTS results are offered the additional second trimester screening, the results of which are incorporated into the FTS results. Contingent screening distinguishes between increased risk and high risk women by triaging with a first trimester screen. Women who are at an increased risk are initially offered screening while high risk women are initially offered second trimester diagnostic testing.[41,43,45]

Table 1 Summary of Prenatal Screening Detection and False Positive Rates

Screening Test for Common Trisomies	**Detection Rate**			**False Positive Rate**		
	21	18	13	21	18	13
Anatomic Ultrasound[35,38,39]	73%	80%	90-100%*	4%	n/a	n/a
Multiple Marker Screen[46–48]	70-75%	60%	n/a	5%	8%	n/a
First Trimester Screen[46,47]	90%	90%	90%	5%	5%	5%

*When complete structural survey, including the heart, is completed[39]

2.1.2.2 Non-Invasive Prenatal Testing (NIPT)

NIPT is a screening test available after 10 weeks gestation. Traditionally, it was recommended for high-risk pregnancies, although it is now an option available to all women. NIPT utilizes cffDNA found in maternal blood samples. cffDNA are DNA fragments originating from the placenta. Like in CVS, placental tissue and fetal tissue differentiate from the same totipotent stems cells and therefore are thought to be representative of fetal tissue for the purposes of a screening test.

In 1996, cell free DNA (cfDNA) unique to a patient's cancer cells was identified in blood samples.[49] In 1997, researchers took the detection of cfDNA further by looking for fetal cfDNA (cffDNA) in pregnant women. Researchers were able to extract DNA from plasma and serum samples and accurately detect the presence of Y chromosome signaling in the PCR samples of 24 of the 30 male fetuses. Furthermore, none of the 13 female fetuses and the ten non-pregnant control women had a positive Y chromosome signaling.[50] A year later, the same group showed

that fetal DNA can be detected in 10μL of maternal serum and plasma. The fetal fraction was reported to be 3.4-6.2% of the maternal sample in both early and late pregnancy.[51] This work led to the utilization of cffDNA for prenatal screening.[50,51]

After multiple validation studies were conducted, NIPT became clinically available in 2011.[52] A review of 16 studies from 1997-2012 evaluating the accuracy of NIPT to detect Down syndrome in high-risk women indicated an overall 99.3% detection rate for Down syndrome with a false positive rate of 0.16%. Detection and false positive rate were 97.4% and 0.15% for trisomy 18 and 78.9% and 0.41% for trisomy 13.[53] Overall, these detection rates are increased compared other prenatal screening methods.

Given that the detection of Y chromosomes initiated NIPT, it is not surprising that NIPT also allows for screening of sex chromosome aneuploidy. A review article discussing the testing of sex aneuploidies analyzed the combined detection rates of three previous studies: 89% for 45,X, 82% for XXY, 87% for XXX, and 90% for XYY.[54]

Given the high detection rate for aneuploidies in high-risk women, NIPT became a test offered to this population. More recently, detection rates have been investigated in low-risk women. Studies of clinical experience using NIPT as a screening method for the common trisomies in the general population show it to be clinically effective. A study published in 2013 followed 288 patients, whose average age was 32.3 years, undergoing NIPT between July 2012 and December 2012. Four of these patients had samples that failed quality control, but the remaining 284 were given results, all of which indicated low risk for trisomy. FTS results were available for 267 of these patients. One patient who had an abnormal FTS and low risk NIPT result underwent invasive testing which revealed the FTS to be a false positive result. One other patient whose NIPT result was low risk but FTS risk was one in five, underwent invasive testing

and was found to have a euploid fetus. Of note, this study was supported by Ariosa (Harmony), one of the laboratories currently offering NIPT.[55] A meta-analysis determined that specifically in regard to the detection of Down syndrome, there was high sensitivity (0.993) and specificity (0.999) in pregnant women from the general population. Due to the limited number of trisomy 18 and 13 cases in the dataset, their corresponding specificity and sensitivity could not be calculated.[56]

There are a number laboratories offering NIPT testing in the United States. **Table 2** summarizes the sensitivity and specificity of the different tests and **Table 3** indicates what microdeletion/duplications are available.

Table 2 Comparison of Sensitivity and Specificity Clinically Available NIPT Testing Options

	MaterniT21 Plus[18]		**Verifi**[21,57,58]		**Panorama**[16,59]		**Harmony**[17,60]		**informaSeq**[19,61]		**QNatal Advanced**[20]	
Aneuploidy	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec
13	91.7%	99.7%	87.5%	>99.9%	>99.9%	100%	93.8%	99.98%	98.2%	99.9%	91.7%	99.7%
18	>99.9%	99.6%	97.4%	99.6%	>96.4%	100%	97.4%	99.98%	98.3%	99.9%	>99.9%	99.6^
21	99.1%	99.9%	>99.9%	99.8%	99.4%	100%	99.3%	99.96%	99.1%	99.9%	99.1%	99.9%
XX	99.4%	99.4%	97.6%	99.2%	>99.9%	100%			97.6%	99.2%		
XY	99.4%	99.4%	99.1%	98.9%	>99.9%	100%			99.1%	98.9%		
Sex Aneuploidy	96.2%	99.7%			100%	100%					96.2%	99.7%
Triploidy					>99.9%	100%						

Table 3 Comparison of Clinically Available Expanded NIPT Testing Options

	MaterniT21 Plus[18]		**Verifi**[21,57,58]		**Panorama**[16,59]		**Harmony**[17,60]		**informaSeq**[19,61]		**QNatal Advanced**[20]	
Microdeletion options available	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
22q (DiGeorge syndrome)	•		•		•			•		•	•	
15q (Pradar-Willi/Angelman syndromes)	•		•		•			•		•	•	
11q (Jacobsen syndrome)	•			•		•		•		•	•	
8q (Langer-Giedion syndrome)	•			•		•		•		•	•	
5p (Cri-du-chat syndrome)	•		•		•			•		•	•	
4p (Wolf-Hirschhorn syndrome)	•		•			•		•		•	•	
1p36 deletion syndrome	•		•		•			•		•	•	

Although NIPT has higher detection rates for the common trisomies when compared to other prenatal screening tests and can detect sex aneuploidies, the testing does have limitations. Maternal serum screening and amniocentesis can yield information about the risk for open neural tube defects, whereas NIPT cannot. Women who undergo NIPT, as opposed to other screening methods need to rely on maternal serum AFP screening and an anatomic ultrasound for detecting open neural tube defects.

NIPT currently detects the common trisomies and sex aneuploidies. Chromosome problems that would not be detected include balanced translocations, deletions, and duplications. However, some laboratories have started to include specific microdeletions/duplications as part of their NIPT tests. Currently, the only way to accurately assess chromosomes in their entirety is via diagnostic tests that result in karyotypes or microarrays.

As with any screening test, false positive results can occur due to the nature of the test. False positives can also be caused by vanishing twin, maternal malignancy, or mosaicism of the placenta, fetus, or mother.[50,62–64]The false positive rate is not available for each lab. However, Harmony reports <0.1% for Trisomies 13, 18, and 21; Panorama reports <0.1% for Trisomy 18 and 0% for Trisomies 21 and 13; Verifi reports an observed false positive rate of 0.12%.[16,17,21,57–60]

Inconclusive, no-call, or test failure results can occur with NIPT and can be due to the following factors: maternal obesity, low fetal fraction, low sample volume, and maternal malignancy.[62–64] Although the rate of test failure is not readily available for each lab, the following rates have been reported: Panorama 3.8%, Harmony 3%, MateriT21 1.3%, and Verifi 0.1%.[16–18,21,57–60]

The terminology in which results are disclosed to patients and providers varies across laboratories. For example, Sequenom reports indicate “positive” or “negative”, Verifi reports indicate “aneuploidy detected” or “no aneuploidy detected”, and Panorama reports indicate “high risk” or “low risk”. This may create differences in understanding the results of the test and make result interpretation more difficult.

2.1.2.3 Effects of NIPT

The introduction of NIPT has had a significant effect on prenatal testing. Shortly before NIPT became available in 2011, a 2010 survey of 62 obstetric healthcare providers participating in a continuing education course inquired about perceived impact of cffDNA testing. The survey indicated that only 29% of surveyed practitioners believed they would be offering the testing within the next five years and 52% indicated they were ambivalent about cffDNA.[65] A 2013 study which surveyed 278 maternal-fetal medicine specialists indicated that more than 90% of maternal fetal medicine specialists had adopted NIPT into their practice, showing a rapid uptake in testing.[7] Wallerstein *et al*. conducted a nine-month prospective study in 2013, as they integrated NIPT into their screening model by following the screening decisions of 163 women of advance maternal age. When given the option, patients indicate a preference for NIPT over integrated screening, invasive testing, and no screening.[8] This holds true with the high-risk population as well. A 51-month study evaluated of the uptake of NIPT and its effect on the use of other screening methods as it was implemented within a large academic referral center. It showed a 48.7% decrease in FTS, the previously preferred testing method at that center, after the first year NIPT was available, indicating that NIPT was the preferred test by this high-risk population.[9] In terms of provider preference, a 2015 questionnaire completed by 240 obstetric healthcare providers showed a majority (72%) were in favor of replacing first trimester

combined screening with NIPT, although 43% of respondents would like to maintain NT measurements.[66]

It appears that the higher detection rates are one of the main reasons for NIPT becoming more utilized than other screening tests. However, there has also been a decrease in diagnostic testing since the introduction of NIPT.[67] Diagnostic testing rates were already on the decline and predicted to decrease further with NIPT.[67] In the study conducted by Wallerstein et al., the center saw amniocentesis procedures decrease by 31% due to patients choosing NIPT over invasive testing.[8] The availability of NIPT as early as 10 weeks gestation is also hypothesized to partially explain the decrease in diagnostic tests which are offered during limited windows, later in pregnancy.[67] There is concern that the reduction in diagnostic testing will result in these procedures having a higher risk of complications.[67] With less women electing to have diagnostic testing, there is less opportunity to train new physicians. Although diagnostic procedures are invasive and inherently have a risk for complications associated with them, the rate of test failure and miscarriage decreases as the experience and skill of the physician increase.[67]

2.1.3 Guidelines, Position Statements, and Recommendations

As new technology develops, professional societies utilize position statements and practice guidelines to ensure that healthcare practitioners employ advances properly and apply best practices. The introduction of NIPT is no exception. The professional societies that represent genetic counselors, clinical and laboratory geneticists, and obstetricians and gynecologists have contributed recommendations regarding NIPT since its clinical availability in 2011.

In 2012, the National Society of Genetic Counselors (NSGC) published a practice guideline on the topic of prenatal screening and diagnostic testing options for chromosome

aneuploidy. It stated the importance of being aware of newer testing options like NIPT in order to provide patients with reliable and accurate information. The high detection rates for trisomy 21, 18, and 13 were noted. The guideline recommended confirmatory diagnostic testing for positive NIPT results and that additional serum screening should not be performed in addition to NIPT. [68] Shortly thereafter in 2013, NSGC released a position statement regarding NIPT.[15] The statement highlighted NIPT as a screening test, and reiterated that it should not be considered diagnostic. NSGC supported NIPT as a first-tier aneuploidy screening for high-risk populations, but not low-risk populations. These high-risk populations included women who had positive maternal serum screens, a family history of aneuploidies, abnormal ultrasound findings, or were of advanced maternal age. NSGC did not support the use of NIPT to test for single gene disorders or aneuploidies other than trisomies 21, 18, and 13, and monosomy X. In conclusion, the statement acknowledged the rapid developments being made and that positions would be likely to shift with time.[15] In October 2016, NSGC released a position statement supporting NIPT as an option for patients, while acknowledging that due to a variety of factors it may not be the most appropriate test for every patient. The statement reiterated that diagnostic testing should be offered to those whose results indicate an increased risk.[69]

In 2015, the American College of Obstetricians and Gynecologist (ACOG) released a committee opinion from their Committee on Genetics.[70] They stated that conventional screening methods remain the most appropriate as a first-tier screening method for the general population due to cost effectiveness. It also noted that simultaneous testing of multiple screening methods was not cost effective and was not recommended. If ultrasound indicates a structural abnormality, diagnostic testing should be offered instead of NIPT. Patients should be informed of the limitations of NIPT, including inability to assess neural tube or ventral wall defects, and

that negative results do not ensure an unaffected pregnancy. The opinion also stated that although patients have many options for prenatal screening and diagnosis, they are all optional and can be declined.[70]

However, in 2016, ACOG released an updated Practice Bulletin stating that all women should be offered the option of screening and diagnostic testing, including NIPT. The bulletin discussed that testing chosen should be appropriate based on the concerns, needs, and values of the patients, while also acknowledging that not all testing is available in each center. Regarding microdeletions, diagnostic testing with microarray was recommended as cffDNA for microdeletions had not yet been clinically validated.[6]

In 2016 an updated position statement was released by American College of Medical Genetics and Genomics (ACMG). In a shift from previous guidelines, ACMG recommended that all pregnant women should be informed that NIPT is the most sensitive screening option for common trisomies. It also recommended that all women be informed of the ability to expand testing to sex chromosome aneuploidies, but that providers should deter patients from utilizing NIPT for the sole purpose of sex identification. It did not recommend genome-wide exploration of copy number variants, and stated that diagnostic testing should be recommended if patients seek that level of information. ACMG also made recommendations to laboratories offering testing, calling for clearly stated detection rates, as well as both positive and negative predictive values. They also recommended that laboratories include fetal fraction on all results and specify the reason(s) for inconclusive results. Furthermore, the statement indicates that if an inconclusive result is given, then a repeat blood draw is not appropriate and the patient should be offer diagnostic testing.[71]

2.1.4 The Future is Now: Expanding Noninvasive Prenatal Testing and Diagnosis

Although the introduction and subsequent uptake of NIPT has been rapid, the testing options available with NIPT are continuing to evolve. In 2013, laboratories started to offer microdeletions and microduplications as an add-on possibility to NIPT. **Table 3** indicates eight disorders caused by such genetic changes that are now being offered by NIPT laboratories. Of the six US based laboratories shown, two offer testing for all the microdeletions/duplication, three offer some combinations, and one does not offer microdeletion/duplication testing.

As the technology is developed, it is important to investigate patient preference for NIPT microdeletions/duplications testing. A study aimed at assessing this described six conditions caused by microdeletions/duplications, along with their penetrance, and then asked 124 women if they would choose NIPT, an invasive procedure, or no testing at all for the conditions. Participants indicated higher rates of testing, both invasive and noninvasive, as the penetrance of the condition increased. Overall, more than half of participants made distinctions between the conditions which affected their testing choices; 28% would choose NIPT for all the conditions, and 8% would choose invasive testing for all the conditions. However, 11% indicated that they would not like either testing.[72] Although interest in testing was high, it was not universal. This study highlighted the need for a discussion between patients and providers regarding testing options, and to ensure expanding NIPT aligns with patient views and preferences.

The lynchpin of expanding NIPT to include microdeletion/duplication testing is determining whether such testing can yield accurate results. A study funded by investors of Natera (Panorama) evaluated the performance of SNP-based NIPT for microdeletions/duplications. The study utilized 358 plasma samples from pregnant women and 111 artificial plasma mixtures for a total of 469 test samples. The resulting detection rates were

97.8% for 22q11.2 deletion and 100% for Angelman, Pradar-Willi, 1p36 deletion, and cri-du-chat. False positives occurred only in 22q11.2 deletion syndrome and cri-du-chat at a rate of 0.76% and 0.24%, respectively.[73] The study also called for the consideration of microdeletion/duplication testing for the general obstetric population as they collectively occur in more than 1% of all pregnancies.[73] Conversely, a retrospective cohort study of clinical NIPT use in a MFM practice from March 2013 to July 2015 had 43 cases had abnormal microdeletion results reported using expanded screening. The condition detected were: DiGeorge, Angelman, and Cri-du-chat. Of these, 17 had non-reportable results and 9 were positive. Confirmatory microarray was elected by seven of the nine microdeletion positive cases, and all were found to be false-positives, giving the test a positive predictive value of 0%.[74]

In addition to concerns related to accuracy, provider awareness and knowledge of expanded testing, as well as willingness to utilize the testing are important considerations. A survey conducted between September 2014 and February 2015 of 85 obstetricians revealed that 25% were unaware of expanded testing options and only 14% had ordered an expanded NIPT test. A majority (91%) expressed a need for more information specifically tailored to practitioners.[75]

In addition to microdeletions/duplications, some laboratories have moved beyond common trisomies and sex aneuploidies. For example, Verifi[21,57,58] optionally tests for trisomy 9 and trisomy 16, and MaterniT21 Plus[18] includes trisomy 16 and trisomy 22. The concept of genome-wide analysis for all aneuploidies has been investigated. However, the clinical utility of reporting all aneuploidies is debatable due to false-positive results leading to unnecessary invasive testing.[76,77]

As the sensitivity and specificity of NIPT increases, it is thought that NIPT could move from a screening test to a diagnostic test. A cost-effective analysis of using NIPT as a diagnostic test (NIPT Dx) was conducted. Using a sensitivity and specificity of 0.99 to diagnose Down syndrome, without confirmatory testing, the study found that more infants with Down syndrome would be born. In addition, a higher rate of elective terminations of fetuses not affected with Down syndrome would occur without confirmatory testing.[78]

The development of monogenic disorder testing via NIPT has been slow in comparison to microdeletion/duplication testing. It has been speculated that developing tests for a disease, or even on a patient-specific basis is not a high-throughput model, limiting impetus for commercial development.[79,80] A UK-based article argued that when discussing monogenic disorders, the test shifts from screening to diagnostic (NIPD) in high-risk pregnancies since there is either a known family history or ultrasound indications. The technical complexity of the testing depends on the inheritance pattern of the condition. For example, testing for a paternally inherited autosomal dominant condition would be simpler compared to X-linked or autosomal recessive conditions.[81] Technical challenges of such testing include the size of cffDNA, which is typically shorter than maternal cfDNA, and fetal fraction. The ideal testing methodology would involve separating the cffDNA in a reliable, cost-effective manner, or use of a paternal genotype to compare to maternal plasma.[64,80] An ethical concern raised by NIPD is the routinization of such testing correspondingly decreasing informed choice for patients.[82] However, NIPD would not be appropriate for every situation. Invasive testing would still be necessary for non-singleton pregnancies to determine if one or more fetuses are affected.[80]

2.1.5 Provider Attitudes, Knowledge, and Education

The field of prenatal screening and diagnosis is ever evolving and rapidly changing, presenting a unique challenge to healthcare professionals who provide this information to their patients Understanding how these providers have learned about and reacted to the uptake of NIPT is therefore an important topic to investigate. As the testing became available, an article published in *Obstetrics & Gynecology* called for caution, citing patients and healthcare providers, including geneticists, limited understanding of the test's features and results interpretation. The need for education was underscored as essential, especially as the testing would likely become more complex.[83]

Genetic Counselors

A 2013 study conducted a thorough 67-question survey of 236 genetic counselors regarding their experiences with NIPT. A clear majority of counselors (96.1%) indicated they felt knowledgeable about cffDNA, were confident in offering testing to patients (94.2%), and were confident in their ability to explain subsequent results (93.2%). Respondents could provide additional comments as open text in the survey. Of the 72 who chose to use the open response, 12.5% expressed concern about obstetrician impact on testing. The main themes that were expressed were that obstetricians were not knowledgeable about NIPT, that obstetricians took the testing too lightly, and that patients relied on obstetricians recommendations.[84]

A 2015 survey of 113 genetic counselors assessed NIPT practice, counselor learning methods, and readiness for expanded testing options.[85] Ninety five percent of genetic counselors agreed or strongly agreed that they were familiar with NIPT. The most common methods by which genetic counselors learned about NIPT were discussion with peers, literature review, discussion with laboratory representatives, and conferences. Regarding offering

microdeletion/duplication testing to patients, 45% did not offer such testing, 20% offered it to high-risk pregnancies only, and 16% offered it to all patients. When asked about the possibility of testing for monogenic disorders via NIPT, 32% approved, 21% disapproved, and 47% were neutral.[85] Another survey of genetic counselors conducted in the same year found that participants were split on the idea of universal NIPT testing, with 47% being in favor. Those in opposition to universal screening expressed concern over knowledge of NIPT, specifically citing lack of provider understanding, the need for provider education, and the lack of patient understanding.[86]

Nurses and Nurse-midwives

An article published in *Nursing Outlook* acknowledged that trends in prenatal genetic testing are expected to affect nursing practice, education, research, and policy making. The article reviewed a variety of genetic tests relevant to prenatal care including preconception screening, carrier screening, conventional screening methods, and diagnostic testing with karyotyping and microarray. The newer developments discussed in this article included NIPT for fetal aneuploidies and whole genome testing. The article called for expanding genetic/genomic knowledge, suggesting that nurses take advantage of the resources provided by the American Nurses Association and that patient teaching material be created and maintained by ACNM. In addition, inclusion of genetics/genomics content in undergraduate and graduate training programs and continuing education activities regarding genetic testing would be essential in keeping nurses up to date.[87]

Obstetricians and Maternal-Fetal Medicine

A 2013 study surveyed 101 obstetricians after NIPT had been clinically available for a year. A clear majority (88%) of these providers felt that aneuploidy testing should be offered to

all women. At the time, the most common screening methods they used were second trimester ultrasounds (76%) and second trimester serum screening (58%). Regarding NIPT, 32% were currently using it in their practices at the time of response and 22% indicated they were familiar with the technology, but had not yet ordered the test. Notably, only 12% felt aneuploidy screening should be offered to a high-risk population only, meaning the disagreed with the professional guideline recommendations at that time. Overall, the need for further education was clear if NIPT were to continue on to be widely adopted.[88]

A study published in *Prenatal Diagnosis* surveyed ACOG Fellows between March and August 2012 about their opinions of NIPT. [89] Respondents were asked to assume that NIPT was accurate when considering different testing scenarios. Assuming acceptable accuracy, nearly all (97.5%) felt it should be used for all aneuploidies, and 90.4% believed it should be used for severe early-onset Mendelian disorders. However, of concern to the authors, nearly 50% of participants indicated that a Down syndrome test with a detection rate of 98% and a false positive rate of 0.2% would be an acceptable replacement of invasive testing, even though that would result an estimated one in six false positive NIPT results in a high-risk population.[89]

When 116 maternal-fetal medicine fellows were surveyed in 2016, more than 75% indicated being comfortable with ordering NIPT, but 82% preferred that patients discuss testing options with providers or genetic counselors. Questions regarding the respondents' education on NIPT found that formal educational activities (69%), review of literature (67.3%), and discussion with peers (64.6%) as the most common methods of learning about the test. Six questions evaluated participants' knowledge and the results revealed that 34.8% correctly answered all six questions, 30.4% correctly answered five of six and the remaining 34.8% correctly answered four or less. Overall, participants' responses indicated knowledge of trisomies in NIPT, but

accuracy decreased for questions about twin pregnancies and monosomy X screening. The authors of this study recommended that formal genomic education programs be implemented in MFM fellowships as NIPT advances continue to be made.[90]

A 2016 study surveyed 258 general obstetrics-gynecologists and maternal-fetal medicine subspecialists regarding education of NIPT, practice patterns, and barriers. The most common educational sources were publications from professional organizations, peer-reviewed journals, and online review articles for medical professionals. These were closely followed by continuing education courses.[91]

2.2 PURPOSE OF THIS STUDY

The addition of NIPT as a prenatal screening tool has changed how patients and providers seek information about pregnancies. Patients' desire for NIPT over traditional screening methods is increasing and, as such, more providers are offering the screening. Additionally, as NIPT research has expanded from high-risk populations to the general obstetric population, healthcare provider guidelines have been adapted accordingly. Recent changes to professional guidelines and recommendation now include NIPT as a screening option for all women during their pregnancy. However, the scope of NIPT continues to broaden as testing companies introduce expanded testing. Given the dramatic impact of NIPT, it is important to assess providers offering the testing in its current form and understand their preparedness for its expansion. Knowing this information can identify areas where knowledge or comfort is lacking, be beneficial to professional organizations as they continue to update their guidelines and recommendations, and ensure the quality of patient care. Since a variety of healthcare providers are involved with

offering NIPT to patients, many specialty areas will need to be assessed. Previously, members of the NSGC were surveyed to elicit information from the genetic counseling community. This project continued exploring provider knowledge and comfort of NIPT by seeking the responses of obstetricians who are members of ACOG. The importance of this project is in the addition of another specialty's relationship with NIPT.

2.3 SPECIFIC AIMS

Aim 1: To assess obstetricians' knowledge of NIPT.

Aim 2: To assess readiness of providers for the expansion of NIPT to all pregnancies, and the expansion of NIPT testing options in the future.

3.0 MANUSCRIPT

3.1 INTRODUCTION

Prenatal genetic testing is utilized by healthcare professionals in the care of their patients throughout pregnancy. The purpose of prenatal testing is to screen for and diagnose medical conditions such as aneuploidy. NIPT is a screening test that detects cell free fetal DNA (cffDNA) in a maternal blood sample and has been promoted for its increased accuracy in detecting common fetal aneuploidies: trisomy 21, trisomy 18, trisomy 13, and sex aneuploidies.[5] Although sensitivity varies with specific laboratories, NIPT detects more than 99% of trisomy 21, 96-99% of trisomy 18, 91-99% of trisomy 13, and 96-100% of sex aneuploidy.[17–21,57,58,60,61] It is these high detection rates which have led to its quick adoption in clinical practice.

The uptake of NIPT has been rapid. In a 2011 survey, only 29% of obstetric providers believed they would be offering NIPT in the next five years, but a 2013 survey of maternal-fetal medicine specialists revealed a staggering 90% had adopted NIPT into their clinical practice.[7,65] As more providers make NIPT available, the use of conventional screening methods is declining. Within a year of introducing NIPT, one center experienced a 48.7% decrease in first trimester screenings.[57] Although the use of invasive testing had been declining since the introduction of first trimester screening, the rate increased with the introduction of NIPT.[67] A previous study

found a 31% decrease in amniocentesis that was attributed to patients choosing NIPT over invasive testing.[8,67]

Previously NIPT, has traditionally been recommended only for women who were at an increased risk for aneuploidies, given that the early NIPT validation studies used high-risk populations. Therefore, the clinical validity of NIPT for the general obstetric population had not been shown.[68,70] However, studies evaluating the sensitivity and specificity of NIPT in general obstetric populations showed it to be highly accurate in large populations of low-risk women.[56,92,93]

High-risk patients are identified by a variety of means, including advanced maternal age, abnormal ultrasound findings, and a history of aneuploidy in previous pregnancies. However, in 2016, many organization changed their policies regarding the appropriate testing population for NIPT. The American College of Obstetricians and Gynecologists (ACOG), American College of Medical Genetics (ACMG), and National Society of Genetic Counselors (NSGC) recommended that NIPT should be offered to all women.[6,69,71]

Since its inception, NIPT has evolved to test for conditions other than common aneuploidies. Although each laboratory offering NIPT routinely tests for the trisomies 21, 18, 13, and sex aneuploidies, some have begun to offer testing for other aneuploidies, as well as select microdeletions and microduplications. The use of this expanded NIPT testing is currently not recommended by professional organizations.[6,69,71] Additionally, research is underway to detect monogenic disorders through NIPT. For example, methods to identify thalassemia, a common hemoglobin disorder, via NIPT are being done by exploring the detection of paternally inherited mutations, maternally inherited mutation, and mutations known in both parents.[94]

As NIPT testing became available, studies have explored providers' attitudes, knowledge and education. A 2013 article published in *Obstetrics & Gynecology* called for caution, citing patients and healthcare providers, including geneticists, limited understanding of the test's features and results interpretation. Education was underscored as essential, especially as the testing would likely become more complex.[83] A 2015 survey of genetic counselors identified concerns that obstetricians were not knowledgeable about NIPT, that obstetricians took the testing too lightly, and that patients relied on obstetricians recommendations.[84] Maternal-fetal medicine fellow surveyed in 2016 accurately answered questions regarding trisomies in NIPT but received lower scores on questions of twin pregnancies and monosomy X screening. Additionally, while many these fellows felt comfortable ordering NIPT, most preferred that patients discussed testing options with other providers, such as genetic counselors.[90] The current body of research on these topics should continue to be developed as providers have more experience with NIPT, as NIPT changes and expands, and as more providers become part of the NIPT process.

The purpose of this project was to survey members of ACOG regarding their knowledge of NIPT, elicit their current clinical practices regarding presently available expanded NIPT testing, and assess readiness for future expansions of NIPT. Assessing these specific aims will identify gaps in provider knowledge, differences in recommendations and practices, and how providers are planning to use expanded testing. Assessing providers' knowledge ensures the accuracy of information that patients receive, and helps recognize potential areas for improvement. As technological growth surrounding this test continues to evolve rapidly and professional organizations attempt to update their recommendations to include policies regarding new developments, it is imperative to know if providers can remain up-to-date.

3.2 MATERIALS & METHODS

3.2.1 Participants

The participant population consisted of American Congress of Obstetricians and Gynecologist (ACOG) members. A cover letter along with an anonymous electronic link were distributed via email to a randomized list of 4770 currently practicing, US-based obstetricians who were ACOG members in February 2017. Of these, 1783 members opened the email, 301 clicked on the survey link, 289 began the survey, and 238 completed the survey. The survey was closed in March 2017. A copy of the cover letter and survey are attached in **Appendix B**.

3.2.2 Instrumentation and Procedures

This study and survey (ID: PRO16100624) was approved by the Institutional Review Board of the University of Pittsburgh **(Appendix A**). The survey was created electronically in Qualtrics by Kerrianne Morrow, MS for a previous study that examined genetic counselors' knowledge and opinions of NIPT.[85] The survey contains 34 questions and was originally designed to elicit information from a variety NIPT providers: genetic counselors, obstetricians, and midwives. This survey was previously distributed to genetic counselors in 2016.[85] For accurate comparisons across providers, the same survey was distributed to obstetricians. The survey contains both multiple choice and open-ended response options. The questions were developed to evaluate three areas: (1) assessing provider knowledge of NIPT and for what populations they ordered the test, (2) explore provider opinions and comfort with current and future NIPT testing, including expanded testing options of microdeletion, microduplication and monogenic disorders panels,

and (3) participant demographics. The survey did not elicit identifying information. It was reviewed by healthcare professionals representing a variety of disciplines including prenatal genetics, genetic counseling, obstetrics/gynecology, and an NIPT researcher.

3.2.3 Data Analysis

The data collected from the survey was analyzed using descriptive statistics. Participants were not required to answer all questions; therefore analysis was conducted individually for each question regardless of total respondent pool. All figures illustrating participant responses were created in Qualtrics.

3.3 RESULTS

3.3.1 Participants

An invitation to participate was sent to 4,770 ACOG members, 1,783 members opened the email, 301 clicked on the survey link**,** and a total of 289 participants began the survey. Of these, 238 participants completed the survey (82.4%). The overall response rate was 4.98% (238/4,770). All the participants surveyed identified their specialty as Obstetrics and Gynecology. Most participants (90.72%) reported no subspecialty. Of the 22 participants that indicated a subspecialty, 50% (11) indicated Maternal Fetal Medicine, making it the most commonly reported subspecialty. Participants were asked to indicate how long they have been practicing in

the field. A majority (62.18%) of participants have been in practice for more than 10 years. This demographic information is summarized in **Table 4**.

Table 4 Participant Demographics

	Total (n=238)	
	n	%
Sub-specialty		
Yes	22	9.28%
Maternal Fetal Medicine	11	50%
Other	11	50%
No	215	90.71%
No Response	1	0.42%
Primary Work Setting		
Academic	36	15.13%
Private Practice	160	67.23%
Hospital Based	41	17.42%
Lab	1	0.42%
Number of Years in Practice		
0-2	3	1.26%
2-5	35	14.71%
5-10	52	21.85%
10+	148	62.18

3.3.2 Knowledge of NIPT

Initial survey questions aimed to assess the participants' current knowledge of NIPT. Participants were asked to what extent they agree or disagree with the statement: "I am familiar with

published NIPT clinical data." Most answered positively about the statement with 64.71% indicating they agreed and 20.59% indicating they strongly agreed. Only 5.04% indicated they disagreed while 2.94% indicated they strongly disagreed, with 6.72% indicating they neither agreed nor disagreed **(**Figure 1).

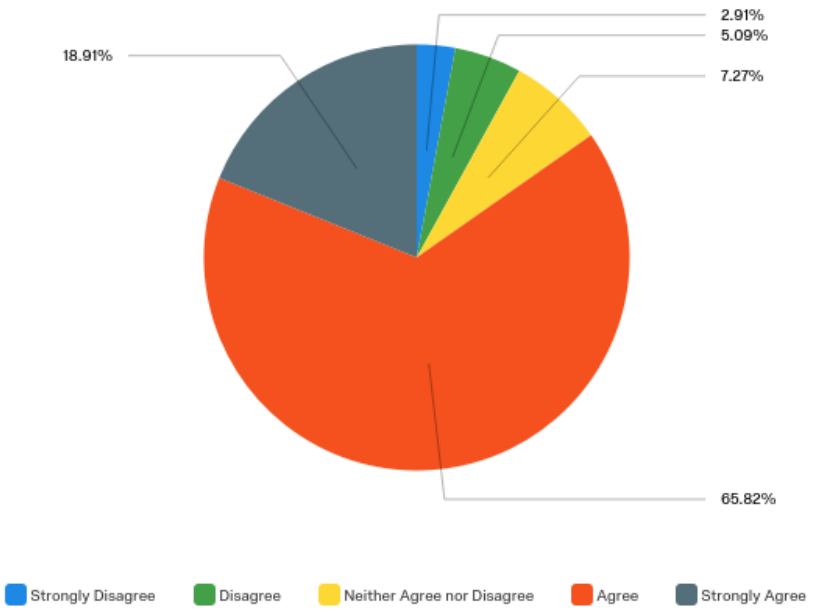

Figure 1 Participant Knowledge of Published NIPT Clinical Data

Participants were asked to select all methods through which they learned about NIPT. Participants who indicated that they had not learned about NIPT were forwarded to the demographics section of the survey and not asked to respond to the remaining survey questions. There were two (0.84%) participants in this survey who indicated that they had not learned about NIPT.

More than half of participants indicated that they learned about NIPT through discussion with peers (n=156, 65.55%) and literature review (n=124, 52.1%). This was followed closely by discussion with laboratory representatives (n=107, 44.96%) and continuing education courses

(n=101, 42.44%). Around a quarter of participants' NIPT education occurred through online research (n=65, 27.31%), conferences (n=63, 26.47%), and formal education (n=63, 26.05%). Only 13.03% indicated laboratory company advertisements as a method of learning about NIPT. Fourteen (5.88%) participants indicated other means of educations. Figure 2 depicts the spread of educational methods from most to least used. In an available open-ended text response, participants had the opportunity to expand their answers. These responses included educational opportunities through their hospital, department meetings, genetic counselors, testing company sponsored dinners, and Maternal-Fetal Medicine consultations and presentations.

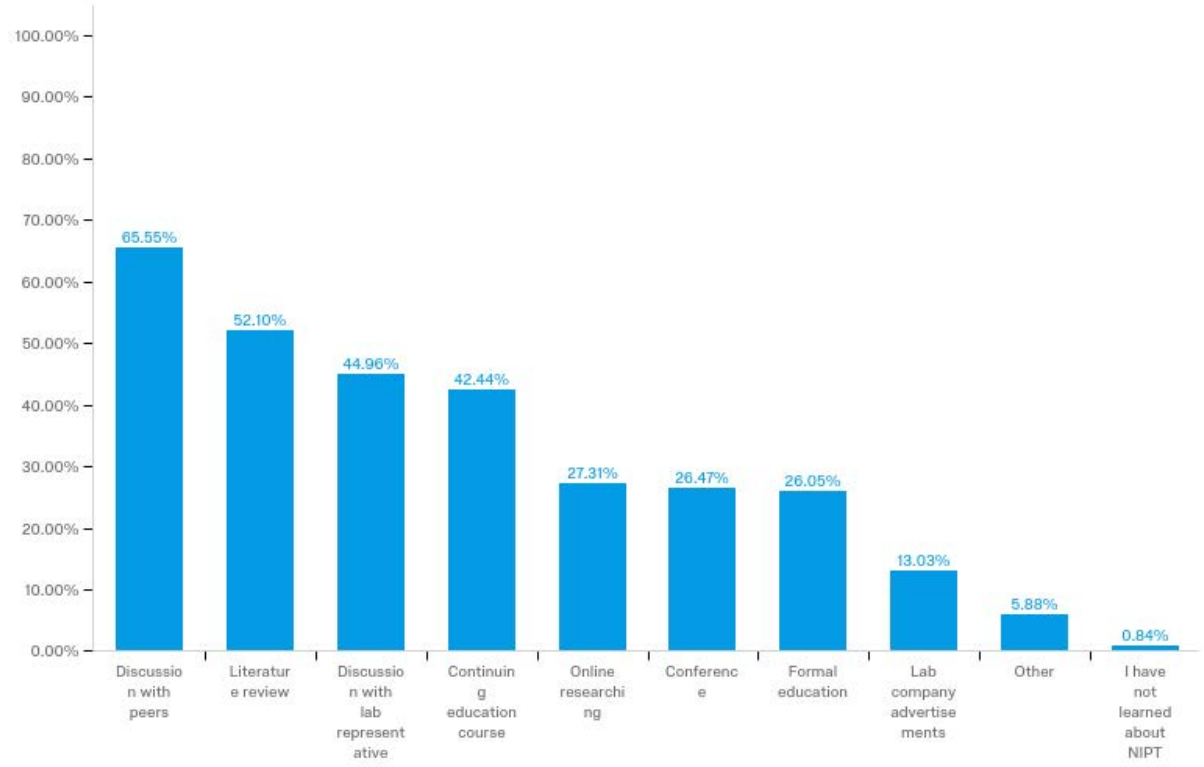

Figure 2 NIPT Education Methods

The final question regarding provider knowledge was the gestational age at which NIPT could be performed. The clear majority of participants (94.89%) correctly answered that the test

could be conducted as early as 10 weeks gestation. Ten (4.26%) participants indicated the test could be done anytime and two (0.85%) indicated as early as 15 weeks.

3.3.3 Current Clinical Practices

The remainder of the survey involved questions pertaining to the participants current practice utilizing NIPT. Nearly all participants (n=230, 97.46%) indicated that they offered NIPT to high-risk pregnancies. Six (2.54%) participants indicated that they did not. Of these six, three expanded on their answer. Their responses included referring patients to a Maternal-Fetal Medicine specialist and/or a genetic counselor who then offers testing. Most participants (n=179, 77.83%) indicated that they offered or referred for NIPT for 90-100% of their high-risk patients. Figure 3 depicts the percentages of high-risk patients to whom participants offer NIPT.

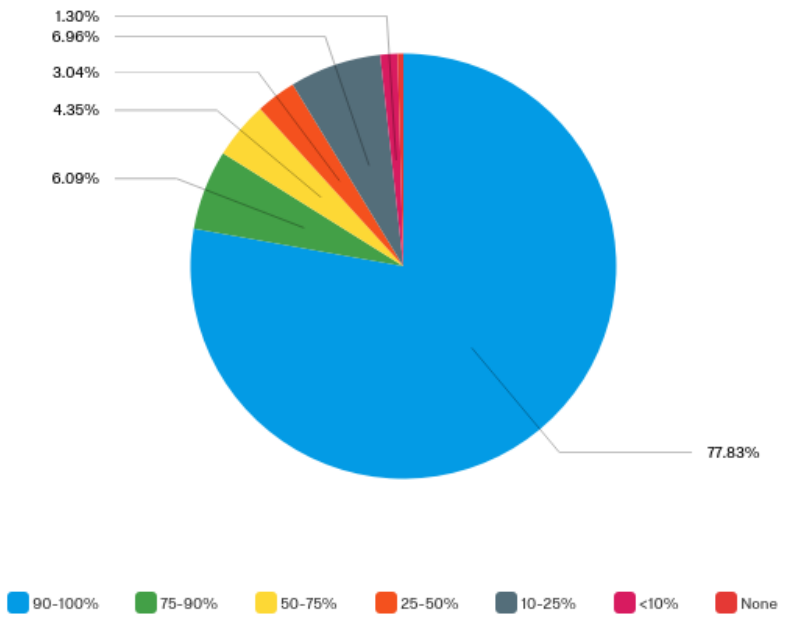

Figure 3 Percentage of Patients Offered/Referred NIPT who are at High-Risk for Aneuploidy

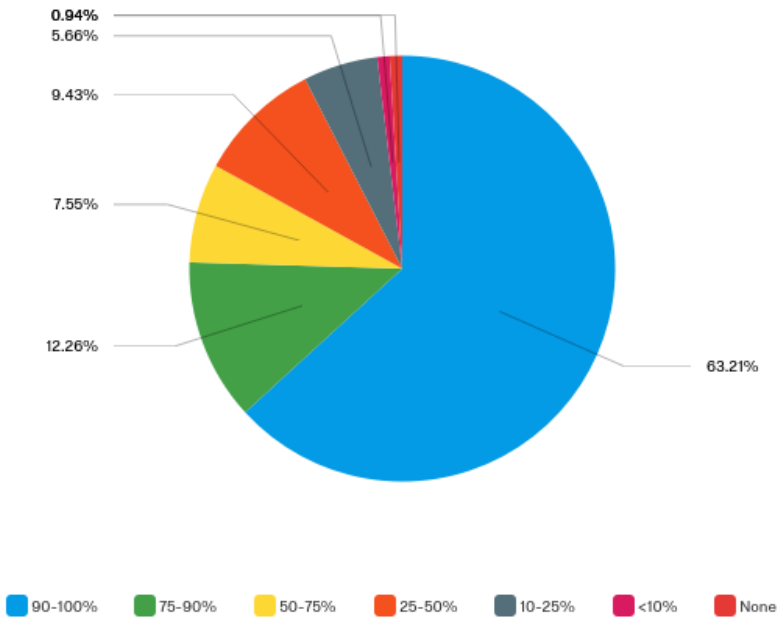

Figure 4 Percentage of Patients Offered/Referred NIPT who are at Low-Risk for Aneuploidy

When asked about pregnancies at low-risk for aneuploidy, participants were more divided, with 44.92% (n=106) offering NIPT and 55.08% (n=130) indicating that offering NIPT was not part of their practice. Following up with respondents who were not currently offering NIPT to the low-risk population, most (n=116, 89.92%) stated that they did not plan to change this practice within the next 12 months. However, 13 participants indicated that they would begin offering NIPT to low-risk pregnancies within the same timeframe. Of the 106 participants who currently offer NIPT to low-risk patients, a majority (n=67, 63.21%) offer NIPT to 90-100% of this patient population. The remaining results are shown in Figure 4.

Participants were asked about perceived advantages and limitations of NIPT compared to other screening methods. The greatest advantages were patient acceptance (88.51%, n=208), availability during gestational age (86.70%, n=202), detection rate (81.28%, n=191), and associated risk to pregnancy (80.49%, n=165). The greatest limitation was coverage by insurance

companies (50.89%, n=114). Figure 5 shows respondents' answers to this question in greater detail. Other limitations mentioned by participants in open-ended responses included sex selection, inability to do NIPT in house and having to refer patients outside to genetics, and the potential to detect abnormalities in the mother rather than the fetus without guidance on how to counsel the patient.

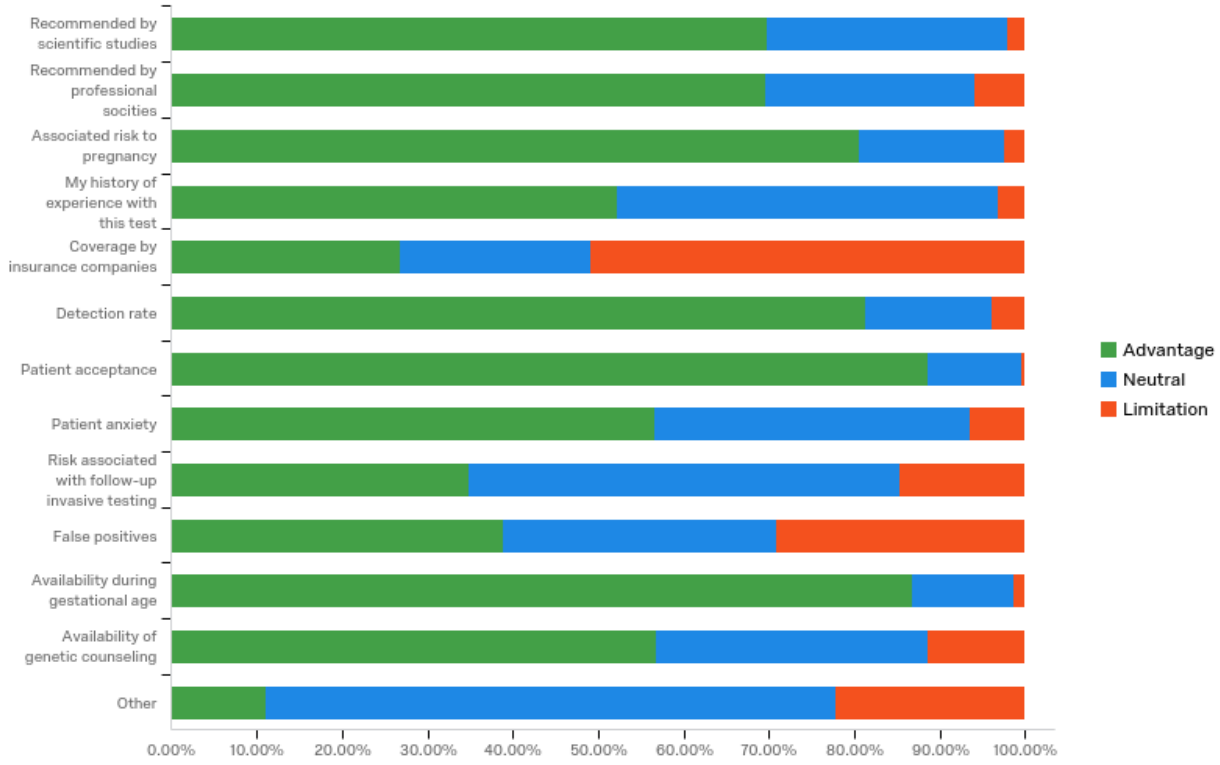

Figure 5 Participant Indications of Advantages and Limitations of NIPT

Participants were asked to indicate all methods by which information about NIPT for aneuploidy is conveyed to the patient prior to testing. The most common method was a discussion between the patient and the participant about NIPT (n=200, 84.75%). The second most common method was an information handout that patients read (n=85, 36.02%). Less often, patients speak to a genetic counselor either face-to-face (n=67, 28.39%) or through telemedicine

(n=13, 5.51%). Some patients spoke to a healthcare provider other than a genetic counselor either in the same office (n=41, 17.37%) or outside of the participant's office (n=26, 11.02%).

Regarding interpreting patient NIPT results, most participants favorably viewed their ability, with 40.6% indicating very confident, 32.05% mostly confident, and 23.50% confident. A similar trend is seen for explaining NIPT results to patients, as 44.26% indicated they were very comfortable, 30.64% mostly comfortable, and 20.85% comfortable.

Following abnormal NIPT results, most (86.44%) participants indicated they would offer invasive diagnostic testing, while a minority (4.24%) would not offer such testing. However, 22 (9.32%) participants indicated that their decision to offer diagnostic testing depends on the situation. In the open-ended response section, eight of eleven indicated that they would refer to Maternal-Fetal Medicine, who would discuss invasive diagnostic testing. Other situations mentioned were the willingness of the patients to risk miscarriage, gestational age, ultrasound findings, and if the patient is requesting pregnancy termination based on their NIPT results.

Participants were asked at what point in the NIPT ordering process they would find access to a genetic counselor helpful. The most common points were before offering NIPT (39.4%) and after results were returned and were abnormal (41.53%). Some participants (16.1%) indicated that access to a genetic counselor would be helpful only when the results were abnormal, while a few (2.97%) indicated that they did not offer genetic counseling to patients.

3.3.4 Expanded NIPT Testing

Since laboratories are beginning to expand NIPT beyond aneuploidy, participants were asked questions regarding the use of NIPT in testing for microdeletion/duplication testing. Participants were initially asked if they were familiar with published clinical data about this testing. Nearly a

third of participants (35.17%) indicated they agreed while another third (30.51%) indicated they disagreed. Only 4.66% strongly agreed. These responses are summarized in Figure 6. The responses indicated that overall, participants were less familiar with NIPT microdeletion/duplications testing when compared to NIPT aneuploidy testing.

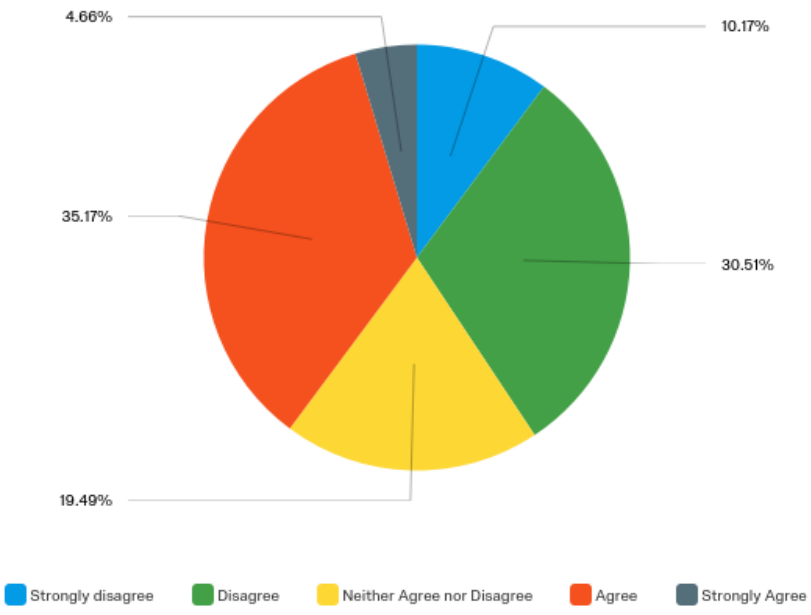

Figure 6 Participant Familiarity with NIPT Microdeletion/Duplication Testing

Participants were also asked to what extent they agreed that microdeletions/duplication testing should be offered to patients. Half (50.42%) of participants were neutral and neither agreed nor disagreed that it should be offered. Of the participants who believed it should be offered, 31.36% agreed and 6.78% strongly agreed. Conversely, 8.47% disagreed and 2.87% strongly disagreed. However, a majority (69.92%) of participants indicated that they did not provide NIPT microdeletion/duplication testing to all pregnancies, with 20.76% offering such testing to only high-risk pregnancies. Only 14 (5.93%) participants were offering this testing to

all of their patients. When asked about offering microdeletion/duplication testing in the future, 70.73% of participants indicated that it was not a test they planned to offer in the next 12 months.

When conveying information about microdeletion/duplication testing, the most common method for those offering the testing was a discussion between the participants and the patient (n=74, 31.35%). The use of genetic counselors was similar to NIPT aneuploidy testing, with 27.54% speaking face-to-face, and 5.93% utilizing telemedicine. Compared to NIPT aneuploidy, slightly more patients were given an informational handout (14.83%).

When compared to NIPT aneuploidy testing, there was an overall decrease in confidence in interpreting NIPT microdeletion/duplication results. Only 15 (7.25%) participants indicated they were very confident. A modest amount indicated they were mostly confident (n=39, 18.83%) or confident (n=41, 19.81%). More participants indicated they were mostly not confident (n=55, 26.54%) or not confident (n=57, 27.54%). A similar trend was found when participants indicated their comfort level explaining microdeletion/duplication results to their patients. Figure 7 illustrates the breakdown of respondent answers.

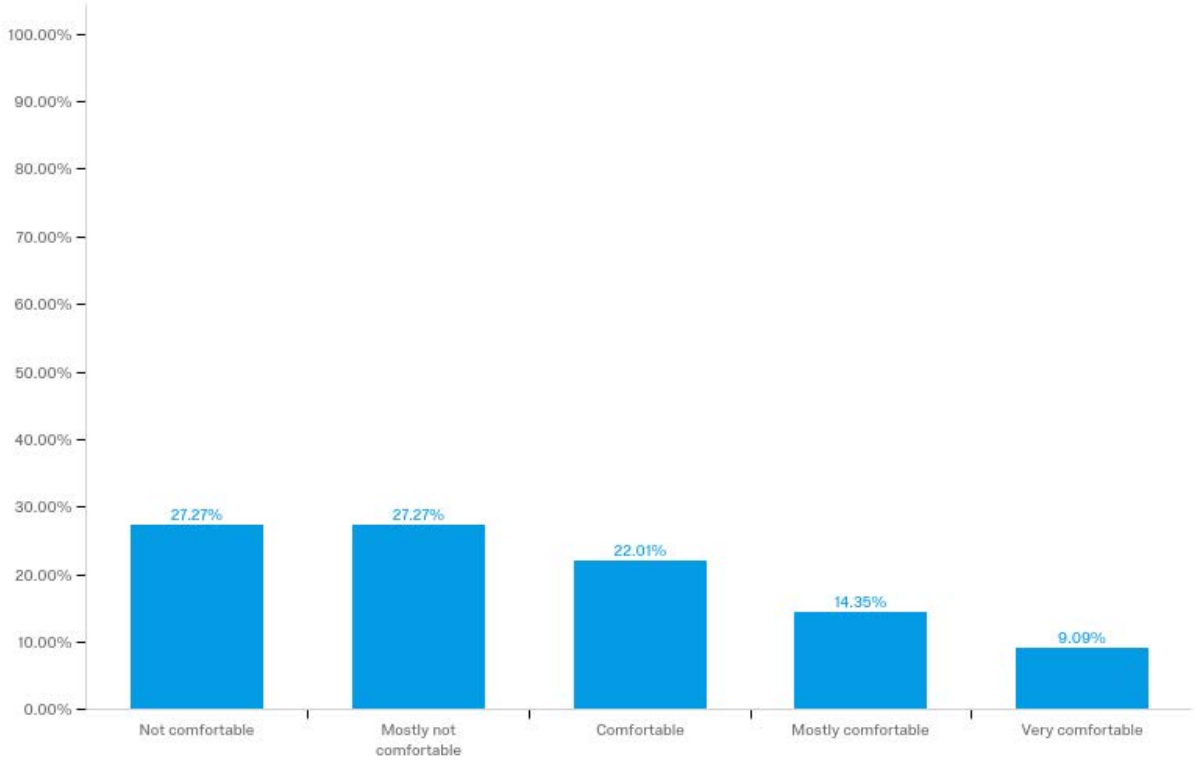

Figure 7 Comfort Levels of Participants Explaining Microdeletion/Duplication NIPT Results to Patients

Participants were less likely to offer invasive diagnostic testing given abnormal NIPT microdeletion/duplication results than abnormal NIPT aneuploidy results. More than half (n=151, 55.51%) indicated that they would offer diagnostic testing, although many (n=97, 41.1%) indicated that there was not enough information at the present time to recommend it. Only 8 (3.39%) participants indicated they would not offer diagnostic testing after abnormal NIPT microdeletion/duplication results.

Analysis of monogenic disorders is another area in which NIPT testing is expanding. In their opinion, most participants (49.15%) neither approved nor disapproved of offering NIPT for monogenic disorder analysis. Favorable positions consisted of 14.41% highly approving and 31.36% mostly approving. Few participants held negative opinions with 4.06% mostly disapproving and 0.42% highly disapproving.

Should patients have abnormal monogenic NIPT results, a majority of participants (72.03%) indicated they would offer invasive diagnostic testing, while very few (3.39%) indicated they would not. Nearly a quarter of participants (24.58%) indicated that it would depend on the situation. Some participants elaborated that they would refer patients who received abnormal results to other specialists, typically Maternal-Fetal Medicine or genetics, or that they would not be offering this testing.

When asked to consider if they would offer all three categories of screening with NIPT (aneuploidy, microdeletion/duplication, and monogenic disorders) to every patient, most participants indicated that they would not and instead preferred to opt-in for expanded testing options on a case-by-case basis. However, 25.54% of participants indicated they would want to offer the fully expanded NIPT testing options to all their patients. This is depicted in Figure 8.

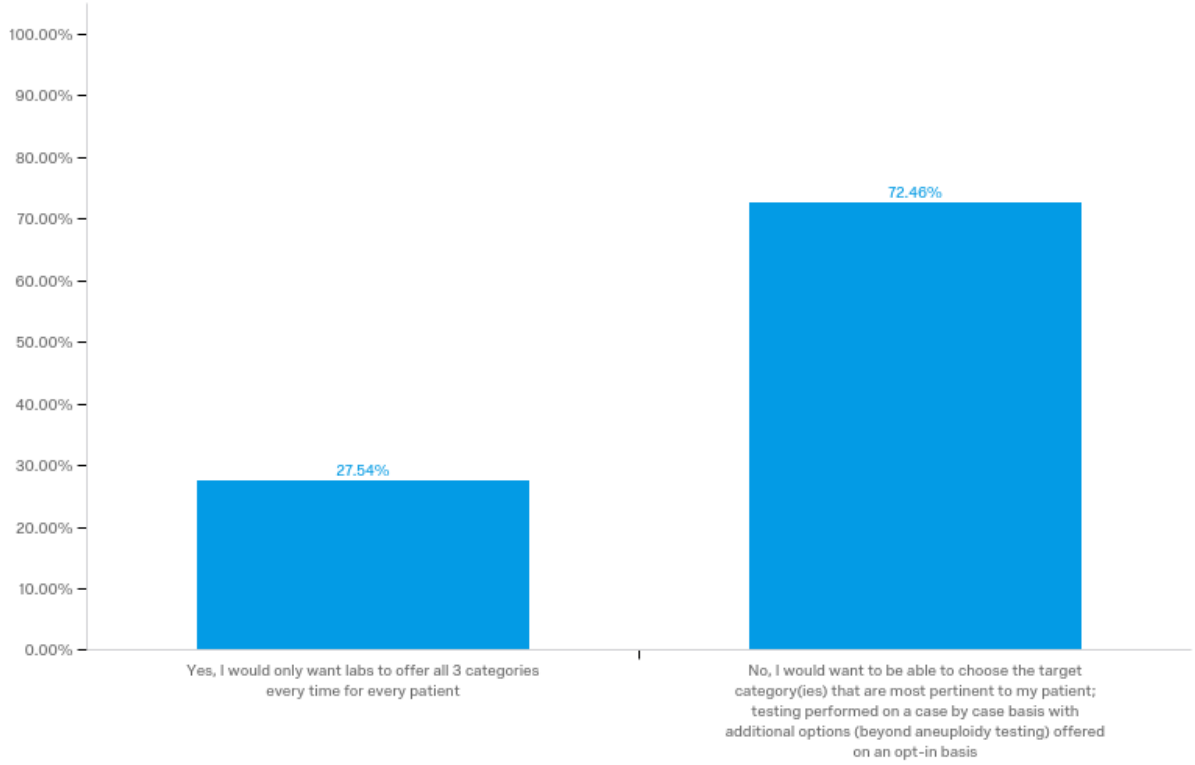

Figure 8 Opinion Regarding Expanded NIPT for All Patients

3.4 DISCUSSION

3.4.1 Knowledge of NIPT

The initial questions asked were meant to elicit respondents' knowledge of NIPT. When indicating methods by which they had learned about NIPT, the obstetricians indicated that the top four were discussion with peers, literature review, discussion with lab representatives, and continuing education. This is consistent with previous research of obstetricians and MFM specialists showing formal educational activities, literature review, and discussion with peers as the most common methods[90,91], and with other NIPT providers, including genetic counselors whose top methods were discussion with peers, in literature review, discussion with lab representatives, and at professional confrences[85]. As with previous studies, the use of laboratory representatives as an education resource could pose an ethical issue.[85,90,91] Laboratories have a conflict of interest when they serve as both the provider and educator. This is not to say that laboratories should not play a role in educating providers, but they should not be the exclusive educator. The vast majority (94.89%) indicated the correct timeframe when NIPT could be performed, i.e. as early as 10 weeks. When a survey of genetic counselors answered with 100% accuracy.[85]

3.4.2 Opinions of NIPT

Participants felt that the greatest advantages of NIPT were patient acceptance, availability during gestational age, and detection rate. They indicated that coverage by insurance companies followed by false positive rates were the greatest limitations. These were the same advantages

and limitations of NIPT that genetic counselors indicated, as well. Where these groups differed was in considering the availability of genetic counselors. Genetic counselors (n=23/113, 20.4%) viewed their limited availability as more of a limitation compared to the opinions of obstetricians (n=26/227,11.5%).[85] Genetic counselors may be particularly sensitive to their limited availability. Workforce data collected by NSGC highlights the need to increase the number of practicing genetic counselors to meet patient demand.[95] However, in some instances, obstetricians may be confident in their ability to provide patient counseling regarding NIPT even given the deficit of training resources and rapid evolution of NIPT. Previous research indicated that access to a genetic counselor would be helpful – and even preferred - with abnormal results,[90] and in this survey, 57.63% indicated they would like access to a genetic counselor when results were abnormal. Additionally, 39.4% indicated that they would find pre-test access to genetic counselors helpful.

3.4.3 Alignment of NIPT Practices with Current Guidelines

This survey was conducted nearly a year after the updated ACOG[6] and ACMG[71] published their updated recommendations which state that all women, not only those at high-risk, should be offered all screening options, including NIPT. When specifically asked about offering NIPT to low-risk patients, 45.72% indicated that it was not something that they currently do. Of those who were offering the testing to low-risk patients, it was still at a lower rate than their high-risk patients: 77.83% of participants were offering NIPT to 90-100% of their high-risk patients; 63.21% were offering to as many low-risk patients. Of those who were not offering testing to their low-risk patients, 90.21% indicated that they had no plans to do so within the next 12 months. These responses indicated that a significant number of participants appeared to be

following an older ACOG committee opinion from 2015[70], which stated that conventional screening remained the best option for general patients, reserving NIPT for high-risk patients. It is interesting to note that the participants in this study were all current members of ACOG, and hopefully would have access to the updated recommendations.

Two possible reasons for the observed difference between recommendations and clinical practice are limited availability of general population NIPT research and the complications of insurance and testing cost to patients. Most of the available literature on NIPT is based on studies that have been conducted on high-risk populations. However, recent large-scale studies of NIPT in general populations have shown the test to have similar positive predictive values to high-risk populations.[92,93,96,97]

A practical limitation of NIPT that may deter providers from offering the test is the cost of the test for the patient. Other studies have explored this issue. The cost of NIPT varies between companies, and reimbursement rates and out-of-pocket costs vary by insurance plan. In a 2013 survey of commercial NIPT in the United States, out–of-pocket costs were found to be up to $1,700, co-pays up to $235, and direct to insurance bills of up to $2,900.[98] A 2016 survey found that genetic counselors were concerned about the cost of the test for patients and insurance issues.[86] Obstetricians may also share these concerns.

Additionally, when queried about offering diagnostic testing after abnormal NIPT results, 4.82% said they did not offer diagnostic testing and 8.56% said that it depends on other factors. Recommendations by professional groups, including ACOG, state that all women who received abnormal NIPT screening results should be offered confirmatory diagnostic testing. In a previous provider knowledge survey, there was a direct correlation between offering confirmatory testing and accurately identifying NIPT as a screening, rather than a diagnostic, test.[90] Therefore, it is

possible that respondents who were not offering confirmatory testing mistakenly viewed NIPT as a diagnostic test.

Furthermore, none of the guidelines put forth by professional organizations recommend NIPT microdeletion/duplication testing and instead maintain that diagnostic testing is the most appropriate method for women who are concerned about their risk for conditions caused by microdeletions or microduplications. The responses gathered indicated that not all obstetricians were following these recommendations; 20.76% were offering this expanded testing to high-risk patients and 5.93% were offering it all their patients. While these obstetricians may want to offer their patients the most cutting-edge testing available, there are risks to using newer technology that have not been extensively researched. Further exploration of these physicians' motivations and their discussions of expanded testing with patients is warranted

3.4.4 Future Directions

Responses showed that most participants currently do not offer microdeletion/duplication to any of their patients, and only 20.76% offer it exclusively to high-risk patients. Compared to interpretation of aneuploidy test results, confidence in test interpretation and explanation of test results to patients decreased for microdeletion/duplications. In regards to confirmatory testing, more respondents indicated they would offer invasive testing after abnormal monogenic results (72.03%, n=170) than after abnormal microdeletion/duplication results (55.51%, n=131). Although NIPT for monogenic disorders is not currently available, 72.03% of participants indicated they would offer confirmatory diagnostic testing after an abnormal result. Another avenue to explore would be the exact motivation for providers who are offering expanded testing to their patients. Open ended survey questions inquiring about motivation should be utilized,

including questions asking about influences of laboratory representatives and exploring the many facets of expanded testing individually.

The majority (72.46%) of participants indicated that they would prefer to opt-in to expanded testing options while (27.52%) would want aneuploidy, microdeletions/duplications, and monogenic disorders for all patients. None of the previously surveyed genetic counselors indicated a preference for the latter option. Instead, each wanted the ability to decide what was most appropriate for their patient.[85] That most providers want to select the scope of NIPT they are offering to their patients implies that they do not feel expanded testing is appropriate for all patients.

3.4.5 Study Limitations

Invitations to participate were sent to 4770 members and only 238 completed the survey. Given the low response rate of 4.98%, it is possible that the participants of this survey do not accurately reflect the full population of ACOG members. Another limitation of the survey was that a reminder email was not utilized, which may have increased the response rate. As with any survey, there is the possibility of selection bias. Participants who were interested in the topic and/or confident in their knowledge of NIPT may have been more inclined to participate. Conversely, obstetricians who were not confident in their knowledge of NIPT may disproportionally represent those who declined to participant. Either of these scenarios would lead to an overestimation of participate knowledge and comfort. Additionally, the data for this study were based on self-reported responses. Participants may not have accurately self-assessed their knowledge or may have reported answers they believed to be correct rather than an accurate

reflection of their clinical practice. In this case, the reported results would overestimate participate knowledge and/or comfort.

3.4.6 Practice Implications

The majority of obstetricians displayed accurate knowledge of NIPT and confidence in result interpretation for aneuploidy test results and their ability to disclose this information to patients, but this confidence decreased in regard to expanded NIPT testing that included microdeletions/duplication and monogenic disorders. This indicates the need for educational materials or CME activities on these newer topics targeted towards providers. Additionally, this study revealed a discordance in some obstetricians' clinical practices compared to recommended guidelines put forth by their professional organization. Possible reasons may be that these providers are not familiar with the updated recommendations, they may not agree with the recommendations, or they may be facing barriers to testing due to insurance complications and financial burdens placed on patients. The exact reason for this difference was not evaluated by this survey, but should be explored in future research to address this difference.

3.4.7 Research Recommendations

As the use of expanded NIPT increases and new professional guidelines regarding it are developed, the opinions and clinical practices of healthcare providers should be sought. Further surveys of these providers should confirm knowledge of NIPT as a screening test, assess awareness of and agreement with current professional guidelines, ask open-ended questions as to why they would or would not use expanded NIPT options, and address cost/insurance issues

associated with the test. Additional research into the average time it takes for healthcare professionals to incorporate new guidelines would also be helpful to assess if the differences in recommendation and practice found in this study are in line with the typical adaption timeframe.

3.5 CONCLUSION

The introduction of NIPT has brought dramatic changes to the prenatal screening for both patients and healthcare practitioners. Even as the test becomes commonplace, both the recommendations for clinical implementation and the conditions that can be detected have been constantly changing. Now that the recommended testing population has been broadened to include all women, it is even more vital for healthcare practitioners to know the benefits and limitations of the test, feel confident in their ability to accurately interpret and convey results to patients, to understand how NIPT has and will continue to expand, and to be familiar with professional guidelines that set standards as to how the test should be implemented. Although participants demonstrated adequate familiarity with NIPT testing for aneuploidy, this was not the case for microdeletion/duplications or monogenic disorders. Additional information and educational support for obstetricians regarding expanded NIPT testing should be developed.

4.0 RESEARCH SIGNIFICANCE TO PUBLIC HEALTH AND GENETIC COUNSELING

The goal of public health is promotion and protection of health within a population. This goal is achieved through the public health core functions of assessment, policy development and assurance. These core functions encompass and guide the ten essential services of public health, including the development of policies in conjunction with stakeholders to implement the most effective strategies and assure a competent public health and healthcare workforce.

Prenatal screening is an intervention offered to all women to identify pregnancies that are at risk for birth defects and chromosome abnormalities. Early detection and identification of these conditions allows for appropriate alterations of medical management, including changes to birthing plans, preparation for surgical interventions immediately after birth, connecting families with specialists and services, and possibly time to consider pregnancy termination. While some women will choose to undergo prenatal screening and/or testing during their pregnancies and other will choose to not undergo any screening, it is important that all women be made aware of their options by a knowledgeable medical provider.

Early prenatal screening methods include sonographic imaging to visualize structural defects and maternal serum alpha fetoprotein (MSAFP) levels to indicate the presence of neural tube defects. In 1990, the American Public Health Association (APHA) released a policy statement acknowledging the multifactorial inheritance of neural tube defects, calling for

awareness and education of MSAFP as a screening tool for healthcare providers, and suggesting follow-up services including genetic counseling. The statement recognized that appropriate guidelines for MSAFP screening had been developed by ACOG and ACMG.[99] MSAFP serves an example of how polices developed by professional organizations and education of providers about testing and its appropriate implementation fall under the purview of public health.

The addition of NIPT as a prenatal screening option can be appreciated in a similar framework. Professional organizations including ACOG, ACMG, and NSGC have developed guidelines for NIPT testing. However, these guidelines, and the practitioners they target, face two challenges: the expanding scope of NIPT and the availability of literature supporting expanded testing. The constant developments in the field continue to advance faster than the literature, which impacts the guidelines. In turn, this can lead to differences in clinical practice as even in the presence of developed policy.

This study revealed some clinical practices that were not congruent with current guidelines. The hesitancy of some providers to offer NIPT aneuploidy to all their patients may indicate that they feel that there is not enough evidence to support such a recommendation. Conversely, providers who were eager to offer expanded NIPT to their patients, against recommendations, may believe that the guidelines are not keeping pace with advancements. Evaluating providers' opinions should assist in addressing differences by helping to shape how these guidelines are presented, acknowledging provider concerns and leading to informed educational supplementation that can be released alongside new guidelines.

The essential service of ensuring a competent workforce can be achieved through provider education. As there are a variety of providers who offer NIPT to patients, understanding these providers' knowledge and confidence in their ability to educate patients about testing,

provide adequate informed consent, and correctly interpret test results are important assessments which lead to policy development. As fellow providers of NIPT, genetic counselors are recognized as valuable assets by some providers, especially regarding interpretation and counseling of abnormal NIPT results.[90] Additionally, genetic counselors who self-identified as working in a public health capacity indicated that 82% of their time was spent educating healthcare professionals.[100] Therefore, genetic counselors should be included as stakeholders and utilized as key resources for the development of provider NIPT education.

5.0 PUBLIC HEALTH ESSAY

5.1 BACKGROUND

From diagnostic testing like amniocentesis and chorionic villus sampling to maternal serum screening methods and imaging via ultrasound, prenatal screening and testing is a rapidly evolving field. This trend continues with the introduction of non-invasive prenatal testing (NIPT), a screening test that can be completed as early as 10 weeks gestation and looks at cell-free DNA from the placenta in the mother's blood. In 2011, aneuploidy NIPT testing was first made commercially available, targeted mainly towards women at increased risk to have a child with a chromosome disorder.[5] In 2013, laboratories started offering expanded NIPT, including select microdeletions and microduplications, triploidy, and less common aneuploidies.[73] Currently, NIPT for monogenic disorders is being developed and is likely to be added to expanded testing options in the near future.

As NIPT continues to change, the professional guidelines and recommendations regarding this screening test have also evolved. Previously, aneuploidy NIPT was recommended only for women who were considered to be at high risk for aneuploidy compared to the general obstetric population.[15,70] This changed in 2016 when guidelines from professional organizations such as the American College of Obstetricians and Gynecologists (ACOG), the American

College of Medical Genetics and Genomics (ACMG), and the National Society of Genetic Counseling (NSGC) broadened the recommended NIPT testing population to all women. [6,69,71]

Now that NIPT is recommended not only to women considered to be at high risk for aneuploidies, but to the general obstetric population, it is important to view the testing through a public health perspective as it becomes a standard of care. Considering the core functions of public health, assessing provider knowledge can identify deficiencies that need to be addressed, informing policy development by professional organizations and addressing deficiencies in a manner that assures a competent workforce.

With the rapid uptake of aneuploidy NIPT, the introduction of expanded NIPT options, and changes to professional guidelines, it is important to assess providers' knowledge and confidence regarding the screening. In order to assess current practice and knowledge regarding NIPT, a survey was developed to assess these across three types of providers: genetic counselors, obstetricians, and nurse-midwives.[85] Nearly all of the genetic counselors were highly knowledgeable about NIPT, confident in interpreting results (99%) and comfortable explaining results to patients (99%). However, when it came to microdeletion/duplication NIPT, genetic counselors' confidence in result interpretation and comfort in explaining results to patients decreased to 86% and 87%, respectively.[85] An even greater decrease between aneuploidy NIPT and expanded NIPT was observed in obstetricians as confidence fell from 96.15% to 45.89% and comfort dropped from 95.75% to 45.45%. Nurse midwives will be surveyed in the next part of this study.

There are a variety of providers involved in providing NIPT. Regardless of where a patient is receiving information about NIPT, it should be consistent across all providers, and providers should be confident in their knowledge of NIPT and comfortable discussing the

screening with patients. Addressing provider education, with an inclusive, interdisciplinary approach, is one avenue to address this issue. This essay proposes utilizing continuing medical education (CME), or continuing education (CE), as an intervention through the creation of NIPT specific online learning modules and educational material for all providers.

5.1.1 Prenatal Screening as a Public Health Intervention

Prenatal screening and testing is currently a standard part of prenatal care. This has evolved over time, because when prenatal screening techniques are first introduced they typically are developed for a certain population before being expanded to all pregnant women. Additionally, as more healthcare providers are involved throughout pregnancy, these screening methods may be discussed at several different points during pregnancy and with a variety of healthcare professionals. As testing options and providers increase, it is important to consider the role of public health in prenatal testing has been examined.

In a 1999 article published in the *American Journal of Preventative Medicine*, Dr. Ellen Clayton explored public health's role in newborn screening and prenatal diagnosis given the new technologies allowing for such at the time.[101] The technology being used for prenatal testing was using maternal serum alpha-fetoprotein (MSAFP) as a marker. There was a push to bring MSAFP to the general obstetric population as evidenced by the Healthy People 2000's goal of offering the testing to 90% of pregnant women.[102] Dr. Clayton discussed how prenatal testing fell within a public health framework, including in utero interventions and alterations to the mode or location of delivery.[101] However, many medical problems indicated prenatally do not have corrective medical interventions, meaning that the testing does not fit completely into a public

health framework. Regardless, Dr. Clayton emphasized that the accuracy and appropriate delivery of prenatal testing techniques was within the purview of public health.[101]

The introduction of NIPT as a new prenatal technology and, now, its general availability is analogous to MSAFP. The need for public health assurance in regard to NIPT is two–pronged: assuring the accuracy of the test and assuring the competency of the providers offering it. The accuracy of the test for detecting common trisomies has been established, and professional organizations have changed their recommendations to include NIPT as a screening option for all women after additional studies were published regarding the accuracy of the testing in women not thought to be at high risk. As a general obstetric screening option, NIPT falls within the purview of public health and, just as with MSAFP, the competency of providers needs to be assured. To accomplish that, new programs and educational endeavors to educate providers may be useful, and one such intervention is proposed here.

5.1.2 Educating Prenatal Care Providers

An article published in the *Journal of the American Medical Association*, describes traditional continuing medical education (CME) as a passive, time-based educational model typically consisting of conferences, workshops, or lectures.[103] However, computer-aided instruction and practice site visits have been described as positive CME interventions.[103] The most effective CME interventions have several components: a learning needs assessment, peer interaction with the opportunity to practice learned skills, and sequenced and multifaceted education activities.[103]

There have been a number of studies that have assessed CME, which has consistently been shown to be effective when certain interventions are implemented. Three systemic review articles assessed the effectiveness of CME spanning from 1975 to 2007.[104–106] A number of

common themes emerged from these studies. Didactic sessions, conferences, and educational materials alone have relatively little impact.[104–106] However, by also engaging physicians in activities, case discussion, role-play and practice sessions, they are more likely to incorporate what they have learned and their behavior is more likely to change.[104–106]

As genetics/genomics in medicine continues to rapidly grow, improving genetic knowledge among healthcare providers is a necessity.[107] Methods by which this can be accomplished include updating pre-service education and providing genetics-focused continuing education for providers.[107] In a 2007 article published in *Nature Reviews Genetics*, the authors outline the importance of genetics, skills and knowledge they believe are essential, and how to integrate genetics into provider education.[107] Recommendations for integrating genetic education for healthcare providers include building connections between research and clinical use, developing educational material with representatives from the target audience, and utilizing case-based, practical examples.[108] In a study that aimed to evaluate the implementation of genetics curriculum on the skills in genetic diagnosis and counseling of obstetrician-gynecologist residents at the George Washington School of Medicine, all 40 residents completed a needs assessment and 28 went on to complete the educational intervention.[109] The implementation of genetic curriculum for obstetrician-gynecologist residents both improved their knowledge, with 25 of 28 scoring higher on their post-test, and increased their confidence in applying the concepts they learned, per debriefing comments. The curriculum of the educational intervention included a combination of didactic sessions and an experiential learning case.[109]

A 2011 article published in the *Journal of Perinatal & Neonatal Nursing* by certified nurse-midwife Diane Angelini, EdD explored key issues in interdisciplinary and interprofessional education.[110] It discussed how interprofessional and interdisciplinary

continuing education lead to increased professional confidence, promotion of mutual understanding between professions, discovery of new resources, an appreciation of other professions' skills, and recognition of overlapping professional functions.[110] Establishing common knowledge of NIPT across specialties is one step that may lead to more consistent prenatal patient care.

Looking to other specialties to illustrate the incorporation of genetic education, primary care physicians (PCPs) provide a useful example. Acknowledging the limited genetics knowledge of many PCPs, a perspective article published in Nature Reviews Genetics in 2002 discussed how to address this knowledge deficit.[111] The authors, Wylie Burke of the University of Washington's Department of Medical history and Ethics and Jon Emery of the University of Cambridge's General Practice and Primary Care Research Unit, suggested methods included the promotion of genetic education in medical school curricula, continuing education, and innovative approaches for delivering genetic information. The promotion of partnerships between PCPs and genetic professionals, especially in joint educational efforts, helped to show areas of overlap between the professions and provide opportunities for mutual learning.[111]

There is very little research regarding interdisciplinary education for genetic counselors. A 2014 study aimed to complete a needs assessment of interdisciplinary education with a focus on oncology procedures.[112] The proposed interdisciplinary program revolved around observations of oncology procedures: colonoscopy, gastroscopy, chemotherapy, and wound care. The goal of the program was to increase counselors' understanding and confidence regarding these procedures and in discussing them with both patients and other providers. A total of 56 registered members of the Australasian Society of Genetic Counsellors (ASGC) who worked in cancer genetics completed the survey. More than 95% of participants felt that interdisciplinary

observations would benefit their professional development and almost 90% felt the proposed program could be implemented in their workplace. These results indicate genetic counselors would also benefit from interdisciplinary education.[112]

5.1.2.1 Education and Integration of Non-Genetic Screening Methods

There have been several examples of successful interprofessional educational programs developed outside of the field of genetics. In 2015, Shaw-Battista *et al*. developed a course around obstetric ultrasound education for nurses, midwives, physicians, and students.[113] The course was composed of online learning modules, case-based seminars, and skill labs. Upon completion of the course, participants felt that having representatives from different professions allowed for collaborative efforts that facilitated learning. Learners also positively cited the varied learning formats and activities as beneficial.[113]

A second study looked at an educational program developed to increase the knowledge of providers involved in newly recommended HIV screening for women during pregnancy.[114] While screening women for HIV during pregnancy to reduce mother to child transmission is now a routine part of prenatal and delivery care, it began as a professional recommendation.[114] The recommendation for the screening by ACOG was implemented in 2004.[114] In response to this change of professional guidelines that expanded access to screening for HIV, a formal educational presentation was developed for all hospital staff who would be involved in the screening.[114] The multiple presentations were given to accommodate the various disciplines and availability of the staff. The presenters were peers of the given audience, in order to take advantage of role modeling and peer to peer teaching. Educational materials were also provided, including fact sheets for nurses' stations, information about the test, and suggested wording for

orders. Participants' knowledge increased by more than 35% after the intervention, as evidenced by higher scores on the post-test evaluation.[114]

5.1.2.2 The Importance of Provider Education About Genetic Screening

Genetic counselors working in prenatal settings are providers of NIPT and are recognized as valuable assets to other providers, especially in regard to interpreting and counseling positive NIPT results. However, there are not currently enough genetic counselors to meet demand. There are, as of 2016, more than 4,000 board-certified genetic counselors.[95] While there has been increasing patient volume and provider referrals for genetic counseling services, in part due to the expanded recommendations for genetic testing and screening, the number of new counselors entering the field is limited by the amount of genetic counseling master's training programs and the capacity of those programs to train students. At the current rate students are entering the workforce, less than 2,400 genetic counselors would be added over the next decade, not even doubling the size of the workforce.[95] While efforts to increase the number of programs and current program sizes are being made, other providers integrating genetics into their clinical practice to meet patient needs. While more straight-forward prenatal screening is sometime done in a patient's obstetrician's office, referrals are still made for newer testing and more complex cases.

A 2016 study surveyed 258 general obstetrics-gynecologists and maternal-fetal medicine subspecialists regarding education of NIPT, practice patterns, and barriers to using NIPT.[115] The barriers that were indicated by respondents included lack of time, limited familiarity and experience with NIPT, limited staff and resources to assist with counseling, and minimal reimbursements for counseling.[115] Genetic counselors were acknowledged as an important educational resource not only for patients, but for providers, as well.[115] However, the shortage of

genetic counselors was also noted. Therefore, the study concluded that educational efforts by professional organizations should target a variety of healthcare providers, including nurses and nurse-midwives, as NIPT expands from high-risk to the general obstetric population.[91]

In the results obtained from our survey, obstetricians indicated that more than half of participants learned about NIPT through discussion with peers and literature review. Discussion with laboratory representatives and continuing education courses were the next most common learning methods. Similarly, more than half of genetic counselors indicated discussion with peers and lab representatives, and literature review.[85] Additionally, they indicated professional conferences and formal education in their training programs.[85]

As NIPT continues to rise in popularity among patients and providers, it is vital that providers can accurately and comfortably discuss, interpret, and utilize the screening. A continuing education course that addresses common genetic knowledge, NIPT specific content, and communicating important NIPT concepts to patients may be an effective strategy to increase knowledge among a variety of healthcare professionals. Considering the benefits of interdisciplinary learning, the course would broadly target the vast array of providers who are involved in offering NIPT, instead of targeting each specialty individually. This may also help to foster collaboration between healthcare providers and increase awareness about prenatal genetic counseling.

5.2 RELEVANCE TO PUBLIC HEALTH

Public health is divided into three core functions: assessment, policy, and assurance. There are ten essential services of public health, each of which are associated with one of these core functions. The proposed intervention directly addressed several of these essential services.

One core function of public health is to assess areas where provider knowledge is deficient and should be addressed, informing the development of policies and guidelines by professional organizations that both oversee continuing education and often serve as sources for continuing education content. As previously mentioned, results from our survey assessing obstetricians' knowledge of NIPT revealed deviations from policy put forth by professional organizations, which may indicate a need to address knowledge and confidence surrounding expanded NIPT.

If providers are not sufficiently informed or lack confidence in their ability to describe and interpret results, the ability for the public to benefit from new advancements is hindered. Identifying these areas for improvement, developing plans to facilitate learning and skill building, and applying these lessons learned to better anticipate and respond to the needs of providers as additional advancements are made in the field, should be central goals of public health professionals.

The goal of the proposed intervention is to increase providers' knowledge, including the benefits and limitations of NIPT, and to increase their comfort and confidence when interpreting and reporting results to patients. In this regard, the intervention will directly contribute to the essential service of assuring a competent workforce. By including a variety of stakeholders to develop and contribute to the learning modules of this intervention, the essential service of mobilizing community partnerships to identify and solve health problems is realized.

Assessing the effectiveness of the intervention may yield data to allow for novel innovations to training healthcare providers about new screening advancements, which incorporates the essential service of using research for new insights and innovative solutions to health problems. As such, evaluation will be an important part of this intervention from the planning stages through implementation.

5.3 INTERVENTION

The need for provider education regarding NIPT is evident based on the results of our study and previous studies as well as recent changes in professional guidelines. This proposed intervention aims to create and implement continuing education modules targeting all prenatal healthcare providers. This would be done by gathering invested stakeholders to create online educational modules and downloadable material. To assess the effectiveness of the intervention, pre-and post-tests will be given to participants to ascertain knowledge of and comfort with NIPT. Figure 9 displays a logic model as an overview of the intervention.

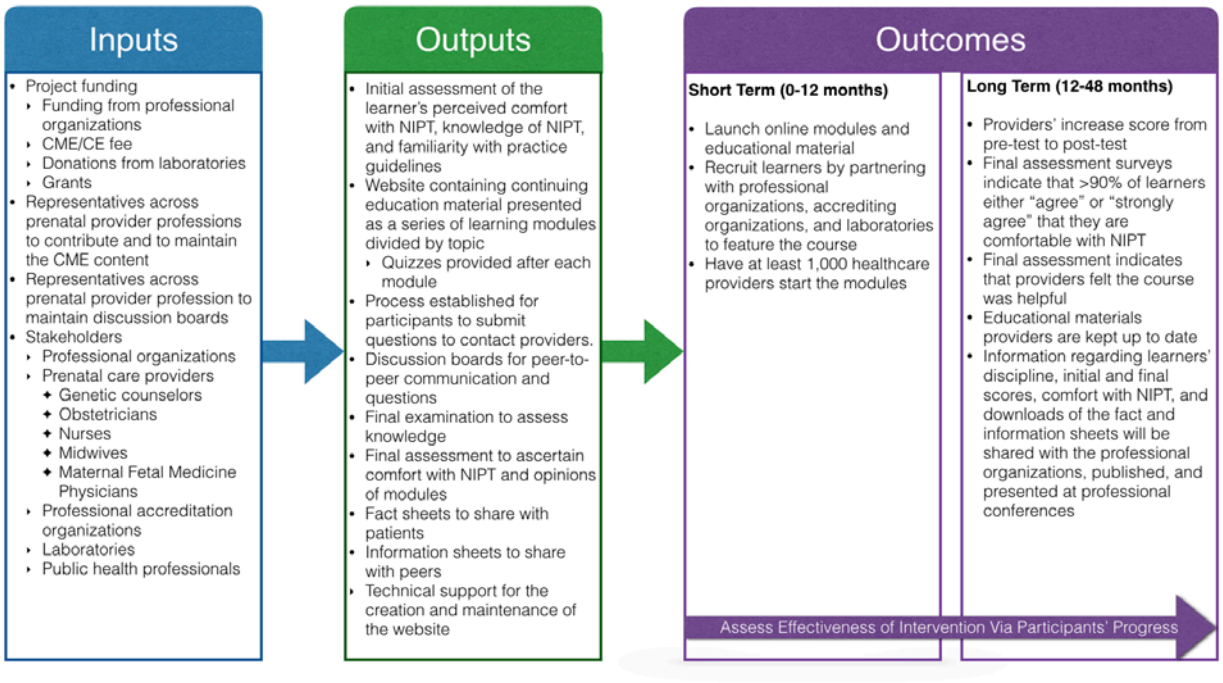

Figure 9 Logic Model of Proposed Intervention

Recorded online videos and an asynchronous method were chosen over live webinars to reduce barriers for participants. They will be able to take advantage of each module at a time that is most convenient for them. Additionally, pre-recorded content will allow for easy review of content, the ability to modify selected portions for updating, and facilitate a consistent, professional presentation of material. The addition of comment sections and discussion boards allow for peer-to-peer interactions that would be present in a synchronous presentation method.

5.3.1 Identifying Stakeholders

There are a wide variety of providers who should be considered as candidate learners, including obstetricians, genetic counselors, nurses, nurse-midwives, and maternal fetal medicine physicians. Other key stakeholders who would ideally be involved would be professional

organizations, accreditation organizations, laboratories, and public health professionals. Representatives from each should be involved in contributing to and approving the educational material. Additionally, attaining approval of the modules for continuing education credit by accrediting organizations would help to incentivize providers to use the material, as well as advertise to the appropriate providers. Including the laboratories is important in order to elicit information about their testing methods and specifications. Furthermore, the laboratories could include a link to the courses on the provider-targeted pages of their websites.

5.3.2 Initial Project Development

The project will be initiated with a series of meetings between representatives from each of the stakeholder groups. These meetings will address funding, content, and responsibilities. Each group will identify how much they can contribute to the project in regards to time, money, and other resources. The group will also discuss possible funding options, including grant funding and will assign individuals to work on the grant application, if appropriate. Additionally, an outline of module topics will be developed. These groups will be asked to also contribute by identifying individuals who would be interested and qualified to create the content, serve as the video educators, and be the discussion moderators. An approval method will be developed for completed modules, post-module quizzes, and the pre- and post-tests to ensure and assess learning.

5.3.3 Creating the Modules and Resources

The course and materials would be found on a website and segmented into several modules covering different topics. Before starting the modules, an initial assessment will be given as a benchmark. Each module will be given in video format and be no more than 10 minutes in length, each with an accompanying outline. There will be comment and discussion sections associated with each video to allow learners to interact with other peers, as well as ask questions about the material. After completing the module, a quiz to assess provider learning will be taken before moving on to the next module.

While the educational materials will be developed by many stakeholders, the following are suggestions of components to include:

- **Introduction**
    - G*enetics Overview*: Genes; Chromosomes; Aneuploidy; Microdeletions/duplications; Monogenic Disorders
    - *Summary of Prenatal Screening and Diagnostic Methods*: First Trimester Screening; Maternal Serum Screening; Ultrasonography; Chorionic Villus Sampling; Amniocentesis
- **NIPT Specific Content**
    - How NIPT works; when can it be done; where does fetal DNA originate
    - Possible test results; differences in wording of results; reasons for inconclusive/no-call results; interpreting results
    - Understanding laboratory specifications: sensitivity, specificity, and positive predictive value

    - Comparing NIPT to other screening and diagnostic methods: benefits and limitations
    - Expanded testing
    - Communicating with patients about NIPT
    - Review the variety of healthcare providers involved with NIPT and their roles
- **Professional Guidelines**

In addition to the module, there will be additional educational material made available to learners. Quick reference sheets aimed at providers will be created and made available for download. Also, materials to assist in discussions of NIPT with patients will be provided. These will include infographics on the benefits and limitations of all screening and diagnostic methods.

5.3.4 Project Goals

After the creation and approval of the content, the short term (0-12 months) goals of this intervention will be to recruit providers to utilize it. Participating laboratories will be asked to share a link to the modules on their provider specific NIPT webpages. Professional and accreditation organizations will be asked to make their members aware of their course by either highlighting it on their respective webpages or emailing their membership bodies. The goal will be to have 1,000 healthcare providers start the modules within the first year they are available.

Upon completing all the modules, learners will take a final assessment that gauges knowledge of NIPT and queries their comfort with the testing. The long-term (12-48 months) goals of this intervention are for learners increase their score from their pre-test to their post-test.

Whether a target increase should be aimed for and what an appropriate increase is would be discussed during the stakeholders meeting during the initial project development. During their final assessment, at least 90% of learners indicate that they “agree” or “strongly agree” that they are comfortable with NIPT. Additional long-term goals include key stakeholders keeping the educational material up to date by reassessing for and adding new developments, research, and guidelines every six months. Participants will have the option of enrolling in a contact program that will email these updates to learners who have already completed the course.

The discipline of the learners, initial and final evaluation scores, comfort with NIPT, use of the fact and information sheets, and opinions on the usefulness of the course will be provided to professional organizations and other interested shareholders, as well as shared at professional conferences and published. Learners will also be asked to indicate if they felt the course was helpful to them, and if they feel it would be beneficial to their peer and other providers. If this intervention proves effective, it may be adaptable for provider education of other topics.

5.3.5 Evaluation of the Effectiveness if the Intervention

The effectiveness of the intervention will be evaluated by comparing participants’ results from their pre-test and post-test. The pre-test determines the baseline of each participants’ general NIPT knowledge, as well as knowledge of expanding NIPT. It will also assesses participants’ confidence in interpreting NIPT results, and gauge their comfort discussing results with patients. These metrics will be re-evaluated on the post-test. Additionally, participants will be asked to give a final assessment of the intervention, indicating if they felt it was helpful to them, if they believe their colleagues would benefit from participating, and if they would like to enroll to receive updates regarding NIPT.

5.4 CONCLUSION

NIPT has become a leading screening method to identify common trisomies and sex aneuploidies and is now a screening option for all women during pregnancy, making it a screening test that has evolved from being utilized in select individuals to now being offered through a model that more closely resembles those used in public health. To fulfill the three-core functions of public health regarding NIPT, provider knowledge should be assessed, to assure patients can be comfortable with their knowledge and confidence, and policies should be developed to address any deficiencies. This study's survey of obstetricians identified a lack of confidence and comfort around expanded NIPT testing.

One method to address these deficiencies is through continuing education. Continuing education is most effective when interactive through peer-to-peer discussion, utilizing activities and practical examples, and taking an interdisciplinary/interprofessional approach. This intervention aimed to incorporate all of these elements while allowing for broad availability of the content via asynchronous, online access. This allows all providers involved in NIPT, regardless of discipline, to participate, learning not only about the content, but their peers' contributions in the multidisciplinary arena of prenatal healthcare.

APPENDIX A: UNIVERSITY OF PITTSBURGH IRB APPROVAL LETTER

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Emily Griffenkranz
From: IRB Office
Date: 12/16/2016
IRB#: PRO16100624
Subject: Provider Knowledge of Non-Invasive Prenatal Testing

The above-referenced project has been reviewed by the Institutional Review Board. Based on the information provided, this project meets all the necessary criteria for an exemption, and is hereby designated as "exempt" under section

45 CFR 46.101(b)(2)

Please note the following information:

- Investigators should consult with the IRB whenever questions arise about whether planned changes to an exempt study might alter the exempt status. Use the "**Send Comments to IRB Staff**" link displayed on study workspace to request a review to ensure it continues to meet the exempt category.
- It is important to close your study when finished by using the "**Study Completed**" link displayed on the study workspace.
- Exempt studies will be archived after 3 years unless you choose to extend the study. If your study is archived, you can continue conducting research activities as the IRB has made the determination that your project met one of the required exempt categories. The only caveat is that no changes can be made to the application. If a change is needed, you will need to submit a NEW Exempt application.

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

APPENDIX B: SURVEY

B.1 COVER LETTER

Dear American Congress of Obstetricians and Gynecologists/American College of Nurse-Midwives member,

You are being invited to participate in a research study by answering the following survey questions about Non-Invasive Prenatal Testing (NIPT). The purpose of this research study is to understand current use of NIPT among different medical fields, determine provider understanding of NIPT, and explore provider readiness for the increase in prenatal testing options offered through NIPT. For that reason, obstetricians and midwives who are members of one of the selected professional organizations in the United States will be asked to complete a brief questionnaire that is expected to take approximately 15 minutes to complete. The questionnaire will include questions regarding demographics, current knowledge of NIPT, and readiness for the evolution of NIPT.

There are no foreseeable risks associated with this project, nor are there any direct benefits to you. There will not be any payment for participation. All responses are confidential, and results will be kept in a password protected document on a password protected computer. The data collected in this survey may be shared with investigators conducting similar research; however, this information will be shared in a de-identified manner (without identifiers). Your participation is voluntary, and you may withdraw from this project at any time.

Due to the nature of this survey, participants must answer all questions in order to submit the survey. This study is being conducted by Emily Griffenkranz, a Master's Degree student in the University of Pittsburgh Genetic Counseling Program, who can be reached at emg88@pitt.edu, if you have any questions.

This study has been reviewed and approved by the University of Pittsburgh Institutional Review Board (IRB#PRO16100624).

Please use the follow anonymous link to enter the survey:
https://pitt.co1.qualtrics.com/SE/?SID=SV_3Fa58nPHxXg3yjr

Thank you in advance for your time,

Emily Griffenkranz
Department of Human Genetics
University of Pittsburgh

B.2 SURVEY

Provider Knowledge of Non-Invasive Prenatal Testing (NIPT)

You are being invited to participate in a research study by answering the following survey questions about Non-Invasive Prenatal Testing (NIPT). The purpose of this research study is to understand current use of NIPT among different medical fields, determine provider understanding of NIPT, and explore provider readiness for the increase in prenatal testing options offered through NIPT. For that reason, obstetricians and midwives who are members of one of the selected professional organizations in the United States will be asked to complete a brief questionnaire that is expected to take approximately 15 minutes to complete. The questionnaire will include questions regarding demographics, current knowledge of NIPT, and readiness for the evolution of NIPT. There are no foreseeable risks associated with this project, nor are there any direct benefits to you. There will not be any payment for participation. All responses are confidential, and results will be kept in a password protected document on a password protected computer. Your participation is voluntary, and you may withdraw from this project at any time. Due to the nature of this survey, participants must answer all questions in order to submit the survey. This study is being conducted by Emily Griffenkranz, a Master's

Degree student in the University of Pittsburgh Genetic Counseling Program, who can be reached at emg88@pitt.edu, if you have any questions.

Emily Griffenkranz

Department of Human Genetics

University of Pittsburgh

Non-Invasive Prenatal Testing (NIPT) is a new technology that is rapidly evolving. The methodology involves the collection of a blood sample from the mother for analysis of cell-free fetal DNA in maternal plasma. Its most common and current utilization is the quantification of cell-free fetal DNA from chromosomes 13, 18, and 21 to detect the presence of an abnormal number of chromosomes in a cell, referred to as aneuploidy.

1. To what extent do you agree or disagree with the following statement: I am familiar with published NIPT clinical data.

   [ ] Strongly Disagree
   [ ] Disagree
   [ ] Neither Agree nor Disagree
   [ ] Agree
   [ ] Strongly Agree

2. How did you learn about NIPT? (Check all that apply.)

   [ ] I have not learned about NIPT
   [ ] Formal education
   [ ] Continuing education course
   [ ] Discussion with lab representative
   [ ] Discussion with peers
   [ ] Lab company advertisements
   [ ] Literature review
   [ ] Online researching
   [ ] Conference
   [ ] Other _____

3. NIPT for aneuploidy can be conducted at what gestational age?

   [ ] Anytime
   [ ] As early as 10 weeks
   [ ] As early as 15 weeks
   [ ] As early as 20 weeks
   [ ] I don't know

4. Which of the following criteria do you use in your practice to determine whether a patient is at high-risk for carrying an aneuploid pregnancy? (Check all that apply.)

   [ ] Maternal age
   [ ] An abnormal first trimester screening result
   [ ] An abnormal maternal serum screening result
   [ ] Abnormal ultrasound finding
   [ ] Family history of aneuploidy
   [ ] Previous pregnancy with aneuploidy
   [ ] Other _____

5. Do you offer NIPT to high-risk pregnancies?

   [ ] Yes
   [ ] No _____

6. If yes, what percent of high-risk patients do you offer/refer NIPT?

   [ ] 90-100%
   [ ] 75-90%
   [ ] 50-75%
   [ ] 25-50%
   [ ] 10-25%
   [ ] <10%
   [ ] None

7. If not, do you plan to offer NIPT to high-risk pregnancies in the next 12 months?

   [ ] Yes
   [ ] No

8. Do you offer NIPT to low-risk pregnancies with no significant risk factors for aneuploidy?

   [ ] Yes
   [ ] No

9. If not, do you plan to offer NIPT to low-risk pregnancies with no significant risk factors for aneuploidy in the next 12 months?

   [ ] Yes
   [ ] No

10. What percent of low-risk patients do you offer/refer for NIPT?

    [ ] 90-100%
    [ ] 75-90%
    [ ] 50-75%
    [ ] 25-50%
    [ ] 10-25%
    [ ] <10%
    [ ] None

11. To what extent do the following factors influence your decision to offer NIPT?

	No Influence	Slight Influence	Strong Influence
Abnormal serum screen result			
Advanced maternal age			
Prior fetus affected with aneuploidy			
Increased nuchal translucency			
Ultrasound markers associated with increased risk of aneuploidy			
Patient presenting late in gestation and past optimal time for screening procedures			
Family history of aneuploidy			
Patient with no indication requested testing			
Other _____			

12. Do you find the following to be advantages or limitations when ordering NIPT as compared to other screening tests such as first trimester screening and quad screening?

	Advantage	Neutral	Limitation	N/A
Recommended by scientific studies				
Recommended by professional societies				
Associated risk to pregnancy				
My history of experience with the test				
Coverage by insurance companies				
Detection rate				
Patient acceptance				
Patient Anxiety				
Risk associated with follow-up invasive testing				
False positives				
Availability during gestational age				
Availability of genetic counseling				
Other _____				

13. How is information about NIPT for aneuploidy provided to your patients prior to testing?

(Check all that apply.)

[ ] Patients speak face-to-face with a genetic counselor
[ ] Patients speak with a genetic counselor through telemedicine
[ ] I discuss NIPT with the patient
[ ] Patients speak to a health care provider other than a genetic counselor in my office
[ ] Patients speak to a health care provider other than a genetic counselor who is not part of my office
[ ] Patients read an information handout first
[ ] I do not order this test
[ ] Other _____

14. How confident are you interpreting patient NIPT results?

[ ] Not confident
[ ] Mostly not confident
[ ] Confident
[ ] Mostly confident
[ ] Very confident
[ ] N/A

15. How comfortable are you explaining NIPT results to your patients?

[ ] Not comfortable
[ ] Mostly not comfortable
[ ] Comfortable
[ ] Mostly comfortable
[ ] Very comfortable
[ ] N/A

16. If a patient has an abnormal NIPT result, do you offer invasive diagnostic testing (amniocentesis or chorionic villus sampling)?

[ ] Yes
[ ] No
[ ] It depends _____

17. When would you find access to a genetic counselor helpful during the process of ordering NIPT?

[ ] Before offering NIPT
[ ] After results come back and are abnormal
[ ] Only if results are abnormal
[ ] I do not offer genetic counseling

Recent research has contributed to the development of expanded testing opportunities through NIPT. This testing includes aneuploidy detection involving additional chromosomes as well as assessment of the presence of microdeletions and microduplications, which may be associated with certain genetic conditions. By definition, a microdeletion is the loss of a small fragment of a chromosome that involves several contiguous genes. A microduplication is a gain of a small fragment of a chromosome. Microdeletions and microduplications are typically too small to be detected by conventional cytogenetic methods such as light microscopy using high resolution karyotyping. Detection for microdeletions and microduplications are traditionally done by procedures such as fluorescence in-situ hybridization (FISH) or microarray analysis.

In the future, NIPT may also have the potential to analyze the presence of monogenic disorders. Monogenic disorders such as cystic fibrosis are known to be caused by mutations in a specific gene. Expansion of NIPT to include analysis of monogenic disorders can allow for recognition of these conditions in a fetus early in pregnancy.

18. To what extent do you agree or disagree with the following statement: I am familiar with published clinical data regarding microdeletions/microduplications within the context of NIPT.
    [ ] Strongly disagree
    [ ] Disagree
    [ ] Neither Agree nor Disagree
    [ ] Agree
    [ ] Strongly Agree

19. To what extent do you agree or disagree with the following statement: microdeletion/microduplication analysis should be offered in NIPT.
    [ ] Strongly disagree
    [ ] Disagree
    [ ] Neither Agree nor Disagree
    [ ] Agree
    [ ] Strongly Agree

20. Do you offer microdeletion/microduplication NIPT to all pregnancies?

[ ] Yes
[ ] No
[ ] Only to high risk pregnancies
[ ] Other _____

21. If not, do you plan to offer NIPT with microdeletion/microduplication in the next 12 months?

[ ] Yes
[ ] No

22. Which of the following criteria do you use to determine that a patient is at increased risk for having a fetus with a microdeletion/microduplication? (Check all that apply.)

[ ] Family with a known microdeletion/microduplication disorder
[ ] Prior fetus affected with a microdeletion/microduplication disorder
[ ] Ultrasound finding
[ ] I don't know
[ ] Other _____

23. How is information about NIPT with microdeletion/microduplication analysis provided to your patients prior to testing? (Check all that apply.)

[ ] Patients speak face-to-face with a genetic counselor
[ ] Patients speak with a genetic counselor through telemedicine
[ ] I discuss NIPT with the patient
[ ] Patients speak to a health care provider other than a genetic counselor in my office
[ ] Patients speak with a health care provider other than a genetic counselor who is not part of my office
[ ] Patients read an information handout first
[ ] I do not order this test
[ ] Other _____

24. How confident are you interpreting patient microdeletion/microduplication NIPT results?

[ ] Not confident
[ ] Mostly not confident
[ ] Confident
[ ] Mostly confident
[ ] Very confident
[ ] N/A

25. How comfortable are you explaining microdeletion/microduplication NIPT results to your patients?

[ ] Not comfortable
[ ] Mostly not comfortable
[ ] Comfortable
[ ] Mostly comfortable
[ ] Very comfortable
[ ] N/A

26. If a patient has an abnormal microdeletion/microduplication NIPT result, do you offer invasive diagnostic testing (amniocentesis or chorionic villus sampling)?

[ ] Yes
[ ] No
[ ] Not enough information at the present time

27. What is your opinion about offering analysis of monogenic disorders in NIPT?

[ ] Highly disapprove
[ ] Mostly disapprove
[ ] Neither approve nor disapprove
[ ] Mostly approve
[ ] Highly approve

28. Which of the following criteria would you use to determine that a fetus is at an increased risk for monogenic disorders? (Check all that apply.)
[ ] Family history of a known monogenic disorder
[ ] Family where the mother or father is known to be a carrier for the disorder
[ ] Family where the mother or father is suspected to be a carrier for the disorder based on family history
[ ] Prior fetus affected with a monogenic disorder
[ ] Ultrasound finding
[ ] Would offer to all pregnancies
[ ] I don't know
[ ] Other _____

29. If the patient has an abnormal NIPT result regarding a monogenic disorder, would you offer invasive diagnostic testing (amniocentesis or chorionic villus sampling)?

[ ] Yes (1)
[ ] No (2)
[ ] It depends (3) _____

30. In your opinion, would you want all NIPT labs to offer screening only for the 3 categories (aneuploidy, microdeletion/microduplication, and monogenic disorders) without option for fewer categories?

[ ] Yes, I would only want labs to offer all 3 categories every time for every patient
[ ] No, I would want to be able to choose the target category(ies) that are most pertinent to my patient; testing performed on a case by case basis with additional options (beyond aneuploidy testing) offered on an opt-in basis

Demographics

31. What is your field of specialty?

[ ] Certified Nurse Midwife
[ ] Certified Midwife
[ ] Genetic Counselor
[ ] Obstetrics & Gynecology
[ ] Other _____

32. Do you have a sub-specialty?

[ ] Yes _____
[ ] No

33. What is your primary work setting?

[ ] Academic
[ ] Private Practice
[ ] Hospital Based
[ ] Lab

34. How many years have you been practicing

[ ] 0-2 years
[ ] 2-5 years
[ ] 5-10 years
[ ] 10+ years

APPENDIX C: ADDITIONAL RESULTS

These are the remaining findings elicited from the survey that were not included in the manuscript.

Participants were asked to select all criteria used in their practice to determine a high-risk pregnancy. A detailed graph of responses is shown in Figure 10. A majority of participants used maternal age (n=233, 98.73%), ultrasound anomalies (n=220, 93.22%), and previous pregnancy with aneuploidy (n=217, 91.95%) as determinants of a high-risk pregnancy. Many also indicated an abnormal maternal serum screening result (n=207, 87.71%) and an abnormal first trimester screening result (n=199, 84.32%) as meeting their high-risk criteria. More than half (n=165, 69.92%) used family history of aneuploidy as a determining factor. Thirteen (5.51%) participants selected other as a response. When these participants elaborated further in an open-ended text question, ten indicated that they were offering NIPT either to all patients or at patients' request.

Participants were queried about the extent to which several factors influenced their decision to offer NIPT to patients. The strong influences were abnormal serum screening (84.62%, n=198), advanced maternal age (92.70%, n=216), prior fetus affected with aneuploidy (89.7%, n=209), increased nuchal translucency (88.41%, n=206), and ultrasound markers associated with increased risk of aneuploidy (89.74%, n=210). A family history of aneuploidy was indicated as a strong influence (48.26%, n=111) for some and a slight influence (42.68%, n=98) in others. Patients presenting later in gestation were mostly a slight influence (42.49%,

n=99) or no influence (40.39%, n=94). Participants were almost evenly divided regarding patients with no indication who requested testing: 30% (n=67) strong influence, 38.96% (n=90) slight influence, and 32.03% (n=74) no influence. Other factors mentioned by participants included insurance coverage and cost of testing, lack of first trimester screening in their practicing area, and practice of offering NIPT to all patients.

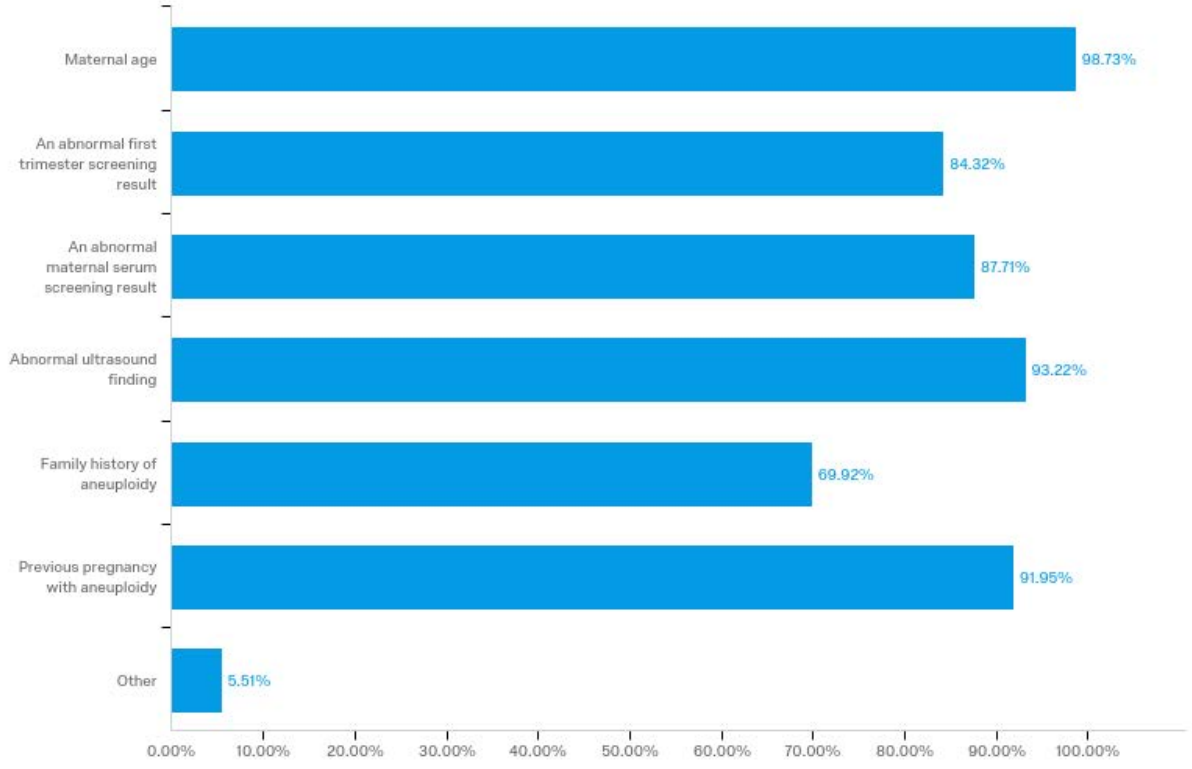

Figure 10 Criteria for Determining Pregnancies at High-Risk for Aneuploidy

A majority of participants indicated that a known family history of a microdeletion/duplication disorder (96.76%, n=179) and a prior fetus affected with a microdeletion/duplication disorder (96.22%, n=178) were criteria used to identify patients at an increased risk. Ultrasound as a criterion was indicated by 55.14% (n=102) of participants. The remaining participants' comments to an open ended question indicated that they did not use a lab

with this kind of expanded testing, that it was not a test that they offered to any patients, or that it was provided to all patients.

The most agreed upon criteria participants would use for determining increased risk for a monogenic disorder were a known family history of the disorder (n=181, 94.27%), family where a parent is a known carrier (n=182, 94.79%), and a prior affected fetus (n=181, 94.27%). Many (n=148, 77.08%) would use suspected parental carrier status and ultrasound findings (n=120, 62.5%) as criteria. A minority (n=16, 8.33%) would offer the expanded testing to all pregnancies.

BIBLIOGRAPHY

1. Jones KL, Jones M, Del Campo M. *Smith's Recognizable Patterns of Human Malformation*. 7th ed. Elsevier Saunders; 2013.

2. Milunsky A, Milunsky J. *Genetic Disorders and the Fetus*. 7th ed. (Milunsky A, Milunsky J, eds.). Wiley-Blackwell; 2015.

3. Gardner RJ., Sutherland G, Shaffer L. *Chromosome Abnormalities and Genetic Counseling*. 4th ed. Oxford: Oxford University Press; 2012.

4. Morris JK, Wald NJ, Mutton DE, Alberman E. Comparison of models of maternal age-specific risk for Down syndrome live births. *Prenat Diagn*. 2003;23(3):252-258. doi:10.1002/pd.568.

5. Norwitz ER, Levy B. Noninvasive Prenatal Testing: The Future Is Now. *Rev Obs Gynecol*. 2013;6(2):48-62.

6. Rose NC, Mercer BM. Practice Bulletin: Screening for Fetal Aneuploidy. *ACOG*. 2016;(163):1-15.

7. Haymon L, Simi E, Moyer K, Aufox S, Ouyang DW. Clinical implementation of noninvasive prenatal testing among maternal fetal medicine specialists. *Prenat Diagn*. 2014;34(5):416-423. doi:10.1002/pd.4301.

8. Wallerstein R, Jelks A, Garabedian MJ. A new model for providing cell-free DNA and risk assessment for chromosome abnormalities in a public hospital setting. *J Pregnancy*. 2014;2014. doi:10.1155/2014/962720.

9. Larion S, Warsof SL, Romary L, Mlynarczyk M, Peleg D, Abuhamad AZ. Uptake of noninvasive prenatal testing at a large academic referral center. *Am J Obstet Gynecol*. 2014;211(6):651.e1-651.e7. doi:10.1016/j.ajog.2014.06.038.

10. Hassold T, Abruzzo M, Adkins K, et al. Human aneuploidy: Incidence, origin and etiology. *Environ Mol Mutagen*. 1996;28(3):167-175. doi:10.1002/(SICI)1098-2280(1996)28:3<167::AID-EM2>3.0.CO;2-B.

11. Pont SJ, Robbins JM, Bird TM, et al. Congenital malformations among liveborn infants with trisomies 18 and 13. *Am J Med Genet Part A*. 2006;140A(16):1749-1756. doi:10.1002/ajmg.a.31382.

12. Centers for Disease Control and Prevention. CDC | Birth Defects | Data & Statistics. Birth Defects. https://www.cdc.gov/ncbddd/birthdefects/data.html. Published 2016.

13. Samango-Sprouse C, Kirkizlar E, Hall MP, et al. Incidence of X and Y chromosomal aneuploidy in a large child bearing population. *PLoS One*. 2016;11(8):1-11. doi:10.1371/journal.pone.0161045.

14. Nicolaides KH. Screening for chromosomal defects. *Ultrasound Obstet Gynecol*. 2003;21(4):313-321. doi:10.1002/uog.128.

15. Devers PL, Cronister A, Ormond KE, Facio F, Brasington CK, Flodman P. Noninvasive prenatal testing/noninvasive prenatal diagnosis: The position of the National Society of Genetic Counselors. *J Genet Couns*. 2013;22(3):291-295. doi:10.1007/s10897-012-9564-0.

16. Natera. Upgrades to the Panorama Prenatal Screen. http://pages.natera.com/natera-references-panorama-test-validation-summary. Published 2016.

17. Ariosa. *Positive Predictive Value and Interpretation of Results of the Harmony ™ Prenatal Test*.; 2016. https://www.ariosadx.com/files/7714/7558/5733/MM-00757_Webpage_PPV-Harmony_Test_Interpretation.pdf.

18. Sequenom. MaterniT 21 Plus Provider Information. https://www.sequenom.com/tests/reproductive-health/maternit21-plus#provider-test-details. Published 2017.

19. Integrated Genetics. informaSeq Prenatal Test. https://www.integratedgenetics.com/test-menu/informaseq®-prenatal-test/efc19619-cc3d-4e8d-a251-9647f4a21fc8. Published 2017.

20. Quest Diagnostics. Clinica Education Center | QNatal Advanced. http://education.questdiagnostics.com/faq/FAQ167. Published 2015.

21. Illumina. Noninvasive Prenatal Testing (NIPT). https://www.illumina.com/clinical/reproductive-genetic-health/nipt.html. Published 2017.

22. Hahnemann JM, Vejerslev LO. Accuracy of cytogenetic findings on chorionic villus sampling (CVS) - Diagnostic consequences of CVS mosaicism and non-mosaic discrepancy in centres contributing to eucromic 1986-1992. *Prenat Diagn*. 1997;17(9):801-820. doi:10.1002/(SICI)1097-0223(199709)17:9<801::AID-PD153>3.0.CO;2-E.

23. Brun JL, Mangione R, Gangbo F, et al. Feasibility, accuracy and safety of chorionic villus sampling: A report of 10 741 cases. *Prenat Diagn*. 2003;23(4):295-301. doi:10.1002/pd.578.

24. Jalal SM, Law ME, Carlson RO, Dewald GW. Prenatal Detection of Aneuploidy by Directly Labeled Multicolored Probes and Interphase Fluorescence In Situ Hybridization. *Mayo Clin Proc*. 1998;73(2):132-137. doi:10.1016/S0025-6196(11)63644-6.

25. Eiben B, Trawicki W, Hammans W, Goebel R, Epplen JT. A prospective comparative study on fluorescence in situ hybridization (FISH) of uncultured amniocytes and standard karyotype analysis. *Prenat Diagn*. 1998;18(9):901-906. doi:10.1002/(SICI)1097-0223(199809)18:9<901::AID-PD369>3.0.CO;2-L.

26. Wapner RJ, Martin CL, Levy B, et al. Chromosomal Microarray versus Karyotyping for Prenatal Diagnosis. *N Engl J Med*. 2012;367(23):2175-2184. doi:10.1056/NEJMoa1203382.

27. Binns V, Hsu N. Prenatal Diagnosis. In: *Encyclopedia of Life Sciences*. Macmillan Publishers Ltd, Nature Publishing Group; 2002:1-17.

28. Shulman L, Elias S. Amniocentesis and chorionic villus sampling have been shown through prospective , multicenter trials to be safe and effective methods of prenatal diagnosis ; accordingly , a knowledge of these tests is important for those physicians who care for women dur. *West J Med*. 1993;Fetal Medi(159):260-269.

29. Aula P, Karjalainen O, Teramo K, Vaara L, Seppala M. Safety and Accuracy of Midtrimester Amniocentesis for Prenatal Diagnosis of Genetic Disorders. *Ann Clin Res*. 1979;11(156):564-566.

30. Tabor A, Alfirevic Z. Update on procedure-related risks for prenatal diagnosis techniques. *Fetal Diagn Ther*. 2010;27(1):1-7. doi:10.1159/000271995.

31. Seeds JW. Diagnostic mid trimester amniocentesis: How safe? *Am J Obstet Gynecol*. 2004;191(2):608-616. doi:10.1016/j.ajog.2004.05.078.

32. Akolekar R, Beta J, Picciarelli G, Ogilvie C, D'Antonio F. Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: A systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2015;45(1):16-26. doi:10.1002/uog.14636.

33. Burton B, Schulz C, Burd L. Limb anomalies assocaited with chorionic villus sampling. *Obstet Gynecol*. 1992;79(5):726-730.

34. Kttliev A, Jackson L, Froster U, Brambati B. Chorionic villus sampling safety Report of World Health Organization / EURO meeting in association with the Seventh International Conference on Early Prenatal Diagnosis of Genetic Diseases, Tel-Aviv, Isreal, May 21, 1994. *Gen Obstet Gynecol*. 1996;(174):807-811.

35. Benacerraf BR. The history of second-trimester sonographic markers for detecting fetal Down syndrome, and their current role in obsetric practice. *Prenat Diagn*. 2010;(30):644-652. doi:10.1002/pd.

36. Agathokleous M, Chaveeva P, Poon LCY, Kosinski P, Nicolaides KH. Meta-analysis of second-trimester markers for trisomy 21. *Ultrasound Obstet Gynecol*. 2013;41(3):247-261. doi:10.1002/uog.12364.

37. Schluter PJ, Pritchard G. Mid trimester sonographic findings for the prediction of Down syndrome in a sonographically screened population. *Am J Obstet Gynecol*. 2005;192(1):10-16. doi:10.1016/j.ajog.2004.08.036.

38. Sonek J, Croom C. Second trimester ultrasound markers of aneuploidy. *Clin Obstet Gynocology*. 2014;57(1):159-181. doi:10.1097/GRF.0000000000000012.

39. Benacerraf BR. *Ultrasound of Fetal Syndromes*. 2nd ed. Philadelphia: Churchill Livingstone Elsevier; 2008.

40. Chitayat D, Langlois S, Douglas Wilson R, et al. Prenatal Screening for Fetal Aneuploidy in Singleton Pregnancies. *J Obstet Gynaecol Canada*. 2011;33(7):736-750. doi:10.1016/S1701-2163(16)34961-1.

41. Dey M, Sharma S, Aggarwal S. Prenatal screening methods for aneuploidies. *N Am J Med Sci*. 2013;5(3):182-190. doi:10.4103/1947-2714.109180.

42. Stefanovic V, Eronen M, Paavonen J, Tikkanen M, Ayras O. Clinical utility of nuchal translucency screening. *Res Reports Neonatol*. 2014;Volume 4:169. doi:10.2147/RRN.S67514.

43. Chitayat D, Langlois S, Wilson RD. Prenatal Screening for Fetal Aneuploidy in Singleton Pregnancies. *J Obstet Gynaecol Canada*. 2011;(187):736-750. doi:10.1016/S1701-2163(16)34961-1.

44. Spencer K, Nicolaides KH. A first trimester trisomy 13/trisomy 18 risk algorithm combining fetal nuchal translucency thickness, maternal serum free β-hCG and PAPP-A. *Prenat Diagn*. 2002;22(10):877-879. doi:10.1002/pd.420.

45. Wald N, Rudnicka A, Bestwick J. Sequential and contingent prenatal screening for Down syndrome. *Prenat Diagn*. 2006;26(10):980-984. doi:10.1002/pd.

46. Bestwick JP, Huttly WJ, Wald NJ. Detection of trisomy 18 and trisomy 13 using first and second trimester Down's syndrome screening markers. *J Med Screen*. 2013;20(2):57-65. doi:10.1177/0969141313484904.

47. Breathnach FM, Malone FD, Lambert-Messerlian G, et al. First- and Second-Trimester Screening. *Obstet Gynecol*. 2007;110(3):651-657. doi:10.1097/01.AOG.0000278570.76392.a6.

48. Christopher Graves J, Miller KE, Sellers AD. Maternal serum triple analyte screening in pregnancy. *Am Fam Physician*. 2002;65(5):915-920.

49. Mulcahy HE, Croke DT, Farthing MJ. Cancer and mutant DNA in blood plasma. *Lancet (London, England)*. 1996;348(9028):628. doi:10.1016/S0140-6736(05)65067-2.

50. Lo YM, Corbetta N, Chamberlain PF, et al. Presence of fetal DNA in maternal plasma and serum. *Lancet*. 1997;350(9076):485-487. doi:10.1016/S0140-6736(97)02174-0.

51. Lo YMD, Tein MSC, Lau TK, et al. Quantitative Analysis of Fetal DNA in Maternal Plasma and Serum: Implications for Noninvasive Prenatal Diagnosis. *Am J Hum Genet*. 1998;62(4):768-775. doi:10.1086/301800.

52. Piechan JL, Hines KA, Koller DL, et al. NIPT and Informed Consent: an Assessment of Patient Understanding of a Negative NIPT Result. *J Genet Couns*. 2016;25(5):1127-1137. doi:10.1007/s10897-016-9945-x.

53. Benn P, Cuckle H, Pergament E. Non-invasive prenatal testing for aneuploidy: current status and future prospects. *Ultrasound Obstet Gynecol*. 2013;42(1):15-33. doi:10.1002/uog.12513.

54. Mennuti MT, Chandrasekaran S, Khalek N, Dugoff L. Cell-free DNA screening and sex chromosome aneuploidies. *Prenat Diagn*. 2015;35(10):980-985. doi:10.1002/pd.4639.

55. Fairbrother G, Johnson S, Musci TJ, Song K. Clinical experience of noninvasive prenatal testing with cell-free DNA for fetal trisomies 21, 18, and 13, in a general screening population. *Prenat Diagn*. 2013;33(6):580-583. doi:10.1002/pd.4092.

56. Iwarsson E, Jacobsson B, Dagerhamn J, Davidson T, Bernabé E, Heibert Arnlind M. Analysis of cell-free fetal DNA in maternal blood for detection of trisomy 21, 18 and 13 in a general pregnant population and in a high risk population - a systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2016;96:7-18. doi:10.1111/aogs.13047.

57. Verinata. *Analytical Validation of the Verifi ® Prenatal Test : Enhanced Test Performance for Detecting Trisomies 21 , 18 , and 13 and the Option for Classification of Sex Chromosome Status*.; 2012.

58. Verinata. verifi® Prenatal Test Advantage | Verinata. http://www.verinata.com/providers/verifi-prenatal-test-advantage/. Published 2017.

59. Natera. Panorama Test. https://www.natera.com/panorama-test. Published 2016.

60. Ariosa. Healthcare Professionals | Performance. http://www.ariosadx.com/healthcare-professionals/performance/. Published 2017.

61. Integrated Genetics. informaSeq® Prenatal Test. http://testmenu.labcorp.com/sites/default/files/informaSeq Prenatal Test - Physician Brochure - January 2016_1.pdf. Published 2016.

62. Choi H, Lau TK, Jiang FM, et al. Fetal aneuploidy screening by maternal plasma DNA sequencing: “False positive” due to confined placental mosaicism. *Prenat Diagn*. 2013;33(2):198-200. doi:10.1002/pd.4024.

63. Osborne CM, Hardisty E, Devers P, et al. Discordant noninvasive prenatal testing results in a patient subsequently diagnosed with metastatic disease. *Prenat Diagn*. 2013;33(6):609-611. doi:10.1002/pd.4100.

64. Benn P, Peter. Non-Invasive Prenatal Testing Using Cell Free DNA in Maternal Plasma: Recent Developments and Future Prospects. *J Clin Med*. 2014;3(2):537-565. doi:10.3390/jcm3020537.

65. Sayres L, Allyse M, Norton M, Cho M. Cell-free fetal DNA testing: A pilot study of obstetric healthcare provider attitudes towards clinical implementation. *Prenat Diagn*. 2011;31(11):1070-1076. doi:10.1002/pd.2835.

66. Tamminga S, Schendel RV Van, Rommers W, et al. Changing to NIPT as a first-tier screening test and future perspectives : opinions of health professionals. *Prenat Diagn*. 2015;25:1316-1323. doi:10.1002/pd.4697.

67. Warsof SL, Larion S, Abuhamad AZ. Overview of the impact of noninvasive prenatal testing on diagnostic procedures. *Prenat Diagn*. 2015;35(10):972-979. doi:10.1002/pd.4601.

68. Wilson KL, Czerwinski JL, Hoskovec JM, et al. NSGC practice guideline: Prenatal screening and diagnostic testing options for chromosome aneuploidy. *J Genet Couns*. 2013;22(1):4-15. doi:10.1007/s10897-012-9545-3.

69. National Society of Genetic Counselors. *Position Statement: Prenatal Cell-Free DNA Screening*.; 2016.

70. Committee on Genetics. Committee Opinion No. 545 Cell-free DNA Screening for Aneuploidy. *Obs Gynecol*. 2015;126:1-7. doi:10.1016/S0140-6736(16)31898-0.

71. Gregg AR, Skotko BG, Benkendorf JL, et al. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College. 2016. doi:10.1038/gim.2016.97.

72. Calonico E, Blumenfeld YJ, Hudgins L, Taylor J. Patient preferences for prenatal testing of microdeletion and microduplication syndromes. *Prenat Diagn*. 2016;36(3):244-251. doi:10.1002/pd.4760.

73. Wapner RJ, Babiarz JE, Levy B, et al. Expanding the scope of noninvasive prenatal testing: Detection of fetal microdeletion syndromes. *Am J Obstet Gynecol*. 2015;212:332.e1-9. doi:10.1016/j.ajog.2014.11.041.

74. Valderramos SG, Rao RR, Scibetta EW, Silverman NS, Han CS, Platt LD. Cell-free DNA screening in clinical practice: abnormal autosomal aneuploidy and microdeletion results. *Am J Obstet Gynecol*. 2016;215(5):626.e1-626.e10. doi:10.1016/j.ajog.2016.06.039.

75. Mayes S, Hashmi S, Turrentine MA, Darilek S, Friel LA, Czerwinski J. Obstetrician and Gynecologist Utilization of the Noninvasive Prenatal Testing Expanded Option. *Am J Perinatol Reports*. 2016;6(1):e18-24. doi:10.1055/s-0035-1566313.

76. Brady P, Brison N, K VDB, T DR, Peeters H, Esch V. Clinical implementation of NIPT – technical and biological challenges. *Clin Genet*. 2016;89:523-530. doi:10.1111/cge.12598.

77. Benn P. Expanding non-invasive prenatal testing beyond chromosomes 21, 18, 13, X and Y. *Clin Genet*. 2016;90(6):477-485. doi:10.1111/cge.12818.

78. Ohno M, Caughey A. The role of noninvasive prenatal testing as a diagnostic versus a screening tool - a cost-effectiveness analysis. *Prenat Diagn*. 2013;33(7):630-635. doi:10.1002/pd.4156.

79. Chitty LS, Bianchi DW. Noninvasive prenatal testing: The paradigm is shifting rapidly. *Prenat Diagn*. 2013;33(6):511-513. doi:10.1002/pd.4136.

80. Lench N, Barrett A, Fielding S, et al. The clinical implementation of non-invasive prenatal diagnosis for single-gene disorders: Challenges and progress made. *Prenat Diagn*. 2013;33(6):555-562. doi:10.1002/pd.4124.

81. Verhoef TI, Hill M, Drury S, et al. Non-invasive prenatal diagnosis (NIPD) for single gene disorders: cost analysis of NIPD and invasive testing pathways. *Prenat Diagn*. 2016;36(7):636-642. doi:10.1002/pd.4832.

82. R. D, M. H, L.S. C, Daley R, Hill M, Chitty LS. Non-invasive prenatal diagnosis: Progress and potential. *Arch Dis Child Fetal Neonatal Ed*. 2014;99(5):F426-F430. doi:10.1136/archdischild-2013-304828.

83. Norton ME, Rose NC, Benn P. Noninvasive Prenatal Testing for Clinical Assessment and a Plea for Restraint. *Obstet Gynecol*. 2013;121(4):847-850.

84. Horsting JMH, Dlouhy SR, Hanson K, Quaid K, Bai S, Hines KA. Genetic counselors' experience with cell-free fetal DNA testing as a prenatal screening option for aneuploidy. *J Genet Couns*. 2014;23(3):377-400. doi:10.1007/s10897-013-9673-4.

85. Morrow KA. Non-Invasive Prenatal Testing: Provider Knowledge and Future Directions. 2016.

86. Suskin E, Hercher L, Aaron KE, Bajaj K. The Integration of Noninvasive Prenatal Screening into the Existing Prenatal Paradigm: a Survey of Current Genetic Counseling Practice. *J Genet Couns*. 2016;25(5):1032-1043. doi:10.1007/s10897-016-9934-0.

87. Founds S. Innovations in prenatal genetic testing beyond the fetal karyotype. *Nurs Outlook*. 2014;62(3):212-218. doi:10.1016/j.outlook.2013.12.010.

88. Musci TJ, Fairbrother G, Batey A, Bruursema J, Struble C, Song K. Non-invasive prenatal testing with cell-free DNA: US physician attitudes toward implementation in clinical practice. *Prenat Diagn*. 2013;33(5):424-428. doi:10.1002/pd.4091.

89. Benn P, Chapman AR, Erickson K, et al. Obstetricians and gynecologists' practice and opinions of expanded carrier testing and noninvasive prenatal testing. *Prenat Diagn*. 2014;34(2):145-152. doi:10.1002/pd.4272.

90. Swaney P, Hardisty E, Sayres L, Wiegand S, Vora N. Attitudes and Knowledge of Maternal-Fetal Medicine Fellows Regarding Noninvasive Prenatal Testing. *J Genet Couns*. 2016;25(1):73-78. doi:10.1007/s10897-015-9844-6.

91. Farrell RM, Agatisa PK, Mercer MB, Mitchum AG, Coleridge MB. The use of noninvasive prenatal testing in obstetric care: educational resources, practice patterns, and barriers reported by a national sample of clinicians. *Prenat Diagn*. 2016;36(6):499-506. doi:10.1002/pd.4812.

92. Taneja PA, Snyder HL, de Feo E, et al. Noninvasive prenatal testing in the general obstetric population: Clinical performance and counseling considerations in over 85000 cases. *Prenat Diagn*. 2016;36(3):237-243. doi:10.1002/pd.4766.

93. Zhang H, Gao Y, Jiang F, et al. Non-invasive prenatal testing for trisomies 21, 18 and 13: Clinical experience from 146 958 pregnancies. *Ultrasound Obstet Gynecol*. 2015;45(5):530-538. doi:10.1002/uog.14792.

94. Hudecova I, Chiu RWK. Non-invasive prenatal diagnosis of thalassemias using maternal plasma cell free DNA. *Best Pract Res Clin Obstet Gynaecol*. 2017;39:63-73. doi:10.1016/j.bpobgyn.2016.10.016.

95. Pan V, Yashar BM, Pothast R, Wicklund C. Expanding the genetic counseling workforce : program directors ' views on increasing the size of genetic counseling graduate programs. 2016;18(8):842-849. doi:10.1038/gim.2015.179.

96. Dar P, Curnow KJ, Gross SJ, et al. Clinical experience and follow-up with large scale single-nucleotide polymorphism-based noninvasive prenatal aneuploidy testing. *Am J Obstet Gynecol*. 2014;211(5):527.e1-527.e17. doi:10.1016/j.ajog.2014.08.006.

97. Willems P, Dierickx H, Sengers N, Castenmiller C, Verschueren S. High Positive Predictive Value (PPV) of Cell-Free DNA (cfDNA) Testing in a Clinical Study of 10,000 Consecutive Pregnancies. *J Mol Biomark Diagn*. 2016;7(3). doi:10.4172/2155-9929.1000285.

98. Agarwal A, Sayres LC, Cho MK, Cook-Deegan R, Chandrasekharan S. Commercial landscape of noninvasive prenatal testing in the United States. *Prenat Diagn*. 2013;33(6):521-531. doi:10.1002/pd.4101.

99. American Public Health Association. Policy Statement: Maternal Serum Alpha Fetoprotein Screening. 1990;(Policy Number:9002).

100. Powell KP, Hasegawa L, McWalter K. Expanding roles: A survey of public health genetic counselors. *J Genet Couns*. 2010;19(6):593-605. doi:10.1007/s10897-010-9313-1.

101. Clayton EW. What should be the role of public health in newborn screening and prenatal diagnosis? *Am J Prev Med*. 1999;16(2):111-115.

102. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics. *Healthy People 2000 Final Review*. Hyattsville, Maryland; 2001. https://www.cdc.gov/nchs/data/hp2000/hp2k01.pdf.

103. Mazmanian PE, Davis D a, Page P. Guide to the Evidence. *JAMA J Am Med Assoc*. 2002;288(9):1057-1060.

104. Davis DA, Thomson MA, Oxman D, Brian R. Changing Physician A Systematic Review of the Effect of Continuing Medical Education Strategies. *JAMA J Am Med Assoc*. 1995;274:700-705.

105. Davis D, O'Brien MAT, Freemantle N, Wolf FM, Mazmanian P, Taylor-Vaisey A. Impact of Formal Continuing Medical Education. *JAMA J Am Med Assoc*. 1999;282(9):867-874. doi:10.1001/jama.282.9.867.

106. Bellolio MF, Stead LG. Continuing Education Meetings and Workshops: Effects on Professional Practice and Health Care Outcomes. *Ann Emerg Med*. 2009;53(5):685-687. doi:10.1016/j.annemergmed.2008.05.034.

107. Hofman KJ, Tambor ES, Chase G a, Geller G, Faden RR, Holtzman N a. Physicians' knowledge of genetics and genetic tests. *Acad Med*. 1993;68(8):625-632. doi:10.1097/00001888-199308000-00013.

108. Guttmacher AE, Porteous ME, McInerney JD. Educating health-care professionals about genetics and genomics. *Nat Rev Genet*. 2007;8(2):151-157. doi:10.1038/nrg2007.

109. Macri CJ, Gaba ND, Sitzer LM, Freese L, Bathgate SL, Larsen JW. Implementation and evaluation of a genetics curriculum to improve obstetrician-gynecologist residents' knowledge and skills in genetic diagnosis and counseling. *Am J Obstet Gynecol*. 2005;193(5):1794-1797. doi:10.1016/j.ajog.2005.08.003.

110. Angelini DJ. Interdisciplinary and Interprofessional Education. *J Perinat Neonatal Nurs*. 2011;25(2):175-179. doi:10.1097/JPN.0b013e318212ee7a.

111. Burke W, Emery J. Genetics education for primary-care providers. *Nat Rev Genet*. 2002;3(7):561-566. doi:10.1038/nrg845.

112. Mann KJ, Taylor JA, James PA, Gaff C. Interdisciplinary Education for Genetic Counselors: Developing the Concept and Assessing the Need in Australasia. *J Genet Couns*. 2014;23(5):708-724. doi:10.1007/s10897-014-9723-6.

113. Shaw-Battista J, Young-Lin N, Bearman S, Dau K, Vargas J. Interprofessional Obstetric Ultrasound Education: Successful Development of Online Learning Modules; Case-Based Seminars; and Skills Labs for Registered and Advanced Practice Nurses, Midwives, Physicians, and Trainees. *J Midwifery Women's Heal*. 2015;60(6):727-734. doi:10.1111/jmwh.12395.

114. Levison J, Williams L, Moore A, McFarlane J, Davila J. Educating Health Professionals in Obsetrics and Gynecology Regarding Rapid Human Immunodeficency Virus (HIV) Testing in Labor and Delivery: A Local Initiative. *Matern Child Heal J*. 2012;16:1748-1753.

115. Gaff C, Williams J, McInerney J. Genetics in Health Practice and Education Special Issue. *J Genet Couns*. 2008;17(2):143-144. doi:10.1007/s10897-008-9149-0.