# Survey of the Genetic Counselor Perspective Regarding the 2020 ACOG Guideline Update Recommending the Routine Offering of NIPT in All Pregnancies

by

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# Survey of the Genetic Counselor Perspective Regarding the 2020 ACOG Guideline Update Recommending the Routine Offering of NIPT in All Pregnancies

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University of Pittsburgh, 2022

Traditionally, Non-Invasive Prenatal Testing (NIPT) is offered to high-risk pregnancies to screen for chromosomal abnormalities. In 2020, the American College of Obstetricians and Gynecologists (ACOG) issued a guideline update that recommended routine offering of NIPT in all pregnancies. However, some studies showed concerns over the universal offering of NIPT citing challenges in informed consent, patients' lack of awareness of possible outcomes, and insurance coverage.

Genetic counselors play an important role in pre- and post-test counseling to facilitate decision-making for patients when considering NIPT. This study surveyed genetic counselors' perspectives regarding the ACOG updated guidelines and aspects surrounding NIPT counseling. The survey was distributed through the listservs of the National Society of Genetic Counselors (NSGC) in two weekly digest emails of October and November 2021.

Out of approximately 850 practicing prenatal genetic counselors, 72 responses were recorded (a 8.9% response rate). Per results, NIPT was deeply integrated into prenatal genetic counseling with high familiarity of the ACOG update. Most genetic counselors (81.25%) are offering NIPT to all patients. Top factors that support offering NIPT to all patients were departmental decision (31.03%), professional opinion (34.48%), and the impact of the ACOG guidelines (26.72%). Lack of insurance coverage and challenges in informed consent were stated as common barriers of universal NIPT screening.

There is a consensus among genetic counselors that patients considering NIPT should be given anticipatory guidance regarding the test's nuances, and that such information was needed to achieve informed consent. Furthermore, there is a strong need for patient friendly resources on NIPT, with the most popular topics being differentiating between diagnostics and screening and the possibility of different types of atypical results.

This study provided insights from the genetic counselor community regarding different aspects of NIPT counseling in ACOG guideline implementation. In terms of public health, this survey results called for additional patient friendly NIPT resources and inspired a creation of a factsheet that addresses patients' need according to genetic counselors' perspectives. The challenges in universal NIPT offering need to be researched and addressed for appropriate and ethical guideline implementation.

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#### Preface

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### **1.0 Introduction**

In the traditional landscape of prenatal screening, Non-invasive Prenatal Testing (NIPT) is offered to high-risk pregnancies to screen for chromosomal abnormalities. For low-risk pregnancies, first trimester screening (FTS) and multiple marker screening (MMS), which is offered in the second trimester, are routinely offered in combination with ultrasound to screen for chromosome abnormalities (Latendresse et al, 2015). These screening techniques carry virtually no risk to the fetus; FTS offers an 86% detection rate of Trisomy 21 (i.e., Down Syndrome) and Trisomy 18, and MMS has the detection rate of approximately 79% for Trisomy 21 and Trisomy 18, 85% for ventral wall defects, and 95% for anencephaly (Dey et al., 2013). Compared to FTS or MMS, NIPT has higher detection rates for aneuploidies of about 99% for Trisomy 21, 97% for Trisomy 18, and 87% for Trisomy 13 (Devers et al., 2013). Despite having higher detection rates and a spreading usage over time, NIPT is still a screening test along with FTS and MMS. In order to get a certain diagnosis of chromosomal abnormality, women have the option of diagnostic testing including chorionic-villus sampling (CVS) or amniocentesis, which carry an inherent risk to the fetus.

Investigation into fetal DNA presence in maternal plasma and serum was first reported in 1997 (Lo et al, 1997). Analysis of fetal DNA was later incorporated into NIPT to determine fetal sex in pregnancies at high risk of having sex-linked conditions (Costa et al, 2002; Hyett et al. 2005), as well as fetal Rhesus D typing in pregnancies with RhD-negative mothers to prevent hemolytic disease of the newborn (HDN) (Faas et al, 1998; Lo et al, 1998). As sequencing technologies became more advanced, NIPT using massive parallel sequencing to screen for Trisomy 21 was validated through multiple large-scale validity studies (Chiu et al, 2011; Ehrich et al, 2011; Palomaki et al, 2011). In the same year, Sehnert et al developed an optimized the algorithm by using normalized chromosomes values to detect Trisomy 18 (Sehnert et al, 2011). This algorithm of comparing the proportional representation of the aneuploid chromosome with that of healthy, euploid pregnancies was used and replicated for other chromosomal aneuploidies such as Trisomy 13 and sex chromosome aneuploidies (Chen et al, 2011; Zimmermann et al, 2012).

Advanced Maternal Age (AMA; Age 35 years or older) is well associated with increased risk of chromosomal aneuploidy in a fetus due to chromosome segregation errors (Mikwar et al, 2020). Because of such high incidence, early validation studies for NIPT focused on the AMA population to assess its efficacy, and found that detection rates, sensitivity, and specificity were high (above 99%) with low false positive rates (less than 1%) (Shah et al, 2015). NIPT provides a sensitive option to identify risk for aneuploidies in high-risk women, potentially reducing the necessity of invasive diagnostic techniques. On the other hand, due to the initially lower prevalence of chromosomal aneuploidies in non-high-risk pregnancies, the overall positive predictive value was lower (90.9%), and as low as 81.4% for Trisomy 13) (DiNonno et al, 2019).

In response to the focus on the high-risk population in early validation studies, initially professional society guidelines recommended offering NIPT to only high-risk pregnancies and not average-risk population (ACOG, 2012). Later studies explored this test's efficacy in average-risk pregnancies. Although not as high as that of the high-risk population statistically, the positive predictive value (PPV) for all aneuploidies detected in the average-risk population was found to be 94.5% in a large study by DiNonno et al, which was higher than other prenatal screening tests (DiNonno et al, 2019). It is however important to note the limitation of this study since it relies on reports from physicians' offices, who may have been more likely to report true positive cases. This landscape has shifted over the years: in 2016, the American College of Obstetricians and

Gynecologists (ACOG) recognized NIPT validity in average-risk women, followed by a guideline update in 2020 stating that obstetricians should offer NIPT as a screening option for any pregnancy, citing the reasons to be the "personal nature" in decision-making of pregnant women in addition to the "inefficiency" of offering such a sensitive, specific screening test to only the AMA population (Rose et al, 2020).

In supporting this recommendation, recent studies have shown that cell-free fetal DNA screening has superior sensitivity, lower false positive rate, and higher positive predictive value in average-risk pregnancies than standard maternal serum screening combined with nuchal translucency (Bianchi et al, 2014; Norton et al, 2015). Some surveys also identified that patients generally preferred NIPT due to the stated reasons as well as minimal risk to the baby, and the earlier availability than FTS or diagnostic testing (Farrell et al, 2014; Tiller et al, 2015).

On the other hand, different perspectives in other studies demonstrated concerns over such universal offering of NIPT in terms of challenges in obtaining proper informed consent, sex selection, and insurance coverage. The complex nature of NIPT may lead to patients' information overload or lack of understanding of the test's possible outcomes or consequences (Kater-Kuipers et al, 2020; Piechan, 2016). Past studies have shown the need for a formal consent process for patients considering NIPT (Cernat et al. 2019; Farrell et al. 2014) and a lack of trained providers (i.e. genetic counselors), as well as appointment times to accommodate the demand for this screening. There are also ethical concerns regarding the possible use of NIPT for sex determination and selection, as more healthcare providers believed that NIPT was increasing sex-selective abortion (Bennett et al, 2018; Crabbe et al, 2019; Madan et al, 2013; van Schendel et al, 2015). Additionally, insurance has also proved to be a barrier in terms of equity in NIPT affordability, with lack of coverage for patients at average-risk from many private agencies (Benoy et al, 2021). Equipped with a thorough understanding of the test, genetic counselors play an important role in pre-test and post-test counseling to facilitate decision-making for patients when considering NIPT. However, there has been little research on this population's perspectives on benefits, challenges, and barriers regarding the new update to the ACOG guidelines. This thesis project will attempt to fill this gap and build on the current literature of the future directions for cell-free DNA testing. The project was done by creating a questionnaire to assess different aspects surrounding NIPT counseling for a GC: demographics, current standard of practices (SOPs), impacting factors (personal/institutional/patient-related), benefits, facilitators, risks, and barriers. The survey also included self-developed multiple-choice and Likert-scale questions and answers informed by past literature, to assess the prenatal genetic counselors' preferences and rationale on whether they agree or disagree with the updated guideline, as well as what can be done for patient support/needs for resources. The survey was anonymously distributed to the National Society of Genetic Counselors (NSGC) student research survey listing, which reached the society's GC members practicing across the United States.

#### 2.0 Literature Review

# 2.1 Background

#### 2.1.1 Aneuploidy

Chromosomal aneuploidy is defined as an abnormal number of chromosomes in the cell. In human pregnancy, aneuploidies are random or sporadic events, mostly caused by nondisjunction in meiosis. The population frequency of aneuploidies is estimated to be between 5-20%. Aneuploidy can lead to spontaneous miscarriage, stillbirth, as well as a wide range of congenital abnormalities (Hassold & Hunt, 2001)

Considering that most forms of aneuploidy are lethal during pregnancy, the most common aneuploidies in liveborn children include Trisomy 21, Trisomy 18, Trisomy 13, and sex chromosomal aneuploidies: monosomy X, Trisomy X (XXX), XXY, and XYY. Trisomy 21, commonly known as Down Syndrome (DS), occurs in 1:707 livebirths in the United States. The frequencies of Trisomy 18 and Trisomy 13 are 1:3,315 and 1:7,409, respectively. Incidences of sex chromosome aneuploidies are estimated to be approximately over 1:500 in the general population (Samango-Sprouse et al, 2016).

Research has established the association between advanced maternal age (AMA) and the increased likelihood of having pregnancies with aneuploidies. As the pregnant person's age increases, the risk of aneuploidy also rises. AMA refers to pregnant people who are age 35 or older at the time of delivery. Beyond AMA, there are multiple risk factors or indications for aneuploidy which place the pregnancy as high-risk, including family history, ultrasound anomalies, and

positive results in prenatal screening tests. For this high-risk population as well as pregnancies with positive screening results, genetic counseling is often offered along with additional testing options (Rose et al., 2020).

#### 2.1.2 NIPT

#### **2.1.2.1 Origins**

Before the introduction of cell-free fetal DNA screening, prenatal screening mainly relied on maternal serum analyte levels paired with sonographic measurement of fetal nuchal translucency (NT)(Burton, 1988; Wald et al., 1974). Early in the pregnancy, women have the option of first trimester screening including measuring free β-hCG (human chorionic gonadotropin), PAPP-A combined with NT to screen for Trisomy 21 and Trisomy 18 (Wald et al., 1999; Wald & Hackshaw, 1997). Later, to screen for Trisomy 21, Trisomy 18, Trisomy 13, and open neural tube defects, there is second trimester screening using levels of Inhibin A, unconjugated estriol (UE3), hCG, and maternal serum alpha-fetoprotein (MS-AFP). These techniques, though carrying no risks, only had detection rates varying from 75-90% for Trisomy 21 and 67-81% for Trisomy 18 (F. Shah et al., 2015). In order to get a certain diagnosis of chromosomal abnormality, women have the option of chorionic-villus sampling (CVS) or amniocentesis, which carry an inherent risk to the fetus.

In 1997, following the detection of cell-free DNA (cfDNA) that originated from tumor in patients' serum, researchers detected fetal cfDNA in pregnant women. Extracting DNA from maternal plasma and serum, Lo et al was able to accurately determine the presence of a Y chromosome in 24 out of 30 male fetuses (Lo et al., 1997). In 1998, in genotyping the fetal RhesusD status using fetal DNA, the same group proved that fetal cfDNA can be detected in a

sample as small as 10µL of maternal serum and plasma with a fetal fraction varying between 3.4%-6.2%. This effort opened the possibility of utilizing cfDNA circulating in maternal serum for prenatal screening (Lo et al., 1998).

Analysis of fetal DNA was later incorporated into non-invasive prenatal testing (NIPT) to determine fetal sex in pregnancies at high risk of having sex-linked conditions, as well as fetal Rhesus D typing in pregnancies with RhD-negative mothers to prevent hemolytic disease of the newborn (HDN) (Costa et al., 2002; Faas et al., 1998; Hyett et al., 2005; Lo et al., 1998). As sequencing technologies became more advanced, NIPT using massive parallel sequencing to screen for Trisomy 21 was validated through multiple large-scale studies. In 2011 alone, Chiu et al, Ehrich et al, and Palomaki et al conducted validity studies to assess the efficacy of NIPT (using massive parallel sequencing) in screening for Trisomy 21 in 753, 480, and 4464 pregnant women, respectively (Chiu et al., 2011; Ehrich et al., 2011; Palomaki et al., 2011). In the same year, Sehnert et al created and optimized an algorithm by using normalized chromosomes values to detect Trisomy 18 (Sehnert et al., 2011). This algorithm of comparing the proportional representation of the aneuploid chromosome with that of healthy, euploid pregnancies was used and replicated for other chromosomal aneuploidies such as Trisomy 13 and sex chromosome aneuploidies (Chen et al., 2011; Zimmermann et al., 2012). Following the conduction of such validity studies, NIPT became one of the prenatal screening options used in clinical settings.

## 2.1.2.2 Validated Studies, Statistical Background, and Population

To assess the accuracy and capacity of a test, researchers utilize different measurements, such as sensitivity and specificity. A 2013 review from Benn et al chronologizing validity studies from 1997 to 2012 quoted, for NIPT, a 99.3% detection rate (sensitivity) for Trisomy 21, 97.4% for Trisomy 18, and 78.9% for Trisomy 13 (Benn, Cuckle, et al., 2013). On the other hand,

specificity for all three conditions is consistently reported to be higher than 95% across different studies. Overall, the high sensitivity and specificity speaks for the improved performance of NIPT in comparison to other prenatal screening options (Chen et al., 2011; DiNonno et al., 2019; H. Zhang et al., 2015)

Aside from sensitivity and specificity, another important characteristic of a test is the positive predictive value (PPV). In the context of NIPT, this number predicts the chance of the fetus being affected given the positive NIPT results (i.e., high risk of aneuploidy).

Throughout the time of NIPT expansion and for individual trisomies, there has been a wide range of estimated PPVs reported in different studies. In general, PPVs vary due to types of trisomy and prior risk factors such as maternal age. Due to the increased prevalence of chromosomal aneuploidies in the high-risk population, early validation studies mainly focused on the high-risk population to assess the test efficacy (Chiu et al., 2011; Ehrich et al., 2011; Palomaki et al., 2011). Whereas, in the average risk population, PPVs have been statistically analyzed and predicted to be lower due to the decreased prevalence of these conditions. Around 2014 to 2017, researchers estimated PPVs of Trisomy 21 for this population in the range of 45-93%, 40-76% for Trisomy 18, and 45% for Trisomy13 (Bianchi et al., 2014; Meck et al., 2015; Petersen et al., 2017).

More recently published studies that include the average risk population also report variable ranges of PPVs, with the concensus that the PPVs of NIPT in Trisomy 18 and Trisomy 13 are generally higher than previously considered. In multiple large-scale studies from China, the reported PPV for Trisomy 21 ranges from 84.67-99.18%, for Trisomy 18 ranging from 50-92.31%, and for Trisomy 13 from 23.08-46.15% (Junhui et al., 2021; Lu et al., 2020; Wang et al., 2020; Zheng et al., 2020). Although the prevalence of aneuploidies are higher among AMA/high-risk pregnancies, one study from Zhang et al noted that the performance of NIPT was not significantly

lower in average-risk populations compared against high-risk populations (Zhang et al., 2018). Another four-year, US-based quality assurance study from DiNonno et al stated that the observed PPVs for all three trisomies were similar between average-risk and AMA population (DiNonno et al., 2019). On the other hand, DiNonno's study data is based on incomplete follow-ups for positive results, where doctors might be more likely to report true positive results leading to a higher-thanexpected PPV. Additionally, this study is conducted by Natera, one of the NIPT testing laboratories. Some other large studies reported higher PPVs of more than 90% for all three trisomies (Lee et al., 2019; Zheng et al., 2020). In Netherlands, where NIPT is first implemented as a first-tier test offered to all pregnant women, first-year data quoted "higher than expected" PPV for all three trisomies: 96% for Trisomy 21, 98% for Trisomy 18, and 53% for Trisomy 13. To explain the consistently high PPVs in non-AMA populations, these studies mentioned the association of lower false positive rates and younger age, citing the increased chance of cell segregation error followed by somatic cell loss in confined placental mosaicism in older women (DiNonno et al., 2019; B. Zhang et al., 2018).

Aside from the validated screening for the three trisomies, high sensitivity sequencing in NIPT has also been explored to detect sex chromosome aneuploidies (SCAs), rare trisomies, and deletions or duplications (Peters et al. 2011; Jensen et al. 2012). Compared to the trisomies, PPVs for sex aneuploidies tend to be even lower, with the reported range of 9-14.29% for monosomy X, 34.1-66.7% for XXX, 50% for XXY, and 71.43% for XYY (Luo et al., 2021; Reiss et al., 2017; Zheng et al., 2020). These PPVs for SCAs highlight the need to follow-up the positive results with diagnostic testing for prenatal decision-making (Zheng et al., 2020)

Since 2014, testing companies have been trying to expand the scope of NIPT to screen for rare trisomies as well as genetic conditions associated with microdeletions/duplications, including

22q11 deletion syndrome, cri-du-chat (5p deletion syndrome), and 1p36 deletion syndrome (Prader-Willi or Angelman). Due to the rarity of these conditions and their uncharted prenatal history, concerns have been raised regarding low PPVs for this role expansion, the lack of prenatal clinical utility, as well as implications of patient's unnecessary emotional distress (Di Renzo et al., 2019; Vora & O'Brien, 2014). As of current, quality control studies for NIPT accuracy in detecting microdeletions/duplications and rare trisomy are limited. Despite controversial viewpoints among clinicians, professional guidelines recommend these panels be considered on a case-by-case basis and not offered in routine screening (Yang & Tan, 2020).

## 2.1.3 ACOG (American College of Obstetricians and Gynecologists)

The American College of Obstetricians and Gynecologists is a professional organization consisting of physicians specializing in obstetrics and gynecology (Rose et al., 2020). ACOG has been providing clinical guidelines to optimize patient care based on systematic review of evidence, as well as outlining the associated benefits and harm of available options.

#### **2.1.3.1 Updated guidelines and Rationale**

Initially, early validation studies were conducted only on the AMA population; therefore, professional guidelines recommended offering NIPT to only the high-risk but not the average-risk population. With more recent publications assessing NIPT efficacy in average-risk pregnancies, the landscape has certainly changed. Considering its higher sensitivity and specificity than other non-invasive options, in 2016, ACOG released new recommendations that recognized the validity in low-risk populations. This was followed by a 2020 update, explicitly stating that OB-GYN specialists should offer NIPT early in the pregnancy "regardless of maternal age and risk."

One rationale for the guideline's updates stressed NIPT as the most sensitive and specific screening test; therefore, patient's baseline risk of having aneuploidies should not limit testing options. Other motivations cited by ACOG include the "personal nature of prenatal testing decision," as well as ensuring the comprehensiveness in patient's decision making. Furthermore, the guidelines also noted the "inefficiency" in screening chromosomal conditions if the test is restricted to only patients at high risk (Rose et al., 2020).

In comparison with ACOG, in 2013, other professional organizations concurrently issued their guidelines for NIPT utilization upon its spreading usage. For instance, the International Society of Prenatal Diagnosis' 2013 (ISPD) position statement stated that NIPT can be considered for high-risk pregnancies (Benn, Borell, et al., 2013). Prior to 2020, its guidelines were updated in 2015 to include multiple protocols that are considered appropriate, among which cfDNA screening can either be used as a primary test for all pregnant women, secondary test post-serum screening, or high-risk pregnancies (Benn et al., 2015). Similar to the ISPD statement, the Royal College of Obstetrician and Gynecologists 2014 statement also endorsed multiple strategies, and provisioned that in time, NIPT technology and cost-improvement would enable it to become primary screening method (RCOG, 2014). Most recently, in April 2021, the National Society of Genetic Counselors (NSGC) issued a statement that supported universal access to NIPT as a screening option in the context of other available prenatal screenings (*Prenatal Cell-Free DNA*, 2021.)These guidelines demonstrate a supporting trend in NIPT being a universal prenatal screening tool.

#### **2.1.4 Challenges and Current Practice**

#### 2.1.4.1 Test Limitations and No call results

Despite all its mentioned benefits, NIPT is not without its limitations. Being inherently a screening method, NIPT cannot give a patient a conclusive answer on whether or not the fetus has chromosomal aneuploidy. In addition, the assessment of the test's false positive and PPV in low-risk population calls for further research. With the discussed shift of data in PPV (where later studies quoted higher PPV values compared to past ones), we need more clinical validation to arrive at a consensus; as of current, the PPV utilized in the clinical settings for low-risk population remains similar to earlier large clinical validation calculated based on conditions' prevalence, or depends on laboratories (NSGC, 2021). Other limitations include the possibility of no-call results due to quality control issues and low fetal fraction, of which patients might not be made aware before consenting to test, leading to inadequate consent and psychosocial distress (Labonté et al., 2019).

#### **2.1.4.2 Incidential findings**

Another consideration for patients and providers when ordering NIPT is incidental findings. An incidental finding is defined as the test producing information with clinical implications unrelated to the testing indication. Since NIPT analyzes maternal and fetal DNA, incidental findings related to unidentified genetic variations from the mother include maternal mosaicism, maternal chromosomal aneuploidies/abnormalities, and, in some rare cases, maternal malignancy, have been reported in patients who had NIPT (Bianchi et al., 2015; L. Wang et al., 2020). Such incidental findings cause discordant results in the fetus (a positive NIPT with a normal fetal karyotype), leading to potential confusion in results interpretation from providers and

emotional distress in patients. Other incidental findings can be due to unique circumstances: for instance, patient's history of organ transplantation causing XY NIPT results in a female fetus or vanishing twins. Many uncertainties remain on how to conduct proper informed consent for NIPT and prepare patients for these possibilities, especially under the scenario of universal NIPT screening (Kater-Kuipers et al., 2020). The inconclusive nature of NIPT screening adds to the complexity in the discussion as well as interpretation of these results, despite its potentially heavily impacted implications (i.e., maternal malignancy) (Bianchi et al., 2015).

## 2.1.4.3 Informed Consent

As powerful a screening test as NIPT might be, there have been concerns among experts regarding multiple ethical aspects surrounding informed consent. Unlike other routine prenatal screening test focusing on the body's temporary phenomena, NIPT by nature is a much more sensitive, specific test than previous technologies. The procedural ease of NIPT in only requiring a blood sample may hinder women from thinking it through in the informed consent process. Combined with the usually information-dense setting of prenatal visits, there are concerns that necessary knowledge may get too little attention regarding the test's aim and the implications of its outcome (Cernat et al., 2019; Kater-Kuipers et al., 2020). A study navigating women's perspectives of NIPT demonstrates women's interest and willingness in incorporating universal NIPT screening, but also shows a strong need (71% of 334 participants) for a formal informed consent process in pre-test counseling (Farrell et al., 2014). Employing NIPT as a universal screening test would introduce new challenges for pregnant patients and healthcare providers responsible for facilitating informed decision-making, raising the question of personnel and preparedness as well as the need for resources.

#### 2.1.4.4 Insurance Coverage

Another challenge in making NIPT universal is the variety of health insurance policy when it comes to coverage for NIPT. Even though multiple professional societies have updated their guidelines to include the low-risk population in offering NIPT, health insurance companies might not accept their claims without a high-risk indication (Benoy et al., 2021; Dondorp et al., 2015). Such delay in updating insurance policies has presented a barrier to care in universal NIPT offerings, raising ethical concerns in terms of affordability and health equity (Benoy et al., 2021).

### 2.1.5 Genetic counselor's perspectives on NIPT

Equipped with a thorough understanding of NIPT, genetic counselors play an important role in facilitating decision-making and providing information for adequate informed consent. Depending on institutions and clinical circumstances, genetic counselors may perform pre-test or post-test counseling for NIPT consideration. Pre-test counseling is often offered in scenarios when there are indications for high-risk pregnancies. Facing the nuances surrounding NIPT including informed consent, interpretation results, or incidental findings, some studies call for the need of genetic counseling when offering of NIPT (Buchanan et al., 2014; Kater-Kuipers et al., 2020; Suciu et al., 2019). However, under the 2020 ACOG guidelines, the most likely scenarios include OB-GYN clinicians obtaining consent for NIPT in average-risk populations, whose results will be followed up with genetic counselors in the case of any concerns. Standards of practice for pre- and post-test counseling are without uniformity, including the results explanation from the ordering obstetricians or genetic counselors depending on the institution (Kater-Kuipers et al., 2020). Such variation leads to multiple facilitating and hindering factors in genetic counseling practice in response to NIPT implementation and guidelines.

#### **2.1.5.1 Benefits and Support**

Some studies have shown that genetic counselors are generally supportive of employing NIPT to screen for common chromosomal aneuploidies due to its high specificity and sensitivity (Agatisa et al., 2018; Benoy et al., 2021; Buchanan et al., 2014). However, information is scarce on identifying supporting factors that facilitate universal NIPT screening, namely the team decision, institutions, guidelines, or professional opinion.

Due to the nature of their trainings, a survey shows that genetic counselors are prepared and equipped with knowledge to provide anticipatory guidance on the test's nuances, as well as interpreting and discussing most unexpected results (Case & Hazel, 2018). On the other hand, the same study finds that significantly fewer counselors are "very prepared" in the specific circumstances of occult malignancies. It is also interesting to note in this study that incidental findings seemed reportedly more common than anticipated, which calls for the need to generate guidelines for practice in light of incidental findings or discordant results, especially if NIPT were to be offered universally. (cite)

#### 2.1.5.2 Concerns in Genetic Counseling

Genetic counselors have expressed concerns over the previously discussed challenges regarding universal NIPT offerings, namely informed consent and insurance coverage. Agatisa et al's study demonstrates that genetic counselors' support NIPT utilization for common chromosomal aneuploidies, but participants reported several barriers in ensuring patient's informed decisions. The authors suggested the necessitation of additional education and resources throughout the steps of offering NIPT, for both obstetricians and patients (Agatisa et al., 2018). When it comes to insurance as a barrier, another study has shown that more genetic counselors would recommend NIPT to patients provided that insurance coverage is not a problem, while they

were more likely to caution patients about financial burden under a non-coverage scenario (Benoy et al., 2021). The consensus seems to be that as prenatal screening moves forward in the direction of offering NIPT (and possibly other sophisticated technologies), interdisciplinary interventions and adaptations need to be made to address to these challenges.

#### 2.1.5.3 Current Practice and The Need for Resources

Despite existing studies demonstrating benefits and barriers of offering universal NIPT, research on current GC practice, their perspectives of such factors, as well as their specific needs following ACOG guidelines has been scarce. Recent studies show an increased usage of NIPT in prenatal screening; however, it was unclear whether these changes are reflected in high-risk, low-risk, or both types of pregnancies. Furthermore, although some described barriers (including informed consent, limited personnel, and anticipatory guidance for patient) can be alleviated by appropriate NIPT resources, there has not been a proper assessment of needs and content for such resources specific to GC's needs. This thesis project will attempt to fill this gap and build on the current literature of the future directions for cell-free DNA testing. The project will be done by creating a questionnaire to assess different aspects surrounding NIPT counseling for a GC: demographics, current standard of practices (SOPs), impacting factors (personal/ institutional/ patient-related), benefits, facilitators, risks, and barriers. The survey's data will be analyzed for the purpose of crafting a patient friendly resource on NIPT with content personalized to GC's needs.

#### 3.0 Manuscript

# **3.1 Background**

Chromosomal aneuploidy in a pregnancy happens when there is an abnormal number of chromosomes, caused by non-disjunction in meiosis. About 5-20% of the population has some kind of aneuploidy, leading to spontaneous miscarriage, stillbirth, or congenital anomalies (Hassold & Hunt, 2001). Most forms of aneuploidy are lethal in-utero; the most common aneuploidies with the potential for survival until livebirth are sex chromosomal aneuploidies, Down syndrome (Trisomy 21), Trisomy 18, and Trisomy 13. Scientists have found that as the age of the pregnant person increases, the risk of chromosomal aneuploidy rises. Advanced maternal age (AMA) is one of the indicators that categorizes a pregnancy as "high risk". Other reasons a pregnancy may be considered high risk are certain abnormal ultrasound findings, family history, previous pregnancy history, or positive prenatal screening results.

Before the availability of cell-free fetal DNA screening (also called Non-invasive Prenatal Testing – NIPT), prenatal screening mostly entailed the analysis of maternal serum analyte levels (β-hCG, PAPP-A) and nuchal translucency in the first trimester; Inhibin A, unconjugated estriol (UE3), hCG, and maternal serum alpha-fetoprotein (MS-AFP) in the second trimester combined with ultrasound findings. These screening methods have a detection rate of around 75-90% for Down syndrome and 67-81% for Trisomy 18 depending on the screening method. In 1997 and 1998, the detection of cell-free fetal DNA in pregnant women led to integration of fetal DNA analysis to determine Rhesus D typing with RhD-negative pregnant people to prevent hemolytic disease of the newborn (HDN) (Costa et al., 2002). Cell-free DNA testing then adopted the name

NIPT, which was short for Non-Invasive Prenatal Testing. The development of massively parallel sequencing later was integrated into NIPT to screen for chromosome conditions, validated by multiple large studies (specifically for Down syndrome and later Trisomy 18 from Sehnert's algorithm) (Ehrich et al., 2011; Palomaki et al., 2011; Sehnert et al., 2011). A similar algorithm that mapped the DNA materials on different chromosomes and compared that with the proportions of healthy, euploid pregnancies was utilized to screen for Trisomy 13 and sex chromosome aneuploidy (Chen et al., 2011; Zimmermann et al., 2012).

Such validity studies assessed the accuracy and capacity of a test through specificity, sensitivity, and positive predictive value (PPV, which ascertained NIPT as a superior method to screen for chromosomal aneuploidies compared to other screening options). Benn et al's 2013 chronological review of validity studies from 1997 to 2002 quoted a 99.3% sensitivity in detecting Down syndrome, 97.4% in Trisomy 18, and 78.9% in Trisomy 13. Other large validity studies also established a 95% specificity for NIPT for the three chromosome conditions (Benn, Cuckle, et al., 2013; H. Zhang et al., 2015). PPV calculates the chance of a real affected case given a positive NIPT result of increased aneuploidy risk. With the established link between AMA/other high-risk indications and increased prevalence of chromosomal conditions, early validity studies mainly assessed the test's effectiveness in this high-risk population. In the low-risk population, PPVs are calculated and predicted based on the decreased prevalence of the stated chromosomal conditions. In 2014 to 2017, NIPT's PPVs for Down syndrome in the low-risk population lies between 45% to 93%, between 40% to 76% for Trisomy 18, and 45% for Trisomy 13 (Bianchi et al., 2014; Meck et al., 2015; Petersen et al., 2017).

Later studies, however, noted that PPVs of NIPT are overall higher than previously analyzed. Several large studies from China reported PPVs from NIPT to be more than 85% to 99%

in Down syndrome, from 50% to 92% in Trisomy 18, and from 23% to 46% in Trisomy 13 (Junhui et al., 2021; Lu et al., 2020; Wang et al., 2020; Zheng et al., 2020). Another 2018 large-scale study from Zhang et al. noted that NIPT performance is similar between low-risk and high-risk pregnancies (B. Zhang et al., 2018). To explain this phenomenon, these studies quoted lower false positive rates in younger ages and somatic cell loss in confined placental mosaicism meiosis error in older ages (DiNonno et al., 2019). Regarding sex chromosome conditions, NIPT performance is much lower in validity studies. Overall, NIPT utility seems to have improved over the years, but it remains a screening test with the need to follow-up positive results with diagnostic testing.

Based on the recent scientific insights, in 2020, the American College of Obstetrics and Gynecologists (ACOG) released a 2020 guideline update recommending OB-GYN specialists to offer NIPT in all pregnancies. This was a follow-up of a previous 2016 ACOG recommendation that recognized NIPT performance in low-risk pregnancies. The rationale for this guideline update cited NIPT to be the most sensitive and specific prenatal screening option for chromosomal aneuploidy, and its universal offering will give the most comprehensive information to aide in patient decision making (Rose et al., 2020).

Aside from the stated benefits, NIPT possesses limitations such as its screening nature (the inability to give a conclusive answer) and the possibility of "no-call" results due to low fetal fraction or quality control issues. NIPT also possesses other nuances behind the testing including incidental findings (mosaicism, maternal chromosomal abnormalities, and even malignancy in the pregnant person), and inconclusive or discordant results (normal fetal karyotype after a positive NIPT) under such circumstances (Bianchi et al., 2015; Kater-Kuipers et al., 2020; L. Wang et al., 2020).

These nuances are often study topics of experts in terms of ethical aspects surrounding the informed consent process, since NIPT utilizes a more sensitive, specific sequencing technology counterintuitive to its logistical ease. Only requiring a blood sample with procedural ease may hinder pregnant people from thinking through the benefits, limitations, and nuances of the screening. Furthermore, the setting of obtaining consent for NIPT (especially in universal offering) is usually the information-dense prenatal visits; researchers are concerned that needed awareness may not get sufficient attention regarding the test's limitations and the implications of the test's possible results. Farrell et al's study surveying women's perspectives of NIPT shows a strong need (71% participants) for a formal consent process in pre-test counseling (Farrell et al., 2014). Implementing ACOG 2020 updates with universal NIPT screening may prompt new challenges for healthcare providers and pregnant people in terms of preparedness and personnel to facilitate informed decision-making.

Another barrier to universal NIPT implementation lies in the variety of health insurance companies in terms of NIPT coverage for low-risk pregnancies. Despite the updated guidelines to offer NIPT to low-risk patients, insurance companies may only cover the test for high-risk indications (Benoy et al., 2021; Dondorp et al., 2015).

Genetic counselors are healthcare professionals who are well-equipped with an in-depth understanding of NIPT and knowledge in facilitation of decision making and informed consent. Genetic counselors may be involved in pre-test and post-test counseling when patients consider NIPT. Facing the stated challenges in informing patients about NIPT nuances and interpreting results, researchers have previously mentioned the need for genetic counseling when offering NIPT (Buchanan et al., 2014). Under the ACOG guideline update, the most likely workflow entails low-risk pregnant patients consenting for NIPT during their initial prenatal visit with their primary obstetrician, and a genetic counselor may follow up with patients if results are concerning. Another study pointed out that standards of practice for pre and post-test counseling are not uniform, where pre-test counseling and/or results explanation may be performed by either physicians or genetic counselors depending on the institution (Kater-Kuipers et al., 2020).

Such variation in guideline implementation leads to supporting or hindering factors in genetic counselor practice in offering NIPT. Studies have shown that overall, genetic counselors favor offering universal NIPT for common chromosomal aneuploidies because of the test's high performance. However, there is not a lot of information on the specific reasons why they favor this option (Agatisa et al., 2018; Benoy et al., 2021). Genetic counselors are shown to be knowledgeable and prepared to provide anticipatory guidance and interpretation of most types of unexpected results (Case & Hazel, 2018). That said, genetic counselors are not exempt from the previously stated challenges, namely challenges and barriers in informed consent and insurance coverage. Pointing out the barrier in ensuring the patient is making an informed choice, Agatisa's study calls for the need of educational materials on NIPT for both providers and patients (Agatisa et al., 2018). Benoy's study mentioned that more genetic counselors would offer NIPT to patients if insurance coverage was not a concern. In contrast, if genetic counselors feel that insurance may not cover, they are more reluctant to offer this screening as an option due to potential financial hardship for the patient (Benoy et al., 2021).

Although such studies mentioning benefits, challenges, and barriers to universal NIPT offering, additional, more in-depth information is needed in terms of genetic counselor's perspectives and needs after the 2020 ACOG Guideline update. Current research studies cite the need for additional patient-targeted resources on NIPT. As a frontline healthcare provider, genetic counselors are well-equipped on NIPT to provide insights on what content should be included in

such newly created patient friendly materials. This thesis study aims to fill such gaps and complement the current literature while contributing to future directions of NIPT utilization and also mitigating challenges. The project will include a survey to gain insights from practicing prenatal genetic counselors on counseling aspects surrounding NIPT, followed by data analysis and creating a patient friendly NIPT resource based on genetic counselor perspectives.

### **3.2 Specific Aims**

Aim 1: Create a survey and distribute to genetic counselors to assess their opinions on and concerns with the ACOG update.

Aim 2: Determine whether genetic counselors have incorporated the ACOG guideline update into practice or plan to put into practice, as well as the current status of implementation (i.e., who facilitates patient decision-making or does informed consent, in which stage/scenarios of the process genetic counselors get involved, etc). In follow-up to this specific aim, determine how this decision was made based on either professional opinion, departmental or institutional agreement.

Aim 3: Identify benefits, facilitators, barriers, challenges, as well as counselors' needs in implementing the guideline update, for example: insurance, informed consent, ethical concerns, patient's understanding.

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#### 3.3 Methods

#### **3.3.1 Ethical Consideration**

Prior to conducting any research methods, the study summary, rationale, methods, protocols, the project proposal and all materials were submitted to the University of Pittsburgh Institutional Review Board (IRB) for approval. Since the main method utilized was anonymous survey, the IRB application along with the introductory text was approved with exempt status. The IRB approval letter is attached in Appendix A.

#### **3.3.2 Survey Development**

The survey questions utilized in the study were developed in reference to multiple previous studies that assess healthcare providers' perspectives on different topics (Agatisa et al., 2018). The survey questions are targeted towards board certified/eligible, currently practicing prenatal genetic counselors in the United States and Canada, who are most likely exposed to and utilizing guidelines or updates from US/Canadian professional organizations. Respondents who indicated that they either are not genetic counselors or genetic counselors not working in the prenatal specialty were automatically directed towards the end of the survey.

Survey questions were edited, added, or omitted according to the outlined aims of the study, as stated in previous sections. They were designed to gather insights into the status of genetic counselors' practice in terms of ordering/facilitation of ordering of NIPT, the implementation of 2020 ACOG guidelines, facilitating or hindering factors that support or challenge universal NIPT screening, insurance coverage and patient's decision, as well as the need for non-laboratory

affiliated NIPT resources. There were scenarios and Likert-scale questions added to further assess genetic counselors' perspectives in informed consent, incidental findings, and patients' reactions. For certain scenario questions, participants will be skipped if they stated to have not encountered that analogous scenario in order to avoid speculation. When appropriate, some questions also included the "Other" choice prompting respondents to answer in a text box, which allowed participants to add in their customized responses and additional insights.

After multiple rounds of edits, the study survey consisted of 36 questions, and completion time was estimated to be about 10-15 minutes. The survey questions were put into Qualtrics, with the option of removal of IP addresses chosen to allow for an anonymous survey. Data was collected in Qualtrics and would potentially be exported to statistical software for further analysis. A copy of the recruitment/introductory text and the survey questions are included in Appendix B.

## 3.3.3 Survey Distribution/Recruitment

The survey was distributed through the listservs of the National Society of Genetic Counselors (NSGC) in two waves: October 2021 and November 2021. Following the application and approval to utilize the NSGC's Student Distribution Survey Program, the NSGC distributed this survey in the organization's weekly digest email on October 19, 2021 with a reminder on October 26, 2021, and on November 8, 2021 with a reminder on November 15, 2021. Most respondents were expected to be NSGC members; however, the introductory text specified the appreciation if the participants could pass the survey onwards to currently practicing non-member prenatal genetic counselors in US and Canada. The survey was closed for responses one week after the reminder email on November 22, 2021.
#### 3.3.4 Data Analysis

Current descriptive methods include extracting and interpreting data from Qualtrics, as well as using the "Crosstabs" function in the platform to compare across groups. Figures and graphs were created using Microsoft Excel and Microsoft PowerPoint, with added labels and headings as appropriate. To maintain as large a sample size as possible, partial answers were counted and analyzed. Further in-depth statistical analysis may be conducted in other software analysis.

The Extended Chi-Square test and the Odds Ratio was conducted using STATA software version 16 (StataCorp., 2019).

#### **3.4 Results**

The survey was designed to elicit insights from practicing prenatal genetic counselors. From the initial 76 respondents, 68 were practicing prenatal genetic counselors and 64 completed the whole survey. Due to the distribution method, the survey respondents were most likely members of NSGC (Table 1). The majority of respondents were at the age between 25 to 34 of age (67.6%, n=46/68). Most genetic counselors have been in the prenatal specialty between 1 to 5 years (47.1%, n=32/68), while others were approximately similarly distributed between less than 1 year (17.7%, n=12), 5-10 years (14.7%, n=10, 14.7%), and 10 years or longer (20.6%, n=14). Most responding genetic counselors have worked in their current positions between 1 to 5 years (n=35/64, 54.7%) or less than a year (29.7%, n=29/64,). Additionally, most responding prenatal

genetic counselors see an average of 10-19 patients per week (70.8%, n=46/65), followed by 1-10

patients per week (16.9%, n=11/65), and 20-29 patients (12.3%, n=8/65).

#### Table 1 Demographics of the Responding Prenatal Genetic Counselors

| Age   | Count |
|-------|-------|
| <25   | 3     |
| 25-34 | 46    |
| 35-44 | 9     |
| 45-54 | 6     |
| 55-65 | 4     |

Table 1a: Age Distribution of Respondents

Table 1b: How long the respondents have practiced in the prenatal specialty

| Duration of working as a   | Count |
|----------------------------|-------|
| prenatal genetic counselor |       |
| <1 year                    | 12    |
| 1-5 year                   | 32    |
| 5-10 years                 | 10    |
| 10 years or longer         | 14    |

Table 1c: How long the respondents have practiced in the prenatal specialty

| Duration of Current Position | Count |
|------------------------------|-------|
| <1 year                      | 19    |
| 1-5 year                     | 35    |
| 5-10 years                   | 5     |
| 10 years or longer           | 5     |

Table 1d: How many patients, on average, a prenatal genetic counselor see per week

| Average Number of New | Count |
|-----------------------|-------|
| Patients Per Week     |       |
| 1 to 10               | 11    |
| 10 to 19              | 46    |
| 20 to 29              | 8     |

### 3.4.1 Current status of NIPT Implementation

NIPT seemed to be deeply integrated into prenatal genetic counseling as indicated by responses to this survey (sampled from a portion of currently practicing genetic counselors), with 97% of respondents offering NIPT to their patients (95%, CI 0.896-0.996). The majority of respondents (44%) order/facilitate the ordering of less than 5 tests a week, 33% with 6-10 tests a week, 15% with 11-16 tests a week, and 8% with 16-20 tests a week. That said, the sample size was small at n=68 (approximately less than 10% of the currently practicing NSGC-member prenatal genetic counselors); therefore, these results might not be representative of the overall practice of this population.

Overall, genetic counselors are familiar with the ACOG guidelines update that recommend offering NIPT to every pregnancy, with 91% (n=58/64) reporting being familiar with the updates (95%, CI 0.81-0.96) and 9% (n=6/64) at least have heard of the updates. This update, however, has had a variety of degree of impact to the genetic counselors' practice: 18% of respondents reported a "significant" extent of impact, 32% reported practice impact "to some extent," 22% reported "a minimal extent," of practice impact and for 28% the guidelines did not change their practice.

Interestingly, when respondents were asked how familiar they were with the new update, the duration of working in the prenatal setting seems to be associated with the familiarity of the ACOG updates guidelines. Extended Chi-square statistic value is 10.49, with p=0.0058<0.05, which indicates a significant difference between genetic counselors practicing in prenatal specialty for less than 1 year, 1-10 years, or more than 10 years. Fisher's Exact Test is then conducted to compare individually within each pair to look where the significance lies. Genetic counselors who have been practicing between 1-10 years were significantly more likely to be highly familiar with

the 2020 ACOG update regarding universal NIPT compared to counselors who have been practicing less than a year (p=0.009 < 0.05). An odds ratio was subsequently calculated between these two groups (OR = 19), denoting that the odd of a respondent being highly familiar with the ACOG update guidelines is 19 times higher for prenatal genetic counselors who have practiced for 1-10 years than those practicing for less than a year. There were no participants answering "No" to this question, suggesting an overall high degree of familiarity with the 2020 ACOG guidelines in the responding population of prenatal genetic counselors.

#### Table 2 The Association Between the Duration of Working in the Prenatal Settings and the Familiarity of the

#### **ACOG Updates**

Extended Chi-square statistic value is 10.49 (p=0.0058 < 0.05) across three groups. Fisher's Exact test is done individually between each pair, and there is a significant difference in familiarity with the 2020 ACOG Guidelines update between genetic counselors who worked less than 1 year and who worked between 1 to 10 years (p=0.009 < 0.05). Odds ratio was calculated to be OR=19 between these two groups.

|  | Duration of working as a prenatal genetic<br>counselor |              |              |  |  |  |
|--|--|--------------|--------------|--|--|--|
|  |  |              |              |  |  |  |
| Familiarity with the 2020 ACOG Guidelines updates    | Less than 1 year                                       | 1 - 10 years | More than 10 |  |  |  |
| recommending the offering of NIPT to all pregnancies |  |              | years        |  |  |  |
| Yes  | 8  | 38           | 12           |  |  |  |
| I have heard of it                                   | 4  | 1            | 1            |  |  |  |

A majority of genetic counselors are offering NIPT to all patients (89.1%), including highrisk and interested patients. Others offer NIPT to high-risk patients only, including high-risk indications (AMA, previous ultrasound findings, etc.) and doctor's referral of an euploidy screening. Fisher's Exact Test statistic value has a p=0.032<0.05, which indicates a significant difference between the population of patients being offered NIPT in the hospital settings compared to others (including private practice and commercial settings). An odds ratio was subsequently calculated between these two groups (OR = 8.8), denoting that the odd of a respondent offering NIPT to all patients is 8.8 times higher for prenatal genetic counselors who practiced in the hospital settings than those practicing in private or commercial settings. Genetic counselors who practice in a hospital setting were significantly more likely to universally offer NIPT than genetic counselors working in other practice settings.

#### Table 3 How Patients are Offered NIPT in Different Practice Settings

Fisher's Exact test finds a significant difference in patient populations being offered NIPT between the hospital settings and the private practice/commercial settings (p=0.032<0.05).

|                                      | Patients being offered NIPT |              |  |  |  |  |
|--------------------------------------|-----------------------------|--------------|--|--|--|--|
| Type of Institutions                 | "High risk" patients only   | All patients |  |  |  |  |
| Hospital                             | 4                           | 47           |  |  |  |  |
| Private Practice/Commercial Settings | 3                           | 4            |  |  |  |  |

\*High risk: Advanced maternal age (AMA), previous ultrasound indication/Anomalies

#### 3.4.2 Facilitating factors of universal offering of NIPT to all patients

Factors that support/facilitate offering NIPT to all patients are identified. Participants were able to select multiple options resulting in a total count of 115, and there was one text-filling option for genetic counselors to be able to list other specific NIPT justification. Among which, some major factors from the existing choices include the departmental decision (31.0%, n=40/115), professional opinion (34.5%, n=36/115), and the impact of the ACOG guidelines (26.7%, n=31/115). The additionally listed reasons include equity, Society of Maternal Fetal Medicine Guidelines (SMFM), and limited availability of ultrasound imaging during COVID-19.



Figure 1 Factors that Support or Facilitate Offering NIPT to All Patients

# 3.4.3 Barriers and challenges surrounding universal offering of NIPT to all patients

Factors that support/facilitate offering NIPT to only high-risk patients were identified (N=12). Some major factors included the departmental decision (33%, n=4/12), and insurance challenges (25%, n=3/12).



Figure 2 Factors that Support/Facilitate Offering NIPT to Only High-Risk Patients

### 3.4.3.1 Impact of insurance on billing considerations and patient's decision

The majority of prenatal genetic counselors decide on which testing laboratory to use based on insurance and billing considerations, in which 59.7% (n=37/62) of genetic counselors reported "frequently," 27.4% (n=17/62) reported "sometimes," with only 9.68% (n=6/62) for "rarely" and 3.2% for "never." Lack of insurance coverage seems to be a barrier to universal NIPT screening with 25% (n=15/60) of respondents reporting that insurance coverage "frequently" prevents patients getting NIPT universally, and more than 40% (n=25/60) reported "sometimes" insurance becomes a challenge in offering NIPT universally.

Scenario questions were given to assess genetic counselors' opinions on the likelihood that insurance policies would cover NIPT. Two scenarios were presented, one representing a high-risk patient and one representing a low-risk patient. In the high-risk pregnancy scenario, 100% of genetic counselors (n=62/62) were confident that insurance would provide coverage for the testing.

Conversely, in the low-risk pregnancy scenario, only 9.9% of genetic counselors (n=6/61) thought that insurance would likely cover the cost of NIPT, while 70.5% (n=41/61) thought it was unlikely by answering "No" and 19.7% (n=12/61) were uncertain. To follow-up with this scenario under the circumstance that insurance does not cover NIPT, genetic counselors were asked about the possibility that the potential out-of-pocket cost would cause the patient to decline the testing (21% (n=13/62) answered "Frequently"; 74.2% answered "Sometimes"; and only 3.2% answered "Never").

### 3.4.3.2 Patient's understanding of NIPT during informed consent process and its

## psychosocial consequences

Genetic counselors who had encountered atypical NIPT findings were asked about patients' level of understanding of NIPT following results discussion with OB-GYN office. There were some concerns that patients do not have a good understanding of potential incidental findings, with a majority of respondents (59.3% - n=32/54) answering "Frequently" when asked about encountering patients who have a limited understanding of these findings. Similar trends were observed in terms of patient understanding of NIPT limitations, only 11.9% (n=7/59) reported "Frequently" encountering patients with good understanding of NIPT limitations following the offering/discussion with OB-GYN doctors, with the majority (67.8% (n=40/59)) reporting "Sometimes" and 20.34% (n=12/59) "Never." Given this scenario, a majority of genetic counselors (84.7%, n=50/59) indicated patients experiencing "psychosocial distress" due to unexpected results, with 62.7% answering "Frequently," 22% answering "Always," and 15.3% answering "Sometimes." None of the participants selected "Never" as an answer for this question.

#### 3.4.3.3 Potential causes of decisional regret



Figure 3 What leads to Patient's Decisional Regret

To follow up, participants were asked about the most common reason leading to patient's decisional regret they encountered. The most significant reason was cited to be "inconclusive results" (32.6%, n=15/46), followed by incidental findings (32.6%, n=7/46), lack of understanding leading to unexpected results (32.6%, n=7/46), no-call results/quality control issues (13%, N=6/46), patient thinking NIPT as mainly a "gender test" (10.9%, n=5/46), and patient misconstrued NIPT to be diagnostic (8.7%, n=4/46). Only one genetic counselor cited pregnancy anxiety or positive results (n=1/46).

#### 3.4.4 Prenatal genetic counselor's perspectives surrounding universal NIPT

Participants were asked about whether they agree or disagree on different statements surrounding the sufficiency of healthcare personnel and the necessity of patient's level of understanding during the informed consent process. The statements were assessed using a 5-point Likert Scale (strongly disagree, disagree, neutral, somewhat agree, and strongly agree). The responds were then aggregated by each statement.

To construct Figure 4, for each statement, the number of neutral responses is divided by 2, denoted by the gray bar in the middle. Towards the right side of the graph past the "0" column for each statement, the number of the "Somewhat Agree" answers is marked by the light blue bar and the number of the "Strongly Agree" answers by the deep blue bar. Towards the left side of the graph past the "0" column for each statement, the number of the "Somewhat Disagree" answers is marked by the cream color bar and the number of the "Strongly Agree" and the number of the "Strongly Agree" answers by the deep blue bar. Towards the left blue bar and the number of the "O" column for each statement, the number of the "Somewhat Disagree" answers is marked by the cream color bar and the number of the "Strongly Agree" answers by the bolder amber bar.

A significant proportion of genetic counselors (42.9%, n=27/63) disagreed that there is a sufficient number of healthcare providers to obtain informed consent, with 27% (n = 17/63) somewhat agreeing with this statement. Most participants (42.9%, n=27/63) somewhat agree that the current number of healthcare providers is sufficient to adequately inform patients about NIPT. There is a consensus among participants (89% (n = 56/63) strongly or somewhat agreed) that patients considering or eligible for NIPT should be given anticipatory guidance regarding the nuances of NIPT including incidental findings, "no-call" results, or inconclusive results. Most participants (73.4%, n = 47/63) also agreed that it is necessary for patients to have such understanding for healthcare providers to achieve informed consent.



Figure 4 Genetic Counselors' Insights on Sufficiency of Healthcare Personnel and Patient Understanding in the Informed Consent Process

Per statement, the answers were aggregated and denoted by colored bars accordingly. The resulted scale at the bottom demonstrated the total number of responses for each and total types of answers.

There are concerns over whether non-genetics healthcare professionals have enough knowledge to educate patients about the stated nuances of NIPT, with 48.3% (n=29/60) answering "No" to this question, followed by 41.7% (n=25/60) with "Somewhat" and only 8.33% (n=5/60) with "Yes."

While the majority (somewhat) agreed that non-genetics healthcare professionals have enough knowledge to achieve informed consent when offering patients NIPT (58.1% - n=36/64answering "Somewhat" and 29% - n=18/62 answering "Yes"), some participants expressed concerns with 11.3% (n=7/64) answering "No" to this question.

#### **3.5 Discussion**

The survey's results suggested a high level of familiarity of the ACOG guidelines in practicing genetic counselors in the United States and Canada. The association between the duration of working in prenatal settings and familiarity of ACOG guidelines is interesting. The results showed that genetic counselors who have been practicing between 1-10 years were significantly more likely to have heard of the 2020 ACOG update regarding universal NIPT than counselors who have been practicing less than 1 year. While this can be explained by the small sample size, another possible explanation for this may be related to the exposure of NIPT integration over the years. Genetic counselors practicing 1-10 years have been through the thick and thin of NIPT increasing popularity and impact on prenatal applications and professional guidelines. They may also be more aware of any changes to the technology use of this screening, its initial utilization as a routine screening for high-risk patients followed by its explaned use. Regarding the less familiarity in the group practicing less than a year, this may be explained by the timing of the guideline's release. Genetic counselors with less than 1 year of experience at the time of this survey were most likely still in school when the ACOG update came out in 2020.

The survey data suggests that the ACOG update guidelines have impacted the practice of genetic counselors in the United States, further promoting the universal offering of NIPT in the prenatal setting. This finding is consistent and correlated with the previous studies in multiple aspects. Since the later validation studies focused on low-risk pregnancies with encouraging results of high sensitivity and the specificity for NIPT in this population, the utilization of NIPT is increasing, encouraged by the ACOG update guidelines and consistent with this study's results (Samura, 2020; Yang & Tan, 2020).

The survey identifies multiple facilitating factors that support universal NIPT offering to patients, including professional opinion, department or genetic counselor team decision, implementation of ACOG updates and other professional guidelines (SMFM), and institution policies. The most common factors include professional opinion (34.5%), departmental decision (31.0%), and to implement the ACOG update guidelines (26.7%). This trend is consistent with the increasing popularity of NIPT as a prenatal screening method discussed in past studies, adding to the confirmation of increasing NIPT utilization in clinical settings (Samura, 2020). Other interesting rationales were stated in the open response option that represented current events (limited ultrasound abilities during COVID-19) and ethical view (offering patients NIPT to maintain equity).

Consistent with this trend, most genetic counselors responding to this survey are offering NIPT to all pregnant patients (89.1%), especially in the hospital settings. There is a significant difference between the population of patients being offered NIPT across different types of institutions, in which NIPT is more likely to be universally offered in the hospital settings compared to private practice and commercial settings. While this result may seem counter-intuitive to a usually more liberal approach in the private settings, the higher prevalence of universal NIPT offering in the hospital settings may be reflected of limited insurance coverage in private policies and the selective acceptance of insurance types in the private/commercial settings. Hospitals are more likely to frequently accept multiple types of insurance (including public insurance policies, Medicaid or Medicare), which may have enabled the feasibility and patient's affordability to have NIPT. This phenomenon is also mentioned in Benoy et al's study, which showed that women with public insurance are 3.43 times more likely to undergo NIPT compared to their low-risk counterparts with private insurance. Still following the 2012 ACOG guidelines only

recommending NIPT to high-risk patients, private insurance companies often do not offer coverage to their low-risk clients (Benoy et al., 2021).

The survey results are also consistent with past studies in terms of hindering factors that might prevent the effort of universal NIPT screening. For the universal NIPT screening to be implemented accordingly from the ACOG 2020 updates, these challenges and barriers need to be researched and addressed. While other stated factors include state-funded prenatal screening programs, preferences in professional opinion, and type of institution, insurance proves to be a major challenge when it comes to coverage for NIPT (Benoy et al., 2021). 25% of respondents stated that insurance coverage "frequently" prevents patients from having NIPT, with another 40% reporting "sometimes."

When comparing "high-risk" versus "low-risk" pregnancy scenarios, participants were highly confident that insurance would cover NIPT cost for high-risk patients (100%) but not low-risk patients (only 9.9% answered "yes"). For the latter group, some genetic counselors (19.7%) expressed uncertainty, while the majority do not think insurance coverage will apply to low-risk scenarios (70.6% answered "no"). This result is consistent with a recent study by Crabbe et al in 2019, in which a thematic analysis reveals that women's insurance "won't pay for both" ultrasound scan and NIPT (Crabbe et al., 2019). Such limitations in insurance coverage seemed to put a financial barrier between low-risk pregnant patients and access to NIPT. In our study's result, a majority of genetic counselors (95.2%) indicated that the potential out-of-pocket cost could lead to a patient's declination of testing between "frequently" and "sometimes," with only 3.2% of respondents denying this possibility.

Insurance coverage does not seem to be the only barrier to universal screening; another challenge elicited from the survey lies in the informed consent process. Overall, participants are

in consensus that awareness of the test's nuances (including the possibility of uncertain results and incidental findings) is necessary for patients to be fully informed when consenting for testing. On that related note, participants have concerns whether we have sufficient healthcare personnel to provide informed consent to patients, with 42.9% of genetic counselor respondents showing disagreement to this statement. There was a pretty even split on whether non-genetics professionals have enough knowledge to inform patients of those NIPT nuances with nearly half (48.3%) of respondents answering "No" to this question.

Interestingly, a large proportion of respondents (58.1%) thought that non-genetics providers have sufficient knowledge to achieve informed consent when offering NIPT. These results may seem counterintuitive to previous questions, when most genetic counselors thought that understanding NIPT nuances are necessary to achieve informed consent, and only 8.33% of respondents answered "Yes" when asked if non-genetics healthcare professionals can educate patients about the stated nuances of NIPT. However, this can be explained that only patient's awareness and mental preparation for unexpected results are needed to achieve informed consent, without going into too many details unless patients are interested. Non-genetics providers can consider adding a few statements to emphasize this awareness when discussing with patients, with resources (and possibly referrals) if patients have more questions. Under the circumstances of unexpected results, non-genetics healthcare providers can refer them to the genetics healthcare professionals for in-depth discussion on what those results mean.

Other results also call for this need of focusing on patient's awareness for proper informed consent. When participants were provided with scenarios of patients facing atypical findings, a lot of respondents felt that patients are not always aware of the test's possible results or have a good understanding of the test's screening nature and its limitations. This issue resonates with another part of the survey results, where a significant portion of respondents mentioned decisional regret in patients undergoing NIPT due to different types of atypical findings (specifically inconclusive results, uncertain results, quality control issues, and incidental findings). Other indicated causes of decisional regret include misunderstanding that the test was diagnostic, thinking that the test was just a "gender revealing" test, and getting a positive result. All those stated causes surround different aspects of understanding about NIPT, signifying the concern that patients undergoing testing may not have had sufficient awareness about the test before consenting.

### **3.5.1 Future Directions**

This study identified potential barriers to universal offering of NIPT to all patients, including challenges in the informed consent process and lack of insurance coverage. A future direction can include a proposed framework on how to manage the challenges in the informed consent process, especially seeing the trend of moving forwards in the direction of universally offering NIPT based on majority professional opinion and guidelines implementation. This framework can provide more details on how to increase a patient's awareness of the possibility of unexpected results as well as the testing limitations of NIPT. To address the barriers in terms of insurance coverage for NIPT in low-risk pregnancies, insurance companies need to review and consider updated professional guidelines in their utilization management of prenatal screening, and there needs to be an advocacy effort or policy incentives to adopt the updated guidelines and adding low-risk patients to NIPT eligibility.

Another exciting perspective coming out of the survey's results include the demonstration of a strong need for additional resources that are patient friendly, accessible, and not associated with the NIPT-providing laboratories. Such resources will aid patients in making an informed decision when choosing NIPT, alleviating the challenges in terms of personnel and lack of time accommodation for a traditional counseling process. Following up with this aim, I will proceed to create this brochure accordingly based on the survey's responses.

### 3.5.2 Limitations of the Study/Analysis

Out of more than 800 prenatal counselors within NSGC, the survey has a small sample size of 72 responses (including completed and incomplete responses), making up 9% of practicing prenatal genetic counselors registered under the NSGC database. This poses the possibility of not being representative of the whole population, and some statistical comparisons will have to be conducted based on small counts. Furthermore, due to the nature of the distribution, this survey most likely does not include the perspectives of non-member prenatal genetic counselors who are practicing.

Another limitation of the survey is the non-direct nature of insights into patients' perspectives. While the study provides some suggestions of patients' emotional response, financial burden, or decisional regret to the current practice of NIPT, such information comes from genetic counselors' perception. While genetic counselors are trained health professionals who help guide patients through these issues, their perspectives add one more layer of interpretation and may not be exactly representative of patients' perspective. Surveying patients directly may elicit more insights on NIPT impacts on patients, which may not be indicative in this study.

The survey results also encourage the making of the patient-focused resources. However, due to the need for multiple content areas being included, it might be challenging to make a concise, patient friendly all-in-one fact sheet that satisfy the inclusion of all these topics. In conclusions, this study elicited insights into genetic counselors' perspectives on NIPT current practice, how the 2020 ACOG guidelines update recommending universal NIPT screening impacts practice and patients, and the facilitators and barriers to its implementation. The survey contributes practical insights to the genetic counseling field in terms of future directions on the ethical and equitable implementation of NIPT universal screening, as well as opportunities to improve patients' experience or access to resources.

#### 4.0 Genetic Counseling and Public Health Significance

With its increasing popularity and testing power, there are benefits of NIPT that professional organizations recognize in recommending offering of NIPT to all pregnancies. For the implementation of these guidelines to be ethical and equitable, the barriers and challenges to universal NIPT screening need to be addressed with practical insights to achieve the best clinical approach and policy changes needed in the prenatal settings. In its practical application, a recent article in the New York Times called "When they warned of rare disorders, these prenatal tests are usually wrong" exposed problems in which NIPT implementation had gone wrong – namely when patients undergoing testing were not informed about possible test results as well as the test limitations. Such incomplete, uninformed consent leads to patients' confusion, emotional distress, and even pregnancy-related decisions based on inconclusive results in worst case scenarios (Kliff & Bhatia, 2022). According to the article, challenges also present in terms of resources and how the test was advertised. Although the screening nature of the test may be mentioned, language such as "peace of mind," "excellent performance," or "high confidence" may lead patient to a false sense of security that the test was diagnostic. Furthermore, laboratory may not provide transparent study results or accessible resources for patient to be aware of unexpected results and what followup testing should be entailed.

Equipped with an in-depth understanding of the test and communication skills, prenatal genetic counselors play a crucial role in pre-test and post-test counseling to facilitate patient's decision-making. With issues on informed consent and nuances associated with NIPT including different types of results or incidental findings, research calls for the need of genetic counseling during NIPT consideration. As NIPT use expands, genetic counselors can play an important role

in educating patients. However, under the ACOG 2020 guidelines update, the most likely scenario to accommodate clinical flow and personnel is for physicians to obtain inform consent for NIPT in average-risk populations, who will follow up as needed. This study assessed the genetic counselor's perspectives on the updated ACOG guidelines on recommending NIPT to all pregnancies, specifically about the informed consent process, its pros, cons, challenges, and barriers.

These survey results showed a high familiarity of NIPT and awareness of guidelines in genetic counselors, and that a majority of respondents universally offer NIPT to prenatal patients, especially in the hospital settings. On the other hand, the results also demonstrated concerns over patient not being aware of NIPT nuances, as well as level of patient's understanding of results following discussions in an OB-GYN office. Furthermore, the survey confirmed previous research on lack of insurance coverage for average-risk patients, potentially leading to guidelines incorporation mostly in hospital but not in commercial or private clinic's settings.

The American Medical Association emphasizes that informed consent is "fundamental in both ethics and law," in which a healthcare provider informs and educates patients about the benefits, risks, and option of a medical intervention (Cernat et al., 2019; P. Shah et al., 2022). The implementation of universal offering of NIPT may necessitate the test discussion and informed consent being obtained in prenatal visits. The Clinical Genome Resource (Clingen) Consent and Disclosure Recommendations Workgroup (CADRe) is a professional organization that supports clinicians in providing genetic services by developing guidance regarding communication approach, named the CADRe framework. Even though NIPT is not explicitly listed under CADRe's scope, the test directly looks into genetic materials of both the pregnant parent and child. Considering the ethical, social, and legal implications (ELSI), it can be argued that its proper

informed consent process should encompass similar elements applicable to CADRe's listed curation. Specifically for genetic counseling, the Clinical Genome Resource (Clingen) Consent and Disclosure Recommendations Workgroup (CADRe) identified core concepts to consent for genetic testing, including (1) voluntariness, (2) reasons for recommendation and what the test is for, (3) what kinds of possible results and to whom it will be returned, (4) other types of testing options, (5) impact of the results and its medical implications, (6) impact on family, (7) the testing limitations, and (8) risk of genetic discrimination and legal protection (Ormond et al., 2021). The results' insights on concerns regarding the informed consent process and potential lack of patient awareness are related to the 5<sup>th</sup>, 6<sup>th</sup>, and 7<sup>th</sup> core concepts to consent. Under the 5<sup>th</sup> and the 6<sup>th</sup> concept, if patients do not think through possible NIPT outcomes, they and their family members may be caught off guard and psychosocially distressed when facing unexpected results. Regarding the 7<sup>th</sup> concept, limited understanding of NIPT (for example, not distinguishing screening and diagnosing) could potentially lead to emotional suffering and decisional regret. In worse case scenarios, this may lead to irreversible, unwarranted pregnancy decisions that have serious emotional and physical implications to patients. To implement offering NIPT universally to all pregnant people ethically and equitably, the patient's informed consent process needs to be improved, and insurance coverage for low-risk population is a major barrier to be addressed. To advance towards this direction in the field of genetic counseling, additional advocacy for insurance coverage and forming NIPT consenting framework are potential actions moving forward.

In light of the three core functions of public health, this survey focuses on assurance, specifically by identifying challenges and barriers in adopting NIPT in an expanded population, and by evaluating effectiveness, quality and accessibility of NIPT universal screening. NIPT, while having the potential to be a sensitive, specific prenatal screening method, is associated with

procedural ease that may not encourage patients to mentally prepare for unexpected results (Kater-Kuipers et al., 2020). From a public health standpoint, valid informed consent is crucial to ensure a free, informed, and accessible choice for patients in this scenario of increasingly prevalent screening. While NIPT effectiveness has been shown in validity studies, whether it is offered universally to patients still varies across clinical places (hospitals more so than others), and its access remains restricted in low-risk populations due to insurance policies not covering the screening. This study contributes knowledge to the current state of NIPT practice and how public policies should be changed to ensure equity and accessibility to testing.

The survey results also inspired a patient friendly fact sheet in the associated project to improve patient's awareness of NIPT prior to testing. This factsheet was created based on genetic counselors' insights on what patients need to know to be informed, containing [nuanced] types of results from which different scenarios stem to encourage mental preparation and anticipatory guidance. In terms of public health, the creation of this factsheet fulfills the service of "communicating effectively to inform and educate people about health, factors that influence it, and how to improve it" under the "policy development function." The distribution of this factsheet will hopefully contribute to spreading awareness on NIPT nuances and discussing prenatal testing between physicians and patients.

#### **5.0 Public Health Essay**

# 5.1 Background

Non-Invasive Prenatal Testing (NIPT) is a blood test that screens for chromosomal aneuploidies during pregnancy. Traditionally, NIPT has been offered only to the high-risk population (including indications such as AMA, ultrasound findings, medical history, or family history) based on the established increased risks of chromosome conditions in this population. Due to recent validity studies that established the performance and utility of NIPT within the low-risk population, multiple professional organizations including the American College of Obstetricians and Gynecologists (ACOG), the International Society of Prenatal Diagnosis (ISPD), and the Royal College of Obstetrician and Gynecologists have provided updates on their guidelines to include low-risk populations in the recommendations for offering NIPT as one of the prenatal screening modalities (Benn et al., 2015; Non-Invasive Prenatal Testing for Chromosomal Abnormality Using Maternal Plasma DNA (Scientific Impact Paper No. 15), n.d.; Rose et al., 2020). The increased utilization of NIPT addresses the need for a highly sensitive and specific test to screen for the most common chromosome conditions, superior to the traditional maternal serum analysis. NIPT universal availability also allows for the comprehensiveness of a patient's choice, for prenatal care decisions are "of personal nature" (Rose et al., 2020).

Aside from the benefits of universal NIPT offering, there have been concerns raised in literature regarding challenges in obtaining proper informed consent, namely due to issues in personnel and limited appointment time leading to patient's lack of understanding (Cernat et al., 2019; Kater-Kuipers et al., 2020). In terms of professional guidelines on prenatal genetic screening, ACOG recommends providers specifically address (1) detection and false positive rates, (2) testing advantages, disadvantages, and limitations of the screening tests, and (3) the option of diagnostic testing (Colicchia et al., 2016; Rose et al., 2020). In a study focus on patient education in discussion with healthcare providers regarding prenatal genetic screening, a conversation about screening for an uploidy typically lasts only 1.5 minutes (between 0.12 minutes to 7.1 minutes). Adherence to ACOG guidelines in terms of prenatal genetic screening counseling was quite low, since providers only covered all of the recommended topics in about 1.1% of the visits. While the screening advantages were discussed in 54.7%, the disadvantages were mentioned in 48.7% and the availability of diagnostic testing only 35.3% of the visits. Furthermore, the explanation that screening results are not diagnostics only happens in 51.5% of the visits (Colicchia et al., 2016). Although this study focuses mainly on the traditional prenatal serum screening, similar inferences may be extrapolated under the clinical scenarios involving NIPT that indicate concerns for not obtaining true informed consent. While the ease of the screening process that both entails only a blood sample remains the same between the serum screening and NIPT, the latter utilizes a different technology that looks directly into the genetic materials with increased sensitivity, specificity, and capacity. NIPT procedural ease may also lead to patients not fully considering the implications of NIPT before consenting. This, combined with the density of information patients and providers need to cover during prenatal visits, necessary knowledge of NIPT may not receive its due attention regarding the test's aim, limitation, and possible results. The limitation in obtaining true informed consent may lead to patients' confusion, emotional distress, and, in worst case scenarios, even uninformed pregnancy-related decisions without the confirmation of a diagnostic results.

The discussed issues in patient education can be alleviated using accessible, patient friendly resources on NIPT. The associated survey of this study has elicited, from genetic counselors' perspectives, a strong need for non-laboratory, patient friendly resources focusing on NIPT. Trained with a thorough understanding of NIPT and its nuances, genetic counselors play a major role in educating patients and facilitating decision-making in counselling patients on NIPT, principally in high-risk pregnancies. To implement the professional organizations' guidelines recommending the offering of NIPT to all pregnancies, the NIPT discussion will most likely occur in prenatal visits (especially in low-risk population). With such increases in NIPT popularity, laboratories, hospitals, or other support organizations supposedly have published materials on the test for patient's references in the attempt to prepare patients for the discussion in prenatal visits. On the other hand, concerns have been raised regarding such resources' transparency, as well as the language used, where marketing the testing advantages and its performance serves as one of their main focus to rise participation (Kliff & Bhatia, 2022). Despite this seemingly resounding need, information on the status of current NIPT materials, their strengths, gaps, and possible room for improvements, is scarce.

To attempt to address this lack of information and contribute to alleviating the issue of patient education, this public health essay consists of two aims: an online review of NIPT resources and a creation of an informed fact sheet. The first aim is to conduct an online review of patient friendly materials on NIPT to see whether they address the patient's needs, specifically their accessibility, level of engagement, and coverage of information. The second aim is to create a fact sheet (a preferred method according to the survey) based on drawn insights from the online review and from the associated survey's results as affirmed by genetic counselors. The process of creating the survey will be detailed including its assessment of readability as well as rationales in its

contents, designs, and visuals aids, for the purpose of spreading and enhancing patient preparedness in NIPT consideration. Through its informative Internet review of existing materials and its final product, this study strives to elicit insights to improve transparency and content in existing materials, as well as provide a timely, engaging resource that addresses patients' need, ultimately enhancing patient experience undergoing NIPT journey.

## **5.2 Methods**

### 5.2.1 Review of Existing Resources on NIPT

A review on the Internet of NIPT patient friendly resources was conducted by visiting major labs that offer NIPT to check if patient resources are available, followed by a broader review using the "Google" search engine. The top eleven NIPT resources directed towards patients were identified and documented, with notes on each resource's pros and cons and suggested comments and/or additions on possible improvements.

### **5.2.2 Survey Questions**

In order to gain additional insights from genetic counselors' perspectives on the need for patient friendly NIPT resources in the context of the test's universal offering, questions were developed and conducted within the survey sent out to currently practicing prenatal Genetic counselors. Participants were able to customize their ideal resource by choosing the most accessible format and the most helpful content, as well as putting their opinion or suggestions in the text box for resource development. The questions' results were assessed and analyzed, and the patient friendly NIPT resource was created to most helpfully address patients' and genetic counselors' needs.

#### **5.2.3** The Creation of the Fact Sheet

Utilizing the insights from the survey's results and the Internet review of NIPT resources, a patient friendly factsheet on NIPT focusing on the stated patients' need perceived by genetic counselors. The factsheet's text was assessed as a whole and then section by section using the Editor plug-in tools within the Microsoft Office Word Software based on the Flesch Reading Ease or Flesch Kincaid Grade Level Calculators. The standards are then compared to that set by the Rapid Assessment of Reading Level in Medicine (REALM), which is a diagnostic tool to help determine the reading level of individuals in healthcare settings.

## **5.3 Results and Production of Resources**

# 5.3.1 Insights from the Online Review of Existing Patient-Targeting Resources on NIPT

The Internet search for a variety of NIPT resources showed a variety of formats, including websites, videos, fact sheets, and brochures. In terms of information coverage, each resource has a different focus on knowledge surrounding NIPT across different domains. Table 4 summarizes the main content categories and how each resource chooses to emphasize (or not) each category; overall, most resources cover genetics background, knowledge on common Trisomies (Trisomy

21, Trisomy 18, and Trisomy 13), sex chromosome conditions, and the virtually zero risk of testing. Some resources indicated the name of common trisomies as the conditions for which the test screened but did not touch on their potential phenotypes. Notably, most resources touched on the differentiation between screening and diagnostic testing, even though only some provide a sufficient explanation of the uncertain nature of screening. From a patient's perspective, this topic is of utmost importance to manage expectations and make pregnancy-related decisions, especially when this seems to be an area with understanding issues based on this study's survey (as one of the causes for decisional regret) and previous research.

The accessibility of the reviewed resources is assessed using Center of Disease Control (CDC)'s Clear Communication Index (CCI) (The CDC Clear Communication Index | Centers for Disease Control and Prevention, n.d.). The CDC Clear Communication Index is a website-based tools to help evaluate public health materials in terms of reading ease and clarity, containing of 4 introductory questions and 20 multiple choices, scored questions in four sections: Core (Part A), Behavioral (Part B), Numbers (Part C), and Risk (Part D). The CCI is specifically based on past research in communication and related fields. Such evaluated items are considered to represent imperative characteristics to aid the public's understanding of information (CDC Clear Communication Index: A Tool for Developing and Assessing CDC Public Communication Products—User Guide, n.d.). Some resources have done a great job in using patient friendly, clear, and concise language as well as using engaging visual aids that hold patients' attention, with CCI score on the upward of 80/100 and even 90/100. On the other hand, some resources lack one or more characteristics in CCI, including not having or emphasizing the main message statement, paragraph summary, or lack of numbers explanation. Due to the density of the content, none of the resources used bulleted lists, which is a criterion of CCI under "Core Functions." Some resources

cover in detail a wide range of NIPT nuances including comparing NIPT with maternal serum screening, explanations on statistical values, and discussion questions for providers. This information can be quite helpful for patients eager to explore the screening and gain a comprehensive understanding, but it can also be confusing and hard to navigate when resources have a lot of text or figures. In terms of accessibility, some resources are easy to find, while certain sites were hard to reach. For instance, to access a patient friendly NIPT flipbook on Harmony's website, one needs to choose "Global" and not "USA" as the region on a previous page for the flipbook to show up. Such technicalities may be barriers for patients if they need more information specific to the test from Harmony lab.

|       | Information Coverage          |                         |   |          |            |           |              |      |                 |  |  |   |                     |  |
|-------|-------------------------------|-------------------------|---|----------|------------|-----------|--------------|------|-----------------|--|--|---|---------------------|--|
| Order | Source                        | Format                  | Title   | Audience | Genetics   |           | Sav          |      | Diagnostic      | Notes  | Possible additions   | Comments  | CDC Clear           |  |
|       |                               |                         |   |          | Background | Trisomies | Aneuploidies | Risk | VS<br>Screening |  |  |   | Communication Index |  |
| 1     | Ariosa Diagnostics            | Brochure                | Answers that matters  | Patient  | Ŷ          | Y         | Ŷ            | Y    | N               | include detection rate/false positives<br>of T21 but not others. List other<br>conditions without these stats  | Test limitation, explain false<br>positive, incidential findings,<br>knowing babies sex, insurance<br>policy   | Makes it look like CVS and<br>armin has a lower<br>detection rate of<br>chromosome conditions -<br>misleading. (CVS-<br>Amniocentesis 98-99% for<br>"chromosome conditions"<br>vs NIPT "99.5%" for T21) | 68/100              |  |
| 2     | Whattoexpect.com              | Website                 | NIPT  | Patient  | Ŷ          | Y         | N            | Y    | Y               | Talk about accuracy (97-99%), good that<br>it does mention CVS/amnio as "more<br>definite results," good that use false<br>alarms  | May need more background on<br>genetics (why testing), add<br>possible types of results<br>(incidental findings,<br>inconclusive), insurance policy    | Mention GC and resources,<br>talk about how NIPT is not<br>100%   | 86/100              |  |
| 3     | Center for Genetics Education | Factsheet               | Fact Sheet 27   NON-INVASIVE<br>PRENATAL TESTING (NIPT)             | Patient  | Y          | Y         | Y            | Y    | Y               | Explain genetics and chromosomes,<br>mention CVS/amnio as "more definite<br>results," use patient friendly language<br>to explain "screening"  | Add possible types of results<br>(incidental findings,<br>inconclusive), insurance policy  | Talk about reasons to test<br>indicative of high risk<br>pregnancy; this resource<br>specifies that NIPT is<br>recommended to high-risk<br>pregnancy. Does not apply<br>for universal NIPT offering     | 72/100              |  |
| 4     |                               | Videos                  | What is NIPT? (non-invasive prenatal testing)                       |          | Y          | Y         | N            | Y    | Y               | Explain false positive (false alarms) and<br>other statistics number, about<br>diagnostic as more definite than<br>screening   |  |   | 92/100              |  |
| 5     | Illumina                      |                         | Understanding non-invasive prenatal<br>testing (NIPT) results       | Patient  |            |           |              |      | Y               | Talk about possible uncertainty of<br>results (no-call)  | Incidential findings, insurance<br>information   |   |                     |  |
| 6     |                               | Website                 | NIPT.com  | Patient  | Y          | Y         | Y            | Y    | Y               | Promote some questions for doctors for discussion  | Incidential findings/no call<br>results, insurance information.<br>Also additional information<br>about the indicated risk of CVS<br>and amniocentesis | Nice interface/organization<br>of information, clear and<br>concise information   | 88/100              |  |
| 7     | Harmony                       | Website and<br>Flipbook | Prenatal Testing Education  | Patient  | Y          | Y         | Y            | Y    | Y               | Hard to navigate, had to choose global<br>and not US to reach the resources, need<br>to emphasize the "definite answer"<br>nature of diagnostic  | Incidential findings/no call<br>results, insurance information   |   | 57/100              |  |
| 8     | Natera                        | Website and<br>Video    | Panorama <sup>™</sup> Non-invasive prenatal testing (NIPT)          | Patient  | Y          | N         | Y            | Y    | Y               | Mentioned no-call results  | Insurance information,<br>incidential findings, more<br>background on genetics may be<br>needed  | Nice interface/organization<br>of information, clear and<br>concise.  | 92/100              |  |
| 9     | Invitae                       | Website                 | Get valuable insights, with non-<br>invasive prenatal screening     | Patient  | N          | Y         | N            | Y    | Y               | Mentioned "prenatal diagnostic testing<br>to confirm," self testing option in case<br>insurance does not cover   | More background on genetics<br>and why you may want testing  | Nice interface/organization<br>of information, clear and<br>concise.  | 96/100              |  |
| 10    | Labcorp                       | Website and<br>Video    | Choice in Genetic Testing in Your First<br>and Second Trimesters    | Patient  | Y          | Y         | Ŷ            | Y    | Y               | Compare between NIPT and other test<br>(serum and diagnostic testings),<br>detailed explanation of genetic<br>background. Include cost estimator, but<br>needs to contact Labcorp and fill out<br>forms to get the information | incidential findings, some<br>common insurance/cost<br>information/scenarios   | Nice and detailed, but may<br>be too much information on<br>one page.   | 80/100              |  |
| 11    | NSGC                          | Factsheet               | A Patient's Guide to Understanding<br>Non-Invasive Prenatal Testing | Patient  | Y          | Y         | Y            | Y    | Y               | Need more genetics background on<br>chromosomes and DNA, nice mention<br>of diagnostic vs screening, nice mention<br>of interpretation, may need more<br>pictures and less text  | Need more genetics<br>background on chromosomes<br>and DNA, incidental findings,<br>insurance, cost  | May need more pictures<br>and less text   | 95/100              |  |

# Table 4 Review of Existing NIPT Resources, Including Suggestions for Content and Suggestions

#### 5.3.2 Potential Challenges and Possible Additions for Existing Resources

Although laboratories generally have NIPT resources available for patients, the need for NIPT resources is still present. The information on NIPT in laboratory resources may emphasize the test's benefits (namely its low risk and its high sensitivity and specificity), without elaborating on the test's limitations. Some resources do a good job in differentiating diagnostic testing versus screening, but some do not convey the necessity of following-up a positive result with a diagnostic method if one wants a sure answer and/or wants to pregnancy-related decisions. For instance, one brochure mentioned the methods "CVS" and "amniocentesis" with the word "diagnostic" but did not explain what they mean, while citing the Trisomy 21 detection rate of NIPT similar to that of diagnostic methods. Without prior healthcare knowledge, it may be challenging for a person to comprehend the limitation of NIPT as a screening test in this context.

Other than laboratories, other sources for patient-targeted NIPT information include a popular pregnancy and parenting brand – Whattoexpect.com, the NSGC organization, and educational institutions. Some nice additions in these resources include references to healthcare professionals to facilitate decision making including OB-GYN doctors and genetic counselors, as well as some information on testing rationale as to why pregnant people may consider testing. One resource, however, followed the traditional guidelines that recommend offering NIPT for high-risk population only, highlighting that some resources that patients may find online can be outdated. Otherwise, since the majority of NIPT resources do not explicitly state why patients should consider NIPT, testing rationales for both low-risk and high-risk populations may be an informative addition to future resources.

More importantly, a common gap in information in current NIPT resources for patients is the lack of possible types of results. Out of the reviewed eleven NIPT resources, only one mentioned no-call results as a possible outcome. Almost none of the existing resources touch on the possibility of incidental findings or uncertain results, which were reported to be potential sources of decisional regret (Crabbe et al., 2019; Farrell et al., 2014; Tiller et al., 2014). Different types of results are a part of the nuances behind NIPT, of which pregnant patients may need to be aware for mental preparation in the informed consent process.

Another scarcity of potentially helpful information in current NIPT patient materials is insurance coverage. Only two resources mentioned insurance and cost for NIPT, in one of which the patient needs to fill out forms to get a price estimation. In our current landscape, the lack of insurance coverage for low-risk patients is reported to be a concern, especially in the context of increasing NIPT offerings (Benoy et al., 2021). Such concerns have implications for access to testing and equity, in which it is important for patients to know their options. Under the circumstances that patients were offered the test and later denied coverage, anticipatory guidance on insurance and financial cost can help avoid psychosocial distress (Benoy et al., 2021; Crabbe et al., 2019).

# 5.3.3 Survey Results and Insights

From a genetic counseling perspective, a majority of respondents (56% - n=33/59) think there is a strong need for additional patient friendly resources on NIPT. Thirty-two percent (n=19/59) think there is a moderate need, and only 12% (n=7/59) think there is little need for resources.



Figure 5 How Strongly Genetic Counselors think there is a Need for Laboratory Independent Resources

Participants were surveyed on what format(s) they think would be helpful and accessible to patients. Participants could choose multiple options or put suggestions in a text box, resulting in a total count of N=160. "Factsheet" was voted as the most helpful and accessible format (N=43, 26.9%), followed closely by brochure (N=37, 23.1%), website (N=36, 22.5%), and video (N=36, 22.5%). One participant also suggested "social media," which could serve as the means to promote and distribute the resource.

Participants were asked about topics that would be the most helpful to patients to include on the brochure. Multiple topics were encouraged to be present on the resource, including the distinction between diagnosis and screening, inconclusive results, incidental findings, quality issues, and knowing the baby's sex. Participants were able to choose multiple options, which resulted in a total count of N=194. The most encouraged topics include the possibility and different types of uncertain results (N=57/194, 29.38%), the difference between diagnostic and screening (N=51/194, 26.29%), and incidental findings (N=43/194, 22.16%).

| Content  | Distribution | Count |
|--|--------------|-------|
| Distinguishing the difference between diagnosis and screening              | 26.29%       | 51    |
| Possibility of uncertainty (including "no-call" and inconclusive findings) | 29.38%       | 57    |
| Possibility of incidental findings   | 22.16%       | 43    |
| Possibility of quality control issues                                      | 14.95%       | 29    |
| Possibility of knowing the baby's sex                                      | 7.22%        | 14    |
| Total  |              | 194   |

#### Table 5 Content Topics for the Patient Friendly Factsheet on NIPT

Participants were encouraged to put any suggestions on resource development in the text box towards the end of the survey. Multiple participants suggested including referring to genetic counseling for informed consent, further questions or concerns, corresponding to this population having familiarity with the test's nuances and the ability to facilitate decision making. One participant suggested the inclusion of where cell-free DNA originates (the placental), for this background can also explain false-positive results. Some genetic counselors suggested multilingualism for this new resource. Although these suggestions are outside of this project's scope due to time constraints, translation of this resource would be helpful to fill in this gap for patients whose English is not their first language. Some participants proposed resources for nongenetics physicians who can explain NIPT nuances during the informed consent process. Creatively, one stated that scripts for non-genetic ordering providers and nurses have "helped reduce misinformation and improve patient knowledge of NIPT" and suggested a "standardize version" or "pocket guide." Similarly, while the availability of such resources would not be available as this project's outcome, the survey elicited the need for additional materials and recommendations for non-genetic healthcare providers for future references.

#### **5.3.4** The Creation of the Fact Sheet

Informed by the survey's results and the Internet review of NIPT resources, a factsheet on NIPT with the focus on the possibility of different results was created, targeting pregnant people in both low-risk and high-risk populations. Some fact sheet templates were reviewed on different websites, including Adobe Factsheet Templates, Canva, Clipart, and other formats (such as infographics). The neutral, pastel color tone (light pink, gray, chiffon, olive green, light brown, etc.) and visual aids were considered to aim for audience engagement.

The layout of the factsheet is ultimately created using Pages, a document-editing software. The factsheet's layout was organized anew; the factsheet's length was two-pages, or one front and back page, making it convenient for distribution purposes. The photos were taken from the site Pexels.com, a database where media resources are available for public use. Similarly, the visual aids were utilized from a public database called Clipart, with modifications to demonstrate chromosomal aneuploidies.

In the first page, information was organized into two columns for reading ease. Genetics background was provided for patients to indicate conditions screened for on the test. Additionally, informed by the review of online resources, the section "Why may you want to screen for these conditions?" serves as potential testing rationales for NIPT as a prenatal service. Last but not least, with participants ranking "distinguishing between diagnostic and screening" the most popular content, the section "What is the difference between diagnostic and screening?" was composed, including the disclaimer to emphasize this "probability" aspect of NIPT.

On the second page, the arrows were hand-drawn to build a clear orientation, as well as to provide readers with suggestions in progressing with the factsheet. The second page's first section, "Before testing?", listed potential considerations that a patient may have. This section is inspired by the literature review where NIPT procedural ease can hinder patient from thinking it through prior to testing, and the survey's results of inadequate understanding of NIPT nuances leading to decisional regret (Kater-Kuipers et al., 2020). These bullet points encourage patients to be aware of testing implications, possible outcomes, and the availability to opt out of knowing the baby's sex. Furthermore, with studies and survey results showing the variety and uncertainty of insurance, it is important for patients to know that their policy may not cover NIPT (especially in low-risk situations), so that they can discuss cost and options with their obstetricians or prenatal genetic counselor (Benoy et al., 2021; Crabbe et al., 2019).

Informed by the survey's results, the possibility of different result types is composed. This section, called "What are some possible results you can expect?", consists of negative/positive results, no-call results/quality control issues, inconclusive results, and incidental findings, with scientific information drawn from NIPT studies (Case & Hazel, 2018; Grati et al., 2017; Y. Wang et al., 2014). The detailed inclusion of possible types of results fills in the gap in existing NIPT resources since patient friendly materials on this topic are scarce. This content hopefully will help mitigate patients' psychosocial distress or decisional regret due to a lack of understanding and mental preparation for such information. Awareness of such information will also increase patients' awareness and encourage discussion with healthcare providers during the informed consent process. The statistics of approximately 1:10,000 residual risk of having chromosome conditions following a negative result is cited from laboratories and studies, representative of most commercially available NIPT tests (Stokowski et al., 2015).
Under this section of possible results, the arrow serves as branches analogous to a mindmap model, in which the "possible results" is the central topic, and each type of result is a subtopic radiating out. The purpose of emulating the "Mind-map" model is to engage attention and help organize the content in the readers' minds, since the Mind mapping method has reportedly been shown to enhance integration of education materials (D'Antoni & Zipp, 2006; Erdem, 2017). Each subtopic is then designed to be an individual flowchart, denoting different steps that the patient may encounter and suggestions on what one can do. The individual flowchart is easily visualized based on the corresponding background color specific to a type of result. The cloud-shaped speech boxes serve as in-depth examples associated with specific types of results (namely, placental mosaicism as an example reason for false positives, or maternal genetic differences as an example of incidental findings) (Case & Hazel, 2018; Grati et al., 2014).

Finally, the "Resources" section is created in case the reader is interested in finding out more about NIPT, other prenatal services, genetic counseling, or community support from fellow expecting parents. These resources are cultivated from patient-targeted websites and existing prenatal resources, including factsheets from a hospital system, how to find a genetic counselor, and a forum where people discuss their journey and experience surrounding prenatal testing and other aspects of pregnancy. In the electronic version of this factsheet, one can choose to click on the direct link to reach the websites for convenience.

To ensure that the fact sheet is accessible to patients in terms of health literacy, the creating process of this resource is monitored, assessed, and refined. To avoid barriers in terms of language, the fact sheet is purposefully scarce of technical or medical terminology; if a term is used for scientific purposes, it will be clearly defined. The fact sheet's language is purposefully clear and

concise. Usage of passive voice is designed to be few and far between, with a focus on active voice, emphasis on behavior, and suggestions on actions patients can take.

The readability of the factsheet's text was assessed based on Rapid Assessment of Reading Level in Medicine (REALM). REALM is a diagnostic tool to help determine the reading level of individuals in healthcare settings. Based on REALM's goals, the written materials should aim to be at a 6-8th grade level. This study's fact sheet overall score was 7.7 on the Flesch-Kincaid Grade Level, which means that one should be in 8th grade to understand the materials. This level generally meets REALM's guidelines; it falls into the category of plain English. When each paragraph is individually assessed, the Flesch-Kincaid Grade Level is generally lower, varying from 5.5 to 6.6. This can be explained by the presence of medical terminology (such as "placental mosaicism," "chromosomes," "diagnostic," or "screening"), with which explanation is provided to ensure patient's understanding. Therefore, the factsheet's Flesch-Kincaid Grade level overall should be considered lower or at least equal to 7.7.

# **NIPT & You**

### Non- Invasive Prenatal Testing A Guide for Your

Preparation



### What is NIPT?

Non-invasive Prenatal Testing is a blood test available for pregnancies as early as *10* weeks. The test screens for the most common

chromosomes\* conditions, such as:Down syndrome (trisomy 21)

- Edwards syndrome (trisomy 18)
- Patau Syndrome (trisomy 13)
- Sex chromosome conditions

## Why you may want to screen for these conditions?

Every pregnancy has a chance of *built-in chances* of having chromosome conditions. They usually happen at random. Some risk factors that can increase the chance a baby having chromosome conditions include :

- Age (the chance increases as age increases)
- Ultrasound findings
- Family/Medical history

Q What is the difference between "diagnostic" and "screening?"

Screening test: results tell you whether or not you have *an increased chance*.

**Diagnostic test:** results gives you a definite answer for certain conditions.

NIPT IS A SCREENING TEST.

#### References:

Bianchi, Diana W et al. "Noninvasive Prenatal Testing and Incidental Detection of Occult Maternal Malignancies." JAMA vol. 314.2 (2015): 162-9. doi:10.1001/jama.2015.7120 NSGC Prenatal Special Interest Group. "A Patient's Guide to Understanding Non-Invasive Prenatal Testing." National Society of Genetic Counselors. NSGC, November 2014. Web. April 18, 2022.

Figure 6 Page 1 of the NIPT Fact Sheet: NIPT and You, A Guide for your Preparation

#### \*What are chromosomes?

Our genetic materials (DNA) are packaged into structures called **chromosomes**. Most people are born with **23 pairs = 46** chromosomes (as pictured), including **22 numbered pairs** and **I pair of sex chromosome** (male: **XY**, female: **XX**).

| )) / K2                                     | <b>∥</b> <sub>3</sub> | X 1/5   |  |  |  |  |  |  |
|---|-----------------------|---|--|--|--|--|--|--|
| <b>K</b> <sub>6</sub> <b>X</b> <sub>7</sub> | K 8 K 9 K 10          | <b>∬</b> <sub>11</sub> <b>)</b> <sup>12</sup> |  |  |  |  |  |  |
| <b>II</b> 13 <b>II</b> 14                   | X <sub>15</sub> 7(16  | 11 17 11 <sub>18</sub>                        |  |  |  |  |  |  |
| ۲ <sup>19</sup> ۲۲ <sub>20</sub>            | 1(1) <sub>21</sub>    |   |  |  |  |  |  |  |
| Sex chromosomes                             |                       |   |  |  |  |  |  |  |
| <b>Q</b> )) or                              | o™),                  |   |  |  |  |  |  |  |

Chromosomes conditions happen usually at random. This results in **an unusual number** of chromosomes, which leads to symptoms.



atau syndrome has thre 13rd chromosomes

**?**)

Turner syndrome has **one X** chromosomes. Turner syndrome is an example of a sex chromosome condition.



Figure 7 Page 2 of the NIPT Fact Sheet: NIPT and You, A Guide for your Preparation

#### **5.4 Conclusions**

This study review found that online patient-directed materials on NIPT include varied content. NIPT resources originating from genetic testing labs often emphasized the test's sensitivity and specificity, which may confuse patients in terms of differentiating between diagnostic and screening. Other online resources sometimes contain helpful information in different aspects, including referrals to healthcare providers or genetic counselors. However, testing rationales for patient population, financial/insurance anticipatory guidance, and especially different types of NIPT results are scarce information in existing materials.

This study's survey also found that genetic counselors call for the need of additional patient friendly resources focusing on distinguishing diagnosis and screening and possible types of results (uncertain results, incidental findings, quality control issues). Combining with other content scarcity found\_in the review of online materials, the NIPT factsheet was developed to address these gaps, given the insurance barriers and informed consent challenges currently existing in universal NIPT offering. The fact sheet contains basic genetic backgrounds, NIPT coverage of conditions, and its screening nature on the front side. Action-inspiring information when considering NIPT is located on the backside, including "before testing" consideration, "What are some possible results you can expect," and "Resources" sections. The reading flow of the factsheet was intentionally designed to be a seamless and informative by using arrows as well as color-coded flow charts to guide patients' order of reading. Information was organized into sections separated by color for reading ease; the text's average reading level was assessed to be 7.7 with clear, concise language and usage of active tense. Visuals and pictures were utilized throughout the fact sheet to aid explanation and engage readers' attention.

In the context of increasing implementation of universal NIPT offering, the review of online NIPT resources provides insights on the availability and quality of patient friendly materials, while identifying gaps in information that may be helpful for patients. The production and distribution of this fact sheet aim to educate and guide patients throughout the NIPT consideration process through both the "inform, educate, and empower" and "mobilize partnerships" core functions. To further ensure ethical and equitable implementation according to professional guidelines, other public health initiatives such as advocating for policy changes in terms of insurance coverage will be beneficial as a next step to facilitate equitable testing in the population, especially within the average-risk community. Additionally, research and recommendations on a formal framework for physicians to obtain informed consent are necessary. Such effort is worthwhile to adapt to the "information density" nature within prenatal visits, while ensuring that patients are making informed decisions and physicians not overwhelmed with information to go through.

#### **Appendix A Institutional Review Board Approval**



### EXEMPT DETERMINATION

| Date:    | September 15, 2021   |
|----------|--|
| IRB:     | STUDY21070179  |
| PI:      | Phuc Do  |
| Title:   | Survey of the Genetic Counselor perspectives regarding the 2020 ACOG guideline update recommending the routine offering of NIPT in all pregnancies |
| Funding: | None   |

The Institutional Review Board reviewed and determined the above referenced study meets the regulatory requirements for exempt research under 45 CFR 46.104.

#### **Determination Documentation**

| Determination    | 9/15/2021   |
|------------------|---|
| Date:            |   |
| Exempt Category: | (2)(ii) Tests, surveys, interviews, or observation (low risk), (2)(i) Tests, surveys, interviews, or observation (non-identifiable) |

| Determinations: |   |
|-----------------|---|
| Approved        | <ul> <li>Survey Questions for GC on 2020 ACOG guidelines, Category: Data Collection;</li> <li>Exemption IRB Form, Category: IRB Protocol;</li> <li>Introductory Script for Recruitment Methods, Category: Recruitment</li></ul> |
| Documents:      | Materials;  |

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, Amy Fuhrman.

Please take a moment to complete our <u>Satisfaction Survey</u> as we appreciate your feedback.

#### **Appendix B Survey Introductory/Recruitment Text and Questions**

#### **Appendix B.1 Qualtrics - Introductory/Recruitment Text**

My name is Phuc Do, and I am a second-year graduate student in the genetic counseling program at University of Pittsburgh. This survey is part of the research for my thesis project, in which I want to assess perspectives of prenatal genetic counselors about the current practice of offering Non-invasive Prenatal Testing (NIPT) following the 2020 ACOG guidelines update, which recommends the routine offering of NIPT in all pregnancies. This research project is approved by the University of Pittsburgh IRB.

You are invited to participate in this study through an online survey on the Qualtrics platform. This survey is designed for genetic counselors who are currently practicing in the prenatal clinical setting (part-time or full-time).

Due to the update in the 2020 ACOG guidelines regarding NIPT and the quickly widening use of NIPT, NIPT could soon be routinely offered by obstetricians for all pregnancies, including the low-risk ones. Your responses to this survey will be helpful in better understanding the clinical opinions and needs of prenatal genetic counselors regarding current practice, benefits, challenges and barriers in NIPT counseling, as more institutions/practices adopt the new guidelines as SOPs. I appreciate the forwarding of this survey to any prenatal genetic counselors who are not NSGC members, who fit the above eligibility criteria and interested in participating in this study. We estimate that survey will take about 15 minutes to complete.

There are no foreseeable risks or direct benefits associated to participating in this project, nor will there be any payments for completing the survey. The survey is anonymous. All answers are kept confidential and kept in a password protected document on a password protected computer. Anonymous data may be shared with other investigators and used for future research. Your participation is voluntary and appreciated. **Please follow the link below to access the survey.** If you have any questions or concerns about the survey, please contact me at <u>ptd8@pitt.edu</u> or Andrea Durst (<u>adurst@pitt.edu</u>). I greatly appreciate your participation in this survey and thank you in advance for your time.

Phuc Do

Genetic Counseling Student

University of Pittsburgh Graduate School of Public Health.

#### **Appendix B.2 Survey Questions**

Are you a board certified/board-eligible genetic counselor?

- Yes
- o No

What is your current area of specialization?

- Prenetal Clinical setting
- Prenatal Non-clinical Setting
- o Other

What is your gender identity?

- $\circ$  Woman
- o Man
- o Non-binary
- o Prefer not to state

#### Age

- o <25
- o 25-34
- o 35-44
- o 45-54
- o 55-65
- o >65

How long have you been working as a prenatal genetic counselor?

- $\circ$  <1 year
- o 1-5 years
- $\circ$  5-10 years
- o 10 years or longer

How long have you been working in your current position?

 $\circ$  <1 year

- o 1-5 years
- $\circ$  5-10 years
- o 10 years or longer

What is the average number of new prenatal patients that you see per week?

- o 10-19
- o 19-29
- o 30-39
- o >39

Which option most closely represents the institution in which you currently work?

- o University Medical Center
- Public Hospital or Care Facility
- Public Hospital or Care Facility
- Private Practice of Physicians
- Commercial Genetic Testing Lab
- Private Practice
- Telegenetics Company

In what region do you currently practice?

- o Region I: CT, MA, ME, NH, RI, VT, CN, Maritime
- o Region II: DC, DE, MD, NJ, NY, PA, VA, WV, PR, VI, Quebec Region
- o Region III: AL, FL, GA, KY, LA, MS, NC, SC, TN
- o Region IV: AR, IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, OK, SD, WI, Ontario Region
- o Region V: AZ, CO, MT, NM, TX, UT, WY, Alberta, Manitoba, Sask
- o Region VI: AK, CA, HI, ID, NV, OR, WA, British Columbia

Do you offer NIPT to patients?

- o Yes
- o No

On average, how many times do you order or facilitate the ordering of NIPT each week?

- o 0-5
- o 6-10
- o 11-15
- o 16-20
- o >20

Are you familiar with the 2020 ACOG Guidelines updates recommending the offering of NIPT to all pregnancies?

- o Yes
- I have heard of it
- o No

To what extent has the (stated) 2020 ACOG Guidelines updates regarding NIPT affected your overall practice?

- o A significant extent
- To some extent
- o A minimal extent
- They have not changed my clinical practice

#### To whom do you offer NIPT?

\* For the purpose of this study, "high-risk" is defined as:

- Advanced maternal age (AMA)
- Ultrasound indication/Anomalies
- Previous pregnancy/child with chromosome anomaly
- Increased risk on maternal serum screening (ex: first trimester screen, quad screen, sequential screening)
- High risk patients only

- All patients
- Interested patients
- Other (please explain) (Text):

If you offer NIPT to all patients, what factors listed below influence your decision?

Select all that apply

- Mandated decision from the institution
- To incorporate the 2020 ACOG guidelines into practice
- Professional opinion
- Decision made by GC team/Department
- Other (Text): \_\_\_\_\_

If you only offer NIPT to high risks patients, what factors listed below influence your decision?

Select all that apply

- Mandated decision from the institution
- Decision made by GC team/Department
- Limited insurance coverage/insurance challenges
- Professional opinion
- Other (Text): \_\_\_\_\_

Please indicate how much you agree or disagree with the following statements regarding offering NIPT to all pregnancies after patients receive genetic counseling:

| Statements  | Strongly | Disagree | Neutral | Agree | Strongly |
|---|----------|----------|---------|-------|----------|
|   | disagree |          |         |       | Agree    |
| There is a sufficient number of healthcare        | 0        | 0        | 0       | 0     | 0        |
| providers to adequately inform patients about     |          |          |         |       |          |
| NIPT nuances.                                     |          |          |         |       |          |
| There is a sufficient number of healthcare        | 0        | 0        | 0       | 0     | 0        |
| providers to obtain proper informed consent.      |          |          |         |       |          |
| Patients who may be eligible for/are              | 0        | 0        | 0       | 0     | 0        |
| considering NIPT should be given anticipatory     |          |          |         |       |          |
| guidance regarding the nuances of NIPT,           |          |          |         |       |          |
| including incidental findings, "no-call" results, |          |          |         |       |          |
| or inconclusive results.                          |          |          |         |       |          |
| It is necessary that the patient have a proper    | 0        | 0        | 0       | 0     | 0        |
| understanding of the nuances regarding            |          |          |         |       |          |
| potential NIPT results for the providers to       |          |          |         |       |          |
| achieve informed consent                          |          |          |         |       |          |

Do you think that non-genetics healthcare professionals have enough knowledge to educate patients about the nuances of NIPT?

(including incidental findings, "no-call" results, or inconclusive results)

o Yes

- o Somewhat
- o No
- o I am not sure

Do you think that non-genetics healthcare professionals have enough knowledge to adequately inform patients about NIPT and achieve informed consent?

- o Yes
- o Somewhat
- o No
- o I am not sure

How much have billing considerations influenced which laboratory your institution uses for

#### NIPT?

(for example: if your institution is contracted to use a specific NIPT laboratory)

- It is frequently a consideration
- It is sometimes a consideration
- It is rarely a consideration
- It is never a consideration

To what extent do you feel lack of insurance coverage is a barrier to universal NIPT screening?

- It is frequently a barrier
- It is sometimes a barrier
- It is rarely a barrier
- It is never a barrier

Considering the following scenario: A 24 year-old, G2P1001 patient with negative first-trimester screening (FTS) results and unremarkable anatomy ultrasound is referred for genetic counseling.

Given the low a-priori risk and no other risk factors, do you think an insurance company would cover testing?

o Yes

- o No
- o I am not sure

Considering the following scenario: A 35-year-old, G3P1101 patient with echogenic bowel and short long bones is referred for genetic counseling.

Given multiple risk factors, do you think an insurance company would cover testing?

- o Yes
- o No
- o I am not sure

If insurance does not cover NIPT, how often do you think that the potential out-of-pocket cost

causes patients to decline NIPT?

- o Yes
- o No
- o I am not sure

How often do you encounter unexpected results/findings in NIPT?

(for example: "no-call" results, inconclusive results, or quality control issues)

- $\circ$  >2 per week
- $\circ$  1-2 times per week
- More than once a month but less than once a week
- Once a month
- Less than once a month

From your counseling perspective, how often do you encounter patients who regret their decision to have NIPT?

- o Always
- Frequently
- Sometimes
- o Never

If the patient regrets their decision, which is the most significant/common reason for decision

regret?

- Incidental findings
- Patient thought NIPT was diagnostic
- o "No-call" results / Quality control issues
- Inconclusive results
- Other (Text): \_\_\_\_\_

Please consider the following scenario:

A patient had NIPT ordered through their OB-GYN office and the result was an atypical finding.

The patient has discussed this result with her physician and is now being referred to you for

genetic counseling. Imagine this is the first time you are seeing this patient.

Have you experienced a similar/same situation to the one stated above?

- o Yes
- o No

Given this scenario, how often do patients seem to have a good understanding of the potential results of NIPT?

o Always

- o Frequently
- o Sometimes
- o Never

Given this scenario how often do patient seem to have a good understanding of the limitations of

#### NIPT?

- o Always
- o Frequently
- o Sometimes
- o Never

Given this scenario, how often do you encounter patients with psychosocial distress due to unexpected results from NIPT?

- o Always
- o Frequently
- o Sometimes
- o Never

With the increasing use of NIPT across institutions, to what extent do you think there is a need

for more NIPT resources for patients to have better informed consent?

- There is a strong need for more patient friendly NIPT resources
- There is a moderate need for more patient friendly NIPT resources
- There is little need for more patient friendly NIPT resources
- There is no need for more patient friendly NIPT resources

What content do you think would be the most helpful to patients if new NIPT resources are

created? Select all that apply

- Distinguishing the difference between diagnosis and screening
- Possibility of uncertainty (including "no call" and inconclusive findings)
- Possibility of incidental findings
- Possibility of quality control issues
- Possibility of knowing the baby's sex

What format do you think would be the most helpful and accessible to patients? Select all that

apply

- Brochure
- Presentation
- Fact Sheet
- Website
- Video
- Other (Text): \_\_\_\_\_

Do you have any other suggestions for NIPT resource content or resource format?

(Text): \_\_\_\_\_

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