NIPT – Emerging Issues:
Genetic Counselors' Experiences & Perspectives with Incidental Findings

Master’s Thesis

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The Faculty of the Graduate School of Arts and Sciences
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Judith E. Tsipis, Ph.D., Advisor

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Master of Science
in
Genetic Counseling

by
Alicia S. Orta

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Thank you very much Judy Jackson and Emily Lazar for your help with my research topic development and for reviewing my survey.

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To my classmates—thank you for providing opportunities for growth and reflection.

To my friends—thank you for providing laughter and inspiration.

To my family—thank you for providing the gift of reflection.

To Matthew, the love of my life. Thank you so much. Your name should be [a footnote] on this document, as well as on my degree.
ABSTRACT

NIPT – Emerging Issues:
Genetic Counselors' Experiences & Perspectives with Incidental Findings

A thesis presented to the Graduate Program in Genetic Counseling

Graduate School of Arts and Sciences
Brandeis University
Waltham, Massachusetts

By Alicia S. Orta, M.P.H.

Since companies began marketing the analysis of cell-free DNA in the maternal plasma as non-invasive prenatal testing (NIPT) to screen for fetal aneuploidy and other conditions, healthcare providers and patients alike have encountered discordant invasive and non-invasive testing results, with unexpected incidental findings as a rare cause. The purpose of this study was to investigate prenatal genetic counselors’ practices and perspectives regarding counseling patients for the possibility of incidental findings identified through NIPT. We emailed a 58-question anonymous survey to the NSGC membership to recruit clinical prenatal genetic counselors that offer NIPT. Of the 147 survey respondents, 74% obtain informed consent for NIPT verbally and over half (54%) do not involve the patient in the documentation of informed consent, as the provider is responsible for documenting the patient’s consent. More than half (57%) do not always include the possibility of incidental findings in their pre-test counseling.
discussions. Yet, 47% of the genetic counselor respondents have had a suspected or confirmed incidental finding identified through NIPT. Almost all respondents indicated that post-test counseling a patient with an incidental finding is challenging, citing a lack of information and variation among NIPT laboratories with how they communicate incidental findings and a lack of clinical guidelines from professional societies as the most important factors. From counselors’ responses, unknown maternal conditions account for a large proportion of the incidental findings identified by NIPT. Given these findings we recommend that pre-test counseling for NIPT include a discussion of possible unexpected findings and to establish clear expectations for the categories of results that may be returned, the creation of professional guidelines outlining how incidental findings should be discussed in both pre- and post-test counseling discussions, and the creation of a centralized database for the collection of findings, outcomes, and clinical follow-up to facilitate appropriate care for patients.

**Keywords:** non-invasive prenatal screening, cell-free DNA screening, genetic counseling, prenatal testing, pre-test counseling, post-test counseling, informed consent, incidental finding
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INTRODUCTION

Lo et al.’s (1997) discovery of cell-free DNA (cfDNA) fragments representing the fetus in maternal plasma has led to ever expanding possibilities for prenatal disease identification non-invasively and has now changed the clinical paradigm of prenatal screening for aneuploidy (ACOG, 2015; Warsof, Larion, & Abuhamad, 2015). Most cfDNA in maternal circulation derives from the mother’s blood cells, with an average of 10% to 15% of the total cfDNA in maternal blood originating from the feto-placental circulation (Chiu et al., 2011; Palomaki et al., 2011). Studies have reported that the fetal component of cfDNA is released into maternal circulation primarily from apoptotic placental cells (Hahn, Huppertz, & Holzgreve, 2005) and increases proportionately as the pregnancy progresses. Screening with fetal cfDNA, also know as non-invasive prenatal testing (NIPT), is available from week 10 of gestation until term, thus women are able to obtain a risk assessment earlier in pregnancy than by traditional serum analyte screening, which have a more limited time during specific stages in pregnancy when they can be performed. Even with its apparent advantages, researchers and professional organizations have identified several limitations of NIPT and recommend that it should be offered in conjunction with other forms of screening, like ultrasonography and/or MSAFP screening, both with uniquely beneficial test characteristics (ACOG, 2016; Gil, Quezada, Revello, Akolekar, & Nicolaides, 2015).
METHODOLOGIES OF cfDNA TESTING

Laboratories performing NIPT to detect the presence of fetal aneuploidies from maternal blood samples vary in their clinical testing methods (Bianchi et al., 2012; Chiu et al., 2011; Jensen et al., 2013; Nicolaides, Syngelaki, Gil, Atanasova, & Markova, 2013; Norton et al., 2012; Palomaki et al., 2011; Zimmermann et al., 2012). The two most widely used methods are massively parallel shotgun sequencing (MPSS) and more targeted methods such as chromosome-selective sequence analysis (CSS) or single nucleotide polymorphism (SNP)-based analysis. Researchers use CSS or SNP-based methods to select the chromosomes of interest and measure their fetal fraction before sequence analysis, while they use MPSS to randomly sequence the entire cfDNA sample, thereby capturing sequence information from a broader sample of the genome. As a result, MPSS can identify not only the major trisomies but other chromosomal abnormalities as well (Jani, Rego de Sousa, & Benachi, 2015).

When Sequenom first launched NIPT in 2011, they primarily provided information on trisomy 21 and, within three years, began screening for trisomy 13 and trisomy 18, as well as X- and Y-chromosome aneuploidies (with fetal sex identification as a derivative) (Palomaki et al., 2012). By 2014, laboratories began to expand their NIPT panels to include screening for specific microdeletion and microduplication syndromes and other chromosomal aneuploidies. In August 2015, Sequenom launched MaterniT GENOME, an expanded screen designed to scan the entire genome for copy number alterations greater than or equal to 7 MB (Sequenom, 2015).

While researchers have reported NIPT as having a higher detection rate and a lower false positive rate compared to traditional screening methods that utilize maternal age, ultrasound, and serum analytes (Gil et al., 2015; Palomaki et al., 2011; Zimmermann et al., 2012), professional
societies stress that NIPT is not a diagnostic test. They cite that the positive predictive value (PPV) of the test, a number unique to each patient, will vary depending on a number of factors like age, the particular condition in question, the gestation at which the screen was performed, and whether or not there are any ultrasound anomalies that suggest there may be a genetic or chromosomal condition. Another concern is that even when a test is accurate, the more rare the condition, the higher the percentage of false positive results. Similarly, as the number of conditions assessed by a test increases, the false-positive rate will also increase. They also acknowledge that counseling will prove challenging when testing for conditions with unclear clinical relevance or which are so rare that the PPV of the test is low.

As with traditional prenatal screens, professional guidelines advise that a positive NIPT result be confirmed with a diagnostic test, either amniocentesis or chorionic villus sampling (ACOG, 2015; Benn et al., 2015; Devers et al., 2013; Gregg et al., 2013). If NIPT is not able to yield a result (an indeterminate or “no-call” result), this slightly increases the risk for chromosomal abnormalities; further counseling, comprehensive fetal ultrasound assessment and the option of diagnostic testing for the fetus are suggested whenever there is a “no call” result (ACOG, 2015).

INCIDENTAL FINDINGS

Occasionally, laboratories detect aneuploidies in the sample that may not be representative of the fetus. Studies show that such false positive findings occur in approximately 1% of test results (Bianchi et al., 2012; Grati et al., 2015; Nicolaides et al., 2013; Norton et al., 2012), with most due to confined placental mosaicism (CPM). Additionally, NIPT may raise suspicion for maternal or fetal conditions other than the fetal aneuploidies for which the test is being performed (Bianchi, 2015a). Researchers have published biological explanations for many of the
discrepancies between NIPT results and diagnostic testing or neonatal outcomes, including: cotwin demise (Curnow et al., 2015; Futch et al., 2013); fetal, placental or maternal mosaicism (Flowers, Kelley, Sigurjonsson, Bruno, & Pertile, 2015; Grati et al., 2014; Lau et al., 2013); unrecognized maternal conditions, including maternal copy number variants (Snyder et al., 2015), undetected maternal malignancies (Bianchi et al., 2015b; Osborne et al., 2013) and maternal sex chromosome aneuploidies (Lau et al., 2013; Wang et al., 2014; Yao et al., 2012). Wang et al. (2014) found that 8.6% of positive NIPT results for sex chromosome aneuploidy were attributable to the maternal karyotype. Recently, Snyder, Curnow, Bhatt, and Bianchi (2016) published clinical outcomes for 79 cases where NIPT reported either a monosomy, a trisomy with a sex chromosome aneuploidy, or multiple aneuploidies, to assist healthcare providers with post-test counseling and management. Out of 79 cases, 9% had a maternal etiology for the abnormal NIPT results, and 53% were discordant with the fetal karyotype and remain unexplained (Snyder et al., 2016). NIPT is not clinically validated to screen for these or other maternal or fetal conditions, and cfDNA screening results cannot be interpreted to preclude them. NIPT laboratories differ with regard to if and how they communicate this type of incidental information to providers. The recent literature suggests a need for considerable caution in interpreting NIPT results because of false positive rates that are higher than previously reported when compared with invasive testing (Cheung, Patel, & Leung, 2015). Sahoo, Strecker, and Commander (2016) reaffirmed such caution upon finding that the false positive rates were uniformly high for the common microdeletions providers tested for using expanded versions of NIPT. Emerging issues related to the detection of maternal findings such as sex chromosome abnormalities,
microdeletions, and malignancies following unusual NIPT results raise complex concerns about informed consent, the duty to inform, and the lack of validation of the tests for maternal findings.

PRE-TEST COUNSELING PRACTICES

Commercialization has driven rapid global dissemination of NIPT (Minear, Lewis, Pradhan, & Chandrasekharan, 2015) and recent advances in this technology have expanded and improved genetic testing options available to women during pregnancy. In providing a wide variety of screening test options, each offering varying levels of information and accuracy, healthcare providers become even more essential in counseling patients as they make very complex decisions. One study proposed general approaches to pre-test counseling and obtaining informed consent for NIPT (Buchanan, Sachs, Toler, & Tsipis, 2014), and Sachs, Blanchard, Buchanan, and Bianchi (2015) published recommendations for genetic counselors regarding pre-test counseling to aid in the informed consent process with patients who are considering NIPT. Comprehensive pre-test counseling is complicated by the continuous emergence of new information about the benefits and limitations of testing, as well as the potential for incidental findings from NIPT.

RESEARCH STUDY GOALS

The purpose of this study was to investigate genetic counselors’ practices and perspectives with counseling patients for incidental findings identified through NIPT. We hoped to highlight challenges that the prenatal field can focus on overcoming as well as ideas that the field can build on. The goals of this study were to: (1) identify the current pre-test counseling practices for NIPT, including methods for obtaining informed consent; (2) learn about genetic counselors’ personal experiences with incidental findings identified by NIPT; and (3) delineate the challenges that counselors face when discussing the possibility of incidental findings with patients.
METHODS

STUDY DESIGN

This cross-sectional study anonymously surveyed clinical genetic counselors practicing in a prenatal setting who are members of the National Society of Genetic Counselors (NSGC) through the use of an online survey tool, Qualtrics®. The Brandeis University Institutional Review Board Committee for Protection of Human Subjects deemed the (IRB Protocol #16022) protocol to be exempt from IRB oversight, effective September 4, 2015.

PARTICIPANTS AND RECRUITMENT

We selected clinical genetic counselors practicing in a prenatal setting who are members of NSGC and subscribe to its listserv as the sampling population, and limited the inclusion criteria to prenatal genetic counselors who are currently providing NIPT to patients either in person, over the phone, or online. We did not exclude based on age, gender, geographic location, or other demographic characteristics. The e-blast recruitment notice (See Appendix A: Recruitment Notification) sought prenatal genetic counselors practicing in a clinical setting.

PROCEDURES

We sent the survey to NSGC members via an e-blast to its listserv that was available for data collection from September 11 through October 14, 2015, with an email reminder sent two weeks
after the initial invitation to participate. Participation in this study was voluntary and those that participated were free to withdraw at any time. Likewise, since all survey questions were voluntary, we anticipated a fluctuation in question-specific response rate.

Prior to beginning the survey, we provided participants with a series of definitions. We defined an **incidental finding** as “an unexpected finding of a maternal or fetal condition other than the typically screened for conditions specifically targeted by NIPT. These unanticipated ‘secondary findings’ may include: unrecognized maternal conditions, co-twin demise, and fetal or placental chromosome differences, among others.” We defined a **no-call NIPT result** as “a failure to receive an interpretable result from cell-free DNA testing. Depending on the NIPT laboratory, the “non-reportable” result may be due to insufficient sample, low feto-placental DNA fraction, or because the interpretation falls into an indeterminate range.” We defined a **positive NIPT result** as “a result that suggests a pregnancy is at risk of having a condition that is among the typically screened for conditions specifically targeted by NIPT. The result may be reported as ‘aneuploidy detected’ or ‘high risk’ and does not include ‘no-call’ NIPT results.”

The survey consisted of several exclusion/inclusion criteria questions followed by questions inquiring into genetic counselor (1) perspectives and practices regarding pre-test counseling (20 items); (2) personal experiences with incidental findings revealed by NIPT (11 items); and (3) experienced challenges, or their perceptions of the challenges, associated with counseling for an incidental finding (5 items). We included an open-ended question to ask about the desirability of national guidelines for clinical follow-up and evaluation for incidental findings from NIPT. We collected professional demographic information and NIPT utilization characteristics (12 items). We used a four-point Likert-type scale to rate (1) the level of
agreement of a statement assessing whether counseling about an incidental finding identified through NIPT is challenging, and (2) the level of importance of thirteen items assessing potentially challenging factors. We presented seven items that provided “yes,” “no,” and “don’t know” options; and thirteen items that used pre-given categorical response options without restriction (e.g., Select all that apply). Lastly, we included a space for comments on each page of items. See Appendix B (Instrument) for a complete list of survey questions.

DATA ANALYSIS

We analyzed survey response data with SPSS statistical software and Microsoft Excel. We used descriptive statistics to summarize responses to each survey item. To facilitate analysis and interpretation, we collapsed response categories for Likert-scale-type items to construct an “important” category combining both “extremely important” and “important” and a corresponding “not important” category. To assess response bias, we performed a bivariate comparison of our respondents’ demographic data to reported estimates of demographic characteristics from the 2014 study conducted among the NSGC membership to determine generalizability. We performed further bivariate analyses using independent sample t-tests, chi-square ($\chi^2$) tests of independence, and cross-tabulations. We set statistical significance at $p = .05$. We manually analyzed responses to open-ended questions using an inductive approach to identify themes in opinions about recommendations for follow-up clinical evaluation approaches to incidental findings identified by NIPT.
RESULTS

The results of the survey are organized into four parts: (1) demographics and NIPT utilization, (2) obtaining informed consent for NIPT and counseling practices, (3) genetic counselors’ experiences with NIPT results, and (4) counseling challenges with incidental findings by NIPT.

DEMOGRAPHICS & NIPT UTILIZATION

Of the 210 responses, we removed 63 from our analysis because they did not meet the inclusion criteria or failed to complete the majority of the survey items. Considering only those who met the inclusion criteria, 147 prenatal genetic counselors completed the majority of the survey questions. All $N$ values in this paper will be reflective of 147 participants, unless otherwise stated. The 147 respondents represent a response rate of 12-15% based on the number of prenatal counselors listed in the 2014 NSGC Professional Status Survey (PSS) (NSGC, 2014).

Respondents were from all six NSGC regions with a slightly higher representation from Regions 2 (19%), 4 (25%), and 6 (20%), than other Regions. The majority of respondents are employed in a private, public, or university hospital setting (80.8%, 118/146), with an average of four prenatal genetic counselors per setting. The years of total genetic counseling experience and years of experience in a prenatal genetic counseling setting ranged from 1 to 33 ($M = 8.6$) and from 1 to 31 ($M = 7.9$), respectively. (see Table 1).
Almost 85% of respondents spend greater than 50% of their counseling time with prenatal patients and most counsel patients in-person and/or over the telephone (82%). Three quarters \((N=145)\) of respondents provide pre-test counseling and/or order NIPT for between 5 and 24 patients per week (see Figure 1). The two most frequently used NIPT companies are Natera, which offers Panorama™ NIPT (51%), and Sequenom Laboratories, which offers VisibiliT™ (15.6%), MaterniT21® PLUS (61.2%), and MaterniT™ GENOME (10.2%), an expanded cfDNA panel that scans the entire genome for microdeletions or duplications greater than or equal to 7 MB. Most respondents (73%) reported using two or more different companies to provide NIPT to patients. (see Table 2).

**Figure 1:** Counselors’ Pre-Test Counseling Sessions and NIPT Orders per week

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Pre-test counseling</th>
<th>Order NIPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>18% ((n=26))</td>
<td>34% ((n=49))</td>
</tr>
<tr>
<td>5-9</td>
<td>28% ((n=40))</td>
<td>38% ((n=55))</td>
</tr>
<tr>
<td>10-14</td>
<td>21% ((n=31))</td>
<td>33% ((n=48))</td>
</tr>
<tr>
<td>15-19</td>
<td>12% ((n=18))</td>
<td>3% ((n=5))</td>
</tr>
<tr>
<td>20-24</td>
<td>7% ((n=10))</td>
<td>3% ((n=4))</td>
</tr>
<tr>
<td>25+</td>
<td>2% ((n=3))</td>
<td>1% ((n=1))</td>
</tr>
<tr>
<td>Table 1</td>
<td>Participant Demographics</td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$n$</td>
<td>%</td>
</tr>
<tr>
<td>Time Spent Counseling Prenatal Patients</td>
<td>147</td>
<td>100</td>
</tr>
<tr>
<td>$&lt; 25%$</td>
<td>13</td>
<td>8.8</td>
</tr>
<tr>
<td>$25–50%$</td>
<td>10</td>
<td>6.8</td>
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<tr>
<td>$51–74%$</td>
<td>18</td>
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</tr>
<tr>
<td>$76–100%$</td>
<td>106</td>
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<tr>
<td>Total Years of Genetic Counseling Experience</td>
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<td>100</td>
</tr>
<tr>
<td>$\leq 5$</td>
<td>77</td>
<td>53.1</td>
</tr>
<tr>
<td>$6–10$</td>
<td>21</td>
<td>14.5</td>
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<td>$11–15$</td>
<td>17</td>
<td>11.7</td>
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<tr>
<td>$16–20$</td>
<td>12</td>
<td>8.3</td>
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<tr>
<td>$21–25$</td>
<td>8</td>
<td>5.5</td>
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<tr>
<td>$26–30$</td>
<td>9</td>
<td>6.2</td>
</tr>
<tr>
<td>$&gt; 30$</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Years as a Prenatal Genetic Counselor</td>
<td>145</td>
<td>100</td>
</tr>
<tr>
<td>$\leq 5$</td>
<td>83</td>
<td>57.2</td>
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<tr>
<td>$6–10$</td>
<td>19</td>
<td>13.1</td>
</tr>
<tr>
<td>$11–15$</td>
<td>17</td>
<td>11.7</td>
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<td>11</td>
<td>7.6</td>
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<td>$21–25$</td>
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<td>6.9</td>
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<tr>
<td>$26–30$</td>
<td>4</td>
<td>2.8</td>
</tr>
<tr>
<td>$&gt; 30$</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Counseling Modalities</td>
<td>147</td>
<td>100</td>
</tr>
<tr>
<td>In-person + Telephone</td>
<td>121</td>
<td>82.3</td>
</tr>
<tr>
<td>Telegenetics + In-person + Telephone</td>
<td>26</td>
<td>17.7</td>
</tr>
<tr>
<td>Primary Work Setting</td>
<td>146</td>
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</tr>
<tr>
<td>Community Hospital</td>
<td>17</td>
<td>11.6</td>
</tr>
<tr>
<td>Government Organization/Medical Facility</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Health Maintenance Organization (HMO)</td>
<td>3</td>
<td>2.1</td>
</tr>
<tr>
<td>Laboratory/Industry</td>
<td>3</td>
<td>2.1</td>
</tr>
<tr>
<td>Outreach/Satellite/Field Clinic</td>
<td>2</td>
<td>1.4</td>
</tr>
<tr>
<td>Private Clinic/Practice</td>
<td>27</td>
<td>18.5</td>
</tr>
<tr>
<td>Private Hospital/Medical Facility</td>
<td>31</td>
<td>21.2</td>
</tr>
<tr>
<td>Region of Practice</td>
<td>147</td>
<td>100</td>
</tr>
<tr>
<td>Region 1 (CT, MA, ME, NH, RI, VT, Canadian Maritime Provinces)</td>
<td>17</td>
<td>11.6</td>
</tr>
<tr>
<td>Region 2 (DC, DE, MD, NJ, NY, PA, VA, WV, Quebec, PR, VI)</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Region 3 (AL, FL, GA, KY, LA, MS, NC, SC, TN)</td>
<td>18</td>
<td>12.2</td>
</tr>
<tr>
<td>Region 4 (AR, IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, OK, SD, WI, Ontario)</td>
<td>37</td>
<td>25.2</td>
</tr>
<tr>
<td>Region 5 (AZ, CO, MT, NM, TX, UT, WY, Alberta, Manitoba, Saskatchewan)</td>
<td>18</td>
<td>12.2</td>
</tr>
<tr>
<td>Region 6 (AK, CA, HI, ID, NV, OR, WA, British Columbia)</td>
<td>29</td>
<td>19.7</td>
</tr>
</tbody>
</table>
Table 2  NIPT Utilization

<table>
<thead>
<tr>
<th>NIPT Companies and Tests</th>
<th>n</th>
<th>%</th>
<th>M</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ariosa Diagnostics (Harmony™)</td>
<td>62</td>
<td>42.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Counsyl (Informed Pregnancy Screen)</td>
<td>36</td>
<td>24.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Integrated Genetics-LabCorp (informaSeq&lt;sup&gt;SM&lt;/sup&gt;)</td>
<td>33</td>
<td>22.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natera (Panorama™)</td>
<td>75</td>
<td>51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perkin Elmer (verifi&lt;sup&gt;®&lt;/sup&gt; from PerkinElmer Labs)</td>
<td>4</td>
<td>2.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progenity (Verifi by Progenity)</td>
<td>25</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quest (QNatal™ Advanced)</td>
<td>16</td>
<td>10.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recombine (ChromoMap)</td>
<td>1</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequenom Laboratories (MaterniT™ GENOME)</td>
<td>15</td>
<td>10.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequenom Laboratories (MaterniT21&lt;sup&gt;®&lt;/sup&gt; PLUS)</td>
<td>90</td>
<td>61.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequenom Laboratories (VisibiliT™)</td>
<td>23</td>
<td>15.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verinata Health - Illumina (verifi™)</td>
<td>10</td>
<td>6.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of Companies utilized to provide NIPT to patients</th>
<th>147</th>
<th>100</th>
<th>2.41</th>
<th>1.36</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>7</td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td>8</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6+</td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OBTAINING INFORMED CONSENT for NIPT & COUNSELING PRACTICES

Over two-thirds of respondents (81%) reported using resources during their pre-test counseling session, with 60% (n=88) using two or more types of resources to inform patients about NIPT. The two most commonly used resources are those created by the NIPT company (46%) and/or published genetic counseling visual aids (43%). (see Figure 2)
A majority of counselors reported obtaining consent for NIPT verbally (74%) and/or by using a form documenting patient consent for NIPT that only the healthcare provider signs (54%). The two least common methods for obtaining informed consent include having the patient sign an informed consent form specifically for NIPT (16%) and having the patient sign a requisition form provided by the NIPT lab company (3%). Two respondents do not routinely obtain informed consent for NIPT (see Figure 3).
Half of the respondents (56.5%, n=83) indicated that they do not always include the possibility of incidental findings in their pre-test counseling discussion of NIPT. The top three reasons for not including incidental findings in pre-test counseling were that the test is not designed nor validated for the detection of incidental findings (65%, n=54), the inclusion of incidental findings complicate the discussion (50%, n=41), and incidental findings are too rare to mention (46%, n=38). However, many respondents would always include the possibility of incidental findings in their pre-test counseling discussion with a patient under certain circumstances, such as a personal or family history of chromosome abnormalities (64% and 44%, respectively), a personal history of recurrent miscarriages (38%) and other individual indications (38%). Other reasons for discussing incidental findings in pre-test counseling were when ordering an expanded NIPT that screens for microdeletions or microduplications, the presence of an ultrasound finding (e.g.,
vanishing twin, heart defect), and if the patient had a history of uterine fibroids, organ transplant, or a previous or current cancer diagnosis. (see Figure 4).

**Figure 4: Indications for Pre-test Counseling for Incidental Findings**

* Individual indications: ordering an expanded NIPT panel, an ultrasound finding (e.g., vanishing twin, heart defect), and a history of uterine fibroids, organ transplant, or a cancer diagnosis.

By contrast, almost all respondents indicated that post-test counseling was necessary whenever an incidental finding was suspected by the NIPT laboratory. Almost 75% of counselors felt that post-test counseling was indicated whenever NIPT identified a sex chromosome aneuploidy (73%), or multiple aneuploidies (74%) (see Figure 5).
Figure 5: NIPT Results that Indicate Post-test Counseling for Incidental Findings

When asked about the frequency with which they had personally counseled patients with a positive NIPT result, all but two respondents had counseled a patient with a positive NIPT result with a range of 1 to more than 15 (see Figure 6).

Figure 6: Counselors’ Experience with Positive NIPT Results
Over 75% of respondents had counseled at least one patient with a positive NIPT result that diagnostic testing or neonatal outcome later found to be discordant. The most commonly seen discordant NIPT results were for sex chromosome aneuploidies, microdeletions, and trisomy 13. Approximately 76% of respondents had counseled one or more patients with a no-call NIPT result after repeat screening, while 47% of respondents had counseled a patient where the NIPT laboratory suspected a possible incidental finding. Nearly 30% of respondents had counseled one or more patients with a confirmed incidental finding identified through NIPT (see Table 3).

Table 3 Genetic Counselors’ Experiences with Various NIPT Results

<table>
<thead>
<tr>
<th>No. of Patients Counseled</th>
<th>Discordant NIPT Result</th>
<th>No-call NIPT Result</th>
<th>Suspected Incidental Finding&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Confirmed Incidental Finding&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>None</td>
<td>31</td>
<td>21.4%</td>
<td>35</td>
<td>23.8%</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>9.7%</td>
<td>32</td>
<td>21.8%</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>11%</td>
<td>21</td>
<td>14.3%</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>17.9%</td>
<td>11</td>
<td>7.5%</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>4.1%</td>
<td>7</td>
<td>4.8%</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>9%</td>
<td>7</td>
<td>4.8%</td>
</tr>
<tr>
<td>More than 5</td>
<td>15</td>
<td>10.3%</td>
<td>24</td>
<td>16.3%</td>
</tr>
<tr>
<td>Don’t know but at least 1</td>
<td>24</td>
<td>16.6%</td>
<td>10</td>
<td>6.8%</td>
</tr>
<tr>
<td>Total</td>
<td>145</td>
<td>100%</td>
<td>147</td>
<td>100%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Pearson χ²<sup>2</sup> (1) = 6.087, p = .019;  <sup>b</sup>Pearson χ²<sup>2</sup> (1) = 10.298, p = .002

Note: Crosstabulation of whether pre-test counseling includes incidental findings versus counselor experience with incidental findings; Chi-square test significant at p < .05.

Counselors reported encountering a total of 107 cases of incidental findings identified through NIPT, 24 of which were cases of maternal sex chromosome aneuploidy, 24 were co-twin demise, 19 were confined placental mosaicism, 14 were maternal copy number variation, 8 were fetal or placental mosaicism, 5 were maternal mosaicism, 3 were maternal cancer, and 2 were maternal uterine leiomyoma. Additionally, 8 were other types of incidental findings identified
through NIPT, including consanguinity, a balanced translocation, and a case of uniparental disomy, among others (see Figure 7).

**Figure 7**: Total Reported Incidental Findings identified through NIPT

<table>
<thead>
<tr>
<th>Incident Findings</th>
<th>Percentage</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-twin demise/vanishing twin</td>
<td>44%</td>
<td>24</td>
</tr>
<tr>
<td>Maternal sex chromosome aneuploidy</td>
<td>44%</td>
<td>24</td>
</tr>
<tr>
<td>Confined placental mosaicism</td>
<td>35%</td>
<td>19</td>
</tr>
<tr>
<td>Maternal copy number variation</td>
<td>25%</td>
<td>14</td>
</tr>
<tr>
<td>Fetal or placental mosaicism</td>
<td>15%</td>
<td>8</td>
</tr>
<tr>
<td>Maternal mosaicism</td>
<td>9%</td>
<td>5</td>
</tr>
<tr>
<td>Maternal cancer</td>
<td>6%</td>
<td>3</td>
</tr>
<tr>
<td>Maternal uterine leiomyoma</td>
<td>4%</td>
<td>2</td>
</tr>
<tr>
<td>Maternal sex chromosome aneuploidy</td>
<td>44%</td>
<td>24</td>
</tr>
<tr>
<td>Maternal copy number variation</td>
<td>25%</td>
<td>14</td>
</tr>
<tr>
<td>Fetal or placental mosaicism</td>
<td>15%</td>
<td>8</td>
</tr>
<tr>
<td>Maternal mosaicism</td>
<td>9%</td>
<td>5</td>
</tr>
<tr>
<td>Maternal cancer</td>
<td>6%</td>
<td>3</td>
</tr>
<tr>
<td>Maternal uterine leiomyoma</td>
<td>4%</td>
<td>2</td>
</tr>
</tbody>
</table>

* Including consanguinity, a balanced translocation, and a case of uniparental disomy, among others.

Of the 55 counselors who reported encountering incidental findings through NIPT in their practice, 44 respondents reported experience with cases of incidental findings that were confirmed by follow-up testing, and 11 respondents reported experience with incidental findings originally suspected by the NIPT laboratory, but that were not confirmed with follow-up diagnostic testing or a neonatal outcome (see Figure 8). Below is a respondent’s experience of how the NIPT laboratory suspected an incidental finding:

“Lab director called to let me know that data indicated a z-score suggestive of monosomy 18. Patient had amniocentesis with microarray, which identified a long stretch of homozygosity along chromosome 18. No ultrasound findings and patient declined to schedule a genetics eval [sic] post delivery”
Additionally, 24 respondents included case descriptions and follow-up testing information that were offered and/or ordered to investigate the finding from NIPT. Six counselors reported that NIPT detected a case of maternal 22q deletion syndrome as the incidental finding, almost half of the total cases of maternal copy number variation reported. Three counselors reported discordance of fetal sex between the NIPT result and ultrasound with different outcomes:

“I have had incorrect gender due to demise of a co-twin”

“There was one congenital adrenal hyperplasia we detected (u/s sex was male while NIPT said female)”

“NIPT positive for Turner syndrome - normal male genitalia on ultrasound, fetal karyotype from amniocentesis 45,X/46,XY fetal mosaicism, pregnancy terminated”

Two respondents noted a cancer diagnosis in the mother as cause for abnormal NIPT results:

“one known breast cancer and NIPT was performed after diagnosis that was positive”
“one lymphoma diagnosed after NIPT was positive for trisomy 13 and monosomy 18”

COUNSELING CHALLENGES WITH INCIDENTAL FINDINGS BY NIPT

When asked if counseling a patient with an incidental finding identified through NIPT is challenging on a four-point scale from “strongly disagree” to “strongly agree,” 94% of respondents who had encountered a suspected or confirmed incidental finding (n=126) either agreed or strongly agreed that it was challenging. Of the genetic counselors who had not experienced counseling a patient with an incidental finding identified through NIPT (n=21), 90.5% either agreed or strongly agreed that it would be challenging. (see Figure 9).

Figure 9: Counseling about an Incidental Finding is Challenging

When asked to rate the importance of factors contributing to the challenge of counseling for a suspected or confirmed incidental finding, the three most important factors selected were: a lack of information on incidental findings from the NIPT laboratory, variation among NIPT
laboratories with how they communicate incidental findings and follow-up, and a lack of clinical guidelines from professional societies. The three factors rated as having the lowest importance were: a lack of institutional guidelines on clinical management of incidental findings, limited time during genetic counseling sessions, and a lack of personal experience in counseling for incidental findings (see Figure 10).

**Figure 10:** Factors Impacting Counseling about Incidental Findings

<table>
<thead>
<tr>
<th>Factor</th>
<th>Frequency</th>
<th>M</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of information on incidental findings from NIPT laboratory</td>
<td>7%</td>
<td>3.43</td>
<td>93%</td>
</tr>
<tr>
<td>Variation among NIPT laboratories with communication of incidental findings and follow-up</td>
<td>11%</td>
<td>3.35</td>
<td>89%</td>
</tr>
<tr>
<td>Lack of clinical guidelines from professional societies</td>
<td>15%</td>
<td>3.29</td>
<td>85%</td>
</tr>
<tr>
<td>Lack of resources to provide the patient about the incidental finding</td>
<td>19%</td>
<td>3.13</td>
<td>81%</td>
</tr>
<tr>
<td>Lack of a centralized database to catalogue incidental findings by NIPT</td>
<td>21%</td>
<td>3.10</td>
<td>79%</td>
</tr>
<tr>
<td>Counseling the patient through an interpreter/language barrier</td>
<td>25%</td>
<td>3.06</td>
<td>75%</td>
</tr>
<tr>
<td>Patient not provided pre-test counseling about possible incidental findings</td>
<td>27%</td>
<td>2.99</td>
<td>73%</td>
</tr>
<tr>
<td>The rarity of incidental findings identified by NIPT</td>
<td>21%</td>
<td>2.91</td>
<td>79%</td>
</tr>
<tr>
<td>Lack of support services from NIPT laboratory</td>
<td>30%</td>
<td>2.89</td>
<td>70%</td>
</tr>
<tr>
<td>Limited time for incidental finding interpretation in the prenatal setting</td>
<td>28%</td>
<td>2.89</td>
<td>72%</td>
</tr>
<tr>
<td>Lack of institutional guidelines on clinical management of incidental findings</td>
<td>41%</td>
<td>2.73</td>
<td>59%</td>
</tr>
<tr>
<td>Limited time during genetic counseling session</td>
<td>42%</td>
<td>2.71</td>
<td>58%</td>
</tr>
<tr>
<td>Lack of personal experience counseling for incidental findings</td>
<td>44%</td>
<td>2.64</td>
<td>56%</td>
</tr>
</tbody>
</table>

**GENETIC COUNSELORS’ RECOMMENDATIONS FOR FUTURE GUIDELINES**

Participants were encouraged to share their recommendations for a hypothetical committee writing national guidelines for follow-up clinical evaluation for incidental findings identified through NIPT. Seventy-four counselors provided written responses.
Some respondents \((n=23)\) expressed support for discussing the possibility of incidental findings in pre-test counseling and during the informed consent process and many \((n=12)\) recommended providing patients the choice of either an opt-in or opt-out provision. Others expressed that they had considered having a discussion with patients about the possibility of incidental findings but struggled with when the appropriate time to do so is or if it is even a necessary discussion.

> “The discussion of incidental findings has to be a part of the consent process. Patient should be able to opt in or out on the consent. All patients should be scheduled for genetic counseling when found.”

> “Risk of identifying incidental findings must be disclosed prior to testing and included on consent form”

Counselors \((n=35)\) also recommended that any patient receiving an unusual result or finding meet with a genetic counselor for post-test counseling regarding the possibility of incidental findings, in addition to appropriate follow-up clinical evaluation and testing options for both the fetus and mother.

> “Consider creating an algorithm for how to clinically follow-up incidental findings (e.g. what is the next best test to confirm the finding)”

Another group of counselors \((n=28)\) emphasized the need for a standard system for reporting results that all NIPT laboratories should be required to adhere to, with many recommending a national centralized database for collection of findings and follow-up outcomes.

> “ALL labs adhere to same system of reporting/which findings they report; there should be adequate pretest counseling based on these standards”

> “Centralized database for collection of follow-up information.”

> “We need clear-cut guidelines for the management of incidental findings.”
DISCUSSION

Through this research study, we sought to explore prenatal genetic counselors’ experiences and characterize their challenges associated with incidental findings identified through NIPT. The study’s findings are consistent with the increasing number of reports of incidental findings first identified by NIPT that have health implications for the fetus and the mother (Bianchi et al., 2015b; Lau et al., 2013; Osborne et al., 2013; Snyder et al., 2016; Wang et al., 2014; Yao et al., 2012). Literature specific to the genetic counseling profession thus far has focused mainly on counseling practices and experiences with findings for which the initial NIPT technology was designed to screen (Horsting et al., 2014; Suskin, Hercher, Aaron, & Bajaj, 2016). This is the first study of prenatal genetic counselors’ perspectives, practices, and challenges with incidental findings identified by NIPT.

Despite the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) professional practice recommendations (2015), more than 60% of respondents in our study routinely offer NIPT that includes an expanded number of conditions, including microdeletions and other autosomal aneuploidies. While these expanded panels increase the chance of incidental findings, participants indicate that they can be useful for certain situations, such as a personal or family history of multiple miscarriages, chromosome conditions, and when there is a fetal indication of a cardiac anomaly on ultrasound. This is consistent with
the recent findings presented by Sequenom in which they found that MaterniT GENOME NIPT is used most frequently for indications that include ultrasound findings and multiple risk factors, suggesting that healthcare providers are using genome-wide NIPT analysis for clinically complex cases (McCullough et al., 2016).

ASSESSMENT OF CURRENT PRE-TEST COUNSELING PRACTICES

Of the genetic counselors who completed the survey, almost half offer three or more different types of NIPT tests to regularly provide pre-test counseling for NIPT to their patients. The more types of cfDNA tests that counselors utilize to provide NIPT for their patients ($M = 2.99, SD = 1.63$), the less likely they are to use NIPT company-specific resources during their counseling session compared to those counselors who offer fewer NIPT options to their patients ($M = 2.37, SD = 1.42$), $t(145) = -2.45, p = .015$. This is most likely due to the differences in technology that each NIPT company uses to analyze their samples, as well as the variety of current conditions screened for on each NIPT panel, making it more challenging to rely on one NIPT company’s patient education resource during pre-test counseling sessions.

The majority of the genetic counselors obtain informed consent for NIPT verbally and over half do not always include the possibility of incidental findings in their pre-test counseling discussions. More than half do not require the patient’s signing of an informed consent form for NIPT, instead the provider is held responsible for documenting the patient’s consent for NIPT. These findings demonstrate a lack of transparency about prenatal screening in practice and extra attention should be given to the process of obtaining consent from patients to find out about their own or their fetus’ health before NIPT is ordered. Efforts need to be made to educate
patients, provide them with a consent form to read and time to ask questions, and to ensure that they have fully contemplated all of the potential implications of electing or declining NIPT.

Our study found that years of experience as a prenatal genetic counselor does not have an influence on the discussion of incidental findings during pre-test counseling with patients. However, our findings do suggest that genetic counselors who have counseled a patient for a suspected or confirmed incidental finding identified through NIPT are more likely to include the possibility of incidental findings in their future pre-test counseling discussions ($p < .05$). This may be due to the counselors’ increased comfort level with discussing the possibilities for unusual findings by NIPT and the ability to call upon their experiences with prior patients as guidance. Many counselors that do not include incidental findings in pre-test counseling cited the complexity of discussing incidental findings considering their infrequency; therefore, they may not feel confident enough with their understanding of the potential causes of a false positive, false negative, or an unusual result to feel comfortable discussing the variety of explanations.

Regardless of the factors associated with counselors’ reported pre-test counseling practices, the ACOG and SMFM reiterate the “absolute requirement” that women understand not only the risk of aneuploidy but also the benefits, risks, and limitations of available screening tests in pre-test counseling, allowing for an informed patient choice “that fits the patient's clinical circumstances, values, interests, and goals” prior to performing the test (ACOG, 2016). Further, genetic counselors are crucial to the provision of complex counseling and test result interpretation, and should serve as a resource for more complicated findings that go beyond other healthcare providers’ scope of understanding. It is not the duty of the patient to keep abreast of developments in prenatal screening and diagnosis. While the concerns of incidental
findings will grow as the breadth of information analyzed in NIPT expands, the findings and reported cases from our study illustrate that there are currently many issues that need attention.

COUNSELING CHALLENGES WITH NIPT

Confirmation of false positive results or unusual findings reported by the NIPT laboratory, and explanation of their significance, can be costly. The incidental findings reported in this study highlight the ongoing process that occurs in NIPT laboratories whereby findings are identified that are clearly abnormal, and there may be suspicion of a particular cause; however, every finding needs to be analytically and clinically validated. Testing companies, if they plan to return these types of findings, may need to reevaluate their reporting policies to determine which suggestive results are actually linked to cancer or other conditions that should be disclosed to maternal patients, and which are not. However, policies on reporting results differs considerably between laboratories. Most laboratories cannot officially report a suspicion of potential cancer of maternal origin, since there are no studies to validate such a claim. Ignoring these suspicions, by not reporting or discussing them with the ordering providers, instead, raises ethical concerns given that there is some evidence that these suspicions could have medically actionable consequences for the patient.

Sequenom has established their reporting of findings suspicious of maternal cancer as “non-informative,” along with the assurance that they alert the ordering provider to their concerning finding (Ashford, 2015). Other companies have chosen to not report or communicate any unusual or suspicious findings in similar circumstances. For instance, Natera has stated that their lab personnel and the clinical team are blinded to any maternal findings due to their SNP-based method of analysis. When offering their Panorama NIPT, they encourage providers to not include
incidental findings in their pre-test counseling discussion for NIPT (Gross, 2015). Yet, Natera’s analysis includes the fetal-risk score, which makes it inherently capable of identifying a partial deletion of chromosome 22 of maternal origin, a common microdeletion syndrome that can be variably expressed within families (Hui, 2016).

PRACTICE IMPLICATIONS

Despite the limitations of self-reporting and smaller frequency of suspected and/or confirmed incidental findings in this study, the examples noted in this study encompass the breadth of possibilities for unusual NIPT findings in the published literature; they include several possible explanations for atypical NIPT results that genetic counselors should consider when addressing the possible underlying explanations for a patient’s test result. The reported frequency of prenatal counselors with experience with suspected or confirmed incidental findings and the consensus of the associated challenges reinforce the importance of confirmatory diagnostic testing, in addition to a review of the patient’s clinical history following any abnormal or unusual NIPT result, all to assist with post-test counseling and management.

The counselors’ responses varied greatly with regards to their recommendations for a national guideline for follow-up clinical evaluation for incidental findings identified through NIPT. The responses also indicate areas of significant concern for genetic counselors, in particular, the variation among NIPT laboratories with information and communication of incidental findings and follow-up, as well as a lack of a centralized database to catalogue incidental findings by NIPT.

As NIPT technology and understanding evolves, the utility and focus of this screening tool will likely expand beyond fetal status prediction to include broader pregnancy health concerns and risks. Understanding and appreciating the potential implications of concordant and discordant
NIPT results alike can greatly assist in the management of pregnancies. False-positive and false-negative rates can only be established if complete follow-up information is obtained from clinical validation studies. Similar to other decentralized laboratory testing, national regulating bodies may need to consider inter-laboratory comparisons to ensure a high standard of cfDNA testing options are available (Jani et al., 2015). Laboratory-specific quality assurance processes which include registry-based clinical follow-up data linked to NIPT results is encouraged by national professional societies (Benn, Cuckle, & Pergament, 2013; Gregg et al., 2013) and should be based on consensus guidelines for cfDNA aneuploidy screening (ACOG, 2016).

An additional consideration is that most established NIPT laboratories offer support by genetic counselors and other experts to interpret unexpected results or provide strategies for further testing when the laboratory is unable to issue a result. With smaller laboratories now offering cfDNA testing, and analyzing fewer samples, this type of follow-up service is much more challenging and less likely to be a part of the laboratory’s services.

STUDY LIMITATIONS

A limitation of this study is the low response rate, estimated at 14%, which raises questions about the generalizability of the findings to the population of clinical prenatal genetic counselors. Another limitation includes selection bias among the respondents. The subject of the recruitment e-blast included the term “incidental findings,” so genetic counselors with experience with these types of NIPT results may have been more likely to complete the survey; conversely, those without experience with incidental findings may not have been interested to participate in this study. Although the inclusion criteria consisted of currently practicing genetic counselors, the survey required a self-report of their counseling practices and relies on their recall bias. Finally,
respondents were not required to answer all questions encountered in the survey, which contributed to minor inconsistencies with data analysis.

RESEARCH RECOMMENDATIONS/FUTURE DIRECTIONS

These findings emphasize the need to develop recommendations for a dynamic informed consent process that will be flexible over time, to accommodate both the changing nature of NIPT offerings and patient values, as well as the potential for incidental findings. We identified common challenges and concerns that genetic counselors face when offering NIPT to their patients. Our findings, and those resulting from future studies, may help to inform alternative models for pre-test counseling and obtaining informed consent, and possibly for other guidelines addressing the return of unusual NIPT results, including incidental findings. Additional studies should be done to characterize the sort of information that facilitates patients’ understanding of various types of unusual NIPT results and the sort of information that is potentially overwhelming and/or unhelpful to them. NIPT is expanding its capabilities rapidly and future research could examine how genetic counselors will respond to the availability of these new tests and new findings. Moreover, the lack of a standardized approach for returning potential incidental findings from NIPT or guidelines for post-test counseling and management warrant further research.
CONCLUSION

The expansion of NIPT and the conditions for which it screens provide greater choice for patients, but come with the inevitable challenges involved in appropriate pre-test counseling and obtaining informed consent due to the possibility of unanticipated findings. The majority of genetic counselor respondents obtain informed consent for NIPT verbally and about half reported that they do not include the possibility of incidental findings in their pre-test counseling discussion of NIPT. Yet, almost half of the genetic counselor respondents have had a suspected or confirmed incidental finding identified through NIPT and almost all of them indicated that post-test counseling a patient with an incidental finding identified through NIPT is challenging.

From counselors’ responses, unknown maternal conditions account for a large proportion of the incidental findings identified by NIPT. Given these findings we recommend that pre-test counseling for NIPT include a discussion of possible unexpected findings and to establish clear expectations for the categories of results that may be returned, the creation of professional guidelines outlining how incidental findings should be discussed in both pre- and post-test counseling discussions, and the creation of a centralized database for the collection of NIPT findings, outcomes, and clinical follow-up to facilitate appropriate care for patients.
REFERENCES


APPENDICES

APPENDIX A: RECRUITMENT NOTIFICATION

Subject: NIPT: Emerging Issues—Genetic Counselors’ Experiences & Perspectives with Incidental Findings

Seeking Prenatal Genetic Counselors to Participate in a Research Study

You are invited to participate in an online research survey to investigate genetic counselors’ practices and perspectives in counseling patients regarding the possibility of unanticipated incidental findings through non-invasive prenatal testing (NIPT).

This study is open to prenatal genetic counselors who provide counseling for NIPT to patients either in person, over the phone, or online.

The specific goals of this research study are to:
• identify the current pre-test counseling practices for NIPT, including methods for obtaining informed consent;
• learn about genetic counselors’ personal experiences with incidental findings by NIPT; and
• delineate challenges counselors face when discussing the possibility of incidental findings by NIPT with patients.

The survey will take 10-15 minutes of your time. All participants who complete the survey will have the opportunity to enter a drawing for one of three $50 gift cards to Amazon.com. Your survey responses will not be connected to your email address.

This study was reviewed and approved by the Brandeis University Institutional Review Board. If you have any questions, concerns, or comments, please feel free to contact me by email at aorta@brandeis.edu, or the Brandeis University faculty sponsor, Judith Tsipis, at tsipis@brandeis.edu.

Click here to take the survey!

Thank you in advance for your time and participation.

Sincerely,

Alicia Orta, MPH
Master’s Degree Candidate, Class of 2016
Genetic Counseling Program
Brandeis University

Judith E. Tsipis, PhD
Director, Genetic Counseling Program
Professor of Biology
Brandeis University
APPENDIX B: INSTRUMENT

NIPT: Emerging Issues

Welcome!

As part of a Master’s thesis research project at Brandeis University, the following study is investigating genetic counselors’ practices and perspectives in counseling patients regarding the possibility of unanticipated incidental findings through non-invasive prenatal testing (NIPT).

This study is open to prenatal genetic counselors who provide counseling for NIPT to patients either in person, over the phone, or online.

The specific goals of this research study are to:
- identify the current pre-test counseling practices for NIPT, including methods for obtaining informed consent;
- learn about genetic counselors’ personal experiences with incidental findings by NIPT; and
- delineate challenges counselors face when discussing the possibility of incidental findings by NIPT with patients.

This anonymous survey is expected to take **10-15 minutes** to complete. You are encouraged to respond to all survey questions; however, you may skip any questions that you are not comfortable answering or end your participation at any point.

If you would like to be eligible to win **one of three $50 gift cards to Amazon.com**, please enter your email address on the separate unlinked site as directed at the end of the survey.

This study was reviewed and approved by the Brandeis University Institutional Review Board (IRB). If you have questions about your rights as a research subject, please contact the Brandeis IRB at irb@brandeis.edu or 781-736-8133.

By clicking the "Next" button below you are consenting to participate in this study.

Thank you!
Definitions
For the purpose of this survey, the following definitions are provided. They will be available throughout the survey by placing your cursor over the colored item.

Incidental Finding: an unexpected finding of a maternal or fetal condition other than the typically screened for conditions specifically targeted by NIPT. These unanticipated ‘secondary findings’ may include: unrecognized maternal conditions, co-twin demise, and fetal or placental chromosome differences, among others.

No-Call NIPT Result: a failure to receive an interpretable result from cell-free DNA testing. Depending on the NIPT laboratory, the “non-reportable” result may be due to insufficient sample, low feto-placental DNA fraction, or because the interpretation falls into an indeterminate range.

Positive NIPT Result: a result that suggests a pregnancy is at risk of having a condition that is among the typically screened for conditions specifically targeted by NIPT. The result may be reported as “aneuploidy detected” or “high risk” and does not include “no-call” NIPT results.

Q1. Do you currently work as a genetic counselor in a clinical prenatal setting?
   - Yes
   - No

   If No Is Selected, Then Skip To End of Survey

Q2. What percentage of your counseling time is spent with prenatal patients?
   - Less than 25%
   - 26-50%
   - 51-75%
   - 76-100%

Q3. Which modalities do you utilize to counsel patients at your clinical practice? (Select all that apply)
   - In-person genetic counseling
   - Telephone genetic counseling
   - Telegenetics (counseling occurring remotely using video conferencing)

Answer if: Telephone genetic counseling Is Selected Or Telegenetics (counseling occurring remotely using video conferencing) Is Selected

Q4. What percent of your patient contact time do you spend each week utilizing telephone genetic counseling or telegenetics (counseling occurring remotely using video conferencing)? (Indicate a percentage)
Q5. Do you offer non-invasive prenatal testing (NIPT) to patients?

☐ Yes
☐ No

If No is selected, then skip to end of block

Q6. For how many patients per week do you typically provide pre-test counseling for NIPT? (Approximately)

☐ 1-4
☐ 5-9
☐ 10-14
☐ 15-19
☐ 20-24
☐ More than 24

Q7. For how many patients per week do you typically order NIPT? (Approximately)

☐ 1-4
☐ 5-9
☐ 10-14
☐ 15-19
☐ 20-24
☐ More than 24

Q8. Which company/companies and corresponding test(s) do you currently use to provide NIPT to your patients? (Select all that apply)

☐ Ariosa Diagnostics (Harmony™)
☐ Counsyl (Informed Pregnancy Screen)
☐ Integrated Genetics - LabCorp (informaSeqSM)
☐ Natera (Panorama™)
☐ Perkin Elmer (verifi® from PerkinElmer Labs)
☐ Progenity (VeriFi by Progenity)
☐ Quest (QNatal™ Advanced)
☐ Recombine (ChromoMap)
☐ Sequenom Laboratories (MaterniT™ GENOME)
☐ Sequenom Laboratories (MaterniT21® PLUS)
☐ Sequenom Laboratories (VisibiliT™)
☐ Verinata Health - Illumina (verifi™)
☐ Other, please specify: ______________________

Q9. How many prenatal genetic counselors (including yourself) work in your clinical practice?

________________
Survey Block: No NIPT Utilization Questions

Q10. Please briefly explain why NIPT has not been incorporated into your clinical practice.

Q11. Does your clinic intend to incorporate NIPT into your clinical practice?
   - Yes
   - No

If No Is Selected, Then Skip To End of Survey

Answer If: Does your clinic intend to incorporate NIPT into your clinical practice? Yes Is Selected

Q12. Please describe when you expect NIPT to be incorporated into your clinical practice.

If No Is Selected, Then Skip To End of Survey

Survey Block: Resources Questions

Q13. Are your patients provided with information about NIPT before their genetic counseling appointment?
   - Yes
   - No

Answer If: Yes Is Selected

Q14. Which types of resources, including web-based or app-based educational tools, are provided for patients about NIPT before their genetic counseling appointment? (Select all that apply)
   - Print materials sent in the mail to the patient’s address
   - Email with links to online written educational information
   - Email with a link to an online educational video to view at home
   - Educational tools and decision aids on my institution's website
   - Educational video in practice waiting room
   - Other, please specify: _________________

Q15. What types of resources do you utilize to inform patients about NIPT during their genetic counseling session? (Select all that apply)
   - Resources created by the Laboratory/Company
   - Resources created by the NSGC Prenatal SIG
   - Resources created by other professional societies (e.g., ISPD, ACOG)
   - Resources developed by my institution
   - Published genetic counseling visual aids
   - Web-based or app-based decision-making aids
   - I do not use any printed resources
   - Other, please specify: _________________
Q16. How do you routinely obtain informed consent for NIPT? (Select all that apply)
- Verbally (either in person, over the phone, or via video counseling)
- There is a form specifically for NIPT signed by the provider documenting the patient’s consent
- NIPT has been incorporated into a pre-existing informed consent form for invasive diagnostic testing that the patient signs
- There is an informed consent form that the patient signs specifically for NIPT
- NIPT has been incorporated into a pre-existing informed consent form for screening that the patient signs
- There is an informed consent form that both the provider and patient signs specifically for NIPT
- Patient signs a requisition form provided by the NIPT lab company
- I do not routinely obtain informed consent for NIPT
- Other, please specify: ______________________

Q17. What other health care provider(s), if any, obtain informed consent for NIPT in your clinical practice? (Select all that apply)
- Genetic Counselor (other than yourself)
- Genetic Counseling Student Intern
- Maternal-Fetal Medicine Specialist
- Medical Geneticist
- Midwife
- Nurse Practitioner
- Obstetrician
- Physician Assistant
- None
- Other, please specify: ______________________

Survey Block: Informed Consent Form Questions

Q18. Is the NIPT informed consent form that you use available in multiple languages?
- Yes
- No

Q19. Does the NIPT informed consent form that you use include the possibility of incidental findings?
- Yes
- No
**Survey Block: Pre-test Counseling Questions**

**Q20.** Which of the following items do you currently discuss with your patients as an option to opt-in or opt-out for the reporting of results with NIPT?

<table>
<thead>
<tr>
<th>Opt-Out option</th>
<th>Opt-In option</th>
<th>NO Opt-In/Out options</th>
<th>Not Applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>___ Fetal sex</td>
<td>___ Fetal sex</td>
<td>___ Fetal sex</td>
<td>___ Fetal sex</td>
</tr>
<tr>
<td>___ Microdeletions</td>
<td>___ Microdeletions</td>
<td>___ Microdeletions</td>
<td>___ Microdeletions</td>
</tr>
<tr>
<td>___ Microduplications</td>
<td>___ Microduplications</td>
<td>___ Microduplications</td>
<td>___ Microduplications</td>
</tr>
<tr>
<td>___ Other autosomal</td>
<td>___ Other autosomal</td>
<td>___ Other autosomal</td>
<td>___ Other autosomal</td>
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<tr>
<td>aneuploidies (e.g.,</td>
<td>aneuploidies (e.g.,</td>
<td>aneuploidies (e.g.,</td>
<td>aneuploidies (e.g.,</td>
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<td>trisomy 22)</td>
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<tr>
<td>___ Sex chromosome</td>
<td>___ Sex chromosome</td>
<td>___ Sex chromosome</td>
<td>___ Sex chromosome</td>
</tr>
<tr>
<td>aneuploidies</td>
<td>aneuploidies</td>
<td>aneuploidies</td>
<td>aneuploidies</td>
</tr>
<tr>
<td>___ Other, please</td>
<td>___ Other, please</td>
<td>___ Other, please</td>
<td>___ Other, please</td>
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<td></td>
</tr>
</tbody>
</table>

**Q21.** Do you currently include the possibility of incidental findings in your pre-test counseling discussion of NIPT with every patient?

- ☐ Yes
- ☐ No

**Survey Block: Pre-test Counseling—No Incidental Findings Questions**

**Q22.** Which of the following are reasons why you do not include the possibility of incidental findings in your pre-test counseling discussion of NIPT with every patient? (Select all that apply)

- ☐ Incidental findings are too rare
- ☐ Incidental findings complicate the discussion
- ☐ There’s a lack of recommendations or guidelines on what to do if an incidental finding is identified
- ☐ The test is not designed nor validated for the detection of incidental findings
- ☐ This information is included on the NIPT informed consent form that I use
- ☐ This information may influence patient’s decision-making about their prenatal screening options
- ☐ The genetic counselors in my practice have been advised – or have decided – as a group to not discuss incidental findings with every patient
- ☐ Other, please specify: _________________________

**Q23.** When would you **definitely** discuss the possibility of an incidental finding with a patient before they elect to have NIPT? (Select all that apply)

- ☐ Whenever there is a personal history of chromosome abnormalities
- ☐ Whenever there is a family history of chromosome abnormalities
- ☐ Whenever there is a personal reproductive history of recurrent miscarriages
Q24. What qualifies as a personal history of chromosome abnormalities?

Answer If: Whenever there is a personal history of chromosome abnormalities Is Selected

Q25. What qualifies as a family history of chromosome abnormalities?

Answer If: Whenever there is a family history of chromosome abnormalities Is Selected

Q26. What qualifies as a personal reproductive history of recurrent miscarriages?

Answer If: Whenever there is a personal pregnancy history of recurrent miscarriages Is Selected

Survey Block: Opt-Out Questions

Q27. When would you definitely discuss the possibility of an incidental finding with a patient after they receive a NIPT result, but before any further (diagnostic) testing? (Select all that apply)

- Whenever a no-call NIPT result is reported
- Whenever 2 or more no-call NIPT results are reported
- Whenever a NIPT result reports a sex chromosome aneuploidy
- Whenever a NIPT result reports an autosomal monosomy
- Whenever a NIPT result reports multiple aneuploidies
- Whenever a NIPT result reports a microdeletion/microduplication
- Whenever a possible incidental finding is suspected by the NIPT laboratory
- Other, please specify: ________________

Q28. Although there is currently no option to opt-out of incidental findings from NIPT, which of the following would you support as opt-out options for your patients? (Select all that apply)

- All potential incidental findings identified through NIPT
- Incidental findings indicative of any maternal health condition
- Incidental findings indicative of a maternal aneuploidy
- Incidental findings indicative of maternal copy number variations
- Incidental findings indicative of an adult-onset condition in the fetus
- Potential incidental findings of consanguinity
- Potential incidental findings of non-paternity
- Other, please specify: ________________

Q29. Has your clinical practice discussed the need for an option to opt-out of the reporting of at least some incidental findings with NIPT?
Q30. Why did your clinical practice begin discussing the need for this option?

Q31. Do you think giving patients an option to choose which incidental findings to receive would improve patient care?

Q32. Do you think an online or web-based tool would facilitate assessment of patient preferences for possible incidental findings through NIPT?

Survey Block: Personal Experience with Incidental Findings from NIPT Questions

Q33. Since you first began practicing in a clinical prenatal setting, how many patients have you personally counseled with a positive NIPT result? (Approximately)

Q34. Of these patients with a positive NIPT result, how many were referrals from a different office (e.g., primary care physician, OB/GYN) with no pre-test counseling prior to testing? (Approximately)
☐ More than 10

Q35. Of all the patients that you have counseled with a positive NIPT result, please approximate the percentage who elected each of the following. (Answers must total to 100%)

_____ Terminated the pregnancy based on NIPT result only (with no additional ultrasound findings)
_____ Terminated the pregnancy based on NIPT result and the presence of ultrasound findings
_____ Confirmed result with amniocentesis or CVS and continued the pregnancy
_____ Confirmed the result with amniocentesis or CVS and terminated the pregnancy
_____ Had an amniocentesis or CVS result that did not confirm the NIPT result
_____ Decided against invasive diagnostic testing and continued the pregnancy

Q36. Of all the patients you have counseled with a positive NIPT result, how many were later found to be negative by diagnostic testing or neonatal outcome (i.e., discordant with NIPT result)?

☐ None or None that I know of
☐ 1
☐ 2
☐ 3
☐ 4
☐ 5
☐ More than 5
☐ Don’t know but at least 1

Q37. Since you first began practicing in a clinical prenatal setting, how many patients have you personally counseled with a no-call NIPT result after repeat screening (i.e., 2 or more blood samples for NIPT)? (Approximately)

☐ None or None that I know of
☐ 1
☐ 2
☐ 3
☐ 4
☐ 5
☐ More than 5
☐ Don’t know but at least 1

Answer If: 1 Or 2 Or 3 Or 4 Or 5 Or More than 5 Or Don’t know but at least 1 Is Selected

Q38. Of the patient(s) you have counseled with a no-call NIPT result after repeat screening, please describe the recommended follow-up testing that was offered and their clinical outcome(s), including the reason(s) for multiple NIPT failures, if known.
Q39. Since you first began practicing in a clinical prenatal setting, how many patients have you personally counseled where the NIPT laboratory suspected a possible incidental finding from NIPT? (Approximately)
   ☐ None or None that I know of
   ☐ 1
   ☐ 2
   ☐ 3
   ☐ 4
   ☐ 5
   ☐ More than 5
   ☐ Don’t know but at least 1

Q40. Since you first began practicing in a clinical prenatal setting, how many patients have you personally counseled with a confirmed incidental finding identified through NIPT?
   ☐ None or None that I know of
   ☐ 1
   ☐ 2
   ☐ 3
   ☐ 4
   ☐ 5
   ☐ More than 5
   ☐ Don’t know but at least 1

Answer If # of CONCERNS Or # of CONFIRMED Incidental Findings Is 1 or more Selected

Q41. Which types of confirmed incidental finding(s) identified through NIPT have you personally encountered? (Select all that apply and include examples if you recall)
   ☐ Confined placental mosaicism
   ☐ Co-twin demise/vanishing twin
   ☐ Fetal or placental mosaicism
   ☐ Maternal cancer
   ☐ Maternal copy number variation
   ☐ Maternal mosaicism
   ☐ Maternal sex chromosome aneuploidy (mosaic)
   ☐ Maternal sex chromosome aneuploidy (non-mosaic)
   ☐ Maternal uterine leiomyoma
   ☐ Other, please specify: ____________________

Q42. Include any examples and additional comments below:

   ____________________

Answer If # of CONCERNS Or # of CONFIRMED Incidental Findings Is 1 or more Selected

Q43. Which resources did you find helpful when preparing to counsel the patient(s) about the incidental finding(s) from NIPT? (Select all that apply)
- Laboratory Director where NIPT was performed
- Genetic Counselor from the NIPT Laboratory
- Pediatric Genetic Counselor
- Cancer Genetic Counselor
- Websites of the testing laboratories/companies
- NSGC Prenatal SIG forum
- OMIM/PubMed—peer reviewed literature search
- Guidelines from professional societies
- Genome Browsers (DECIPHER, ECARUCA, Genecards, Toronto Database, UCSC)
- Other, please specify: ____________________

**Survey Block: Challenges with Experience with Incidental Findings Questions**

**Q44.** To what extent do you agree or disagree with the following statement:

<table>
<thead>
<tr>
<th>“Counseling a patient with an incidental finding identified through NIPT is challenging.”</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

**Q45.** Please indicate the level of importance each of the following factors contribute to the challenge of counseling a patient with an incidental finding identified through NIPT:

<table>
<thead>
<tr>
<th>Factor</th>
<th>Not at all Important</th>
<th>Of Little Importance</th>
<th>Important</th>
<th>Extremely Important</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rarity of incidental findings by NIPT</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Lack of personal experience in counseling for incidental findings</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Lack of information on incidental findings from the NIPT laboratory</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Lack of support services from the NIPT laboratory</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Lack of clinical guidelines from professional societies (e.g., ACOG, NSGC)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Lack of institutional guidelines on clinical management of incidental findings</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Lack of a centralized database to catalogue incidental findings by NIPT</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Variation among NIPT laboratories with communication of incidental findings and follow-up</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>
Patient was not provided pre-test counseling about possible incidental findings
Lack of resources to provide the patient about the incidental finding
Counseling the patient through an interpreter/language barrier
Limited window of time for incidental finding interpretation in the prenatal setting
Limited time during genetic counseling session

Q46. To what extent do you agree or disagree with the following statements regarding the return of incidental findings identified through NIPT:

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most health care providers do not have the time and/or expertise to return incidental findings.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Patients should be allowed to select which incidental findings they want to receive based on their values.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>There is insufficient evidence about the benefits, risks, and costs of reporting incidental findings.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Identifying incidental findings will be burdensome for NIPT laboratories.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Returning incidental findings will increase health care costs.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Patients usually do not know about the possibility of incidental findings and are caught completely off-guard.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

Q47. How often do you review the current published literature or case reports regarding incidental findings from NIPT? (Approximately)
○ Rarely
○ 2-3 Times a Year
○ Once a Month
○ 2-3 Times a Month
○ Once a Week
○ 2-3 Times a Week
Survey Block: Challenges with NO Experience with Incidental Findings Questions

Q48. To what extent do you agree or disagree with the following statement:

“Counseling a patient with an incidental finding identified through NIPT would be challenging.”

- Strongly Disagree
- Disagree
- Agree
- Strongly Agree

Q49. Please indicate the level of importance each of the following factors would contribute to the challenge of counseling a patient with an incidental finding identified through NIPT:

<table>
<thead>
<tr>
<th>Factor</th>
<th>Not at all Important</th>
<th>Of Little Importance</th>
<th>Important</th>
<th>Extremely Important</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rarity of incidental findings by NIPT</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Lack of personal experience in counseling for incidental findings</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Lack of information on incidental findings from the NIPT laboratory</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Lack of support services from the NIPT laboratory</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Lack of clinical guidelines from professional societies (e.g., ACOG, NSGC)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Lack of institutional guidelines on clinical management of incidental findings</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Lack of a centralized database to catalogue incidental findings by NIPT</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Variation among NIPT laboratories with communication of incidental findings and follow-up</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Patient was not provided pre-test counseling about possible incidental findings</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Lack of resources to provide the patient about the incidental finding</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Counseling the patient through an interpreter/language barrier</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Limited window of time for incidental finding interpretation in the prenatal setting</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Limited time during genetic counseling session</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

Q50. To what extent do you agree or disagree with the following statements regarding the return of incidental findings identified through NIPT:
<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most health care providers do not have the time and/or expertise to return incidental findings.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Patients should be allowed to select which incidental findings they want to receive based on their values.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>There is insufficient evidence about the benefits, risks, and costs of reporting incidental findings.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Identifying incidental findings will be burdensome for NIPT laboratories.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Returning incidental findings will increase health care costs.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Patients usually do not know about the possibility of incidental findings and are caught completely off-guard.</td>
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**Q51.** Which resources would you utilize when preparing to counsel a patient with an incidental finding from NIPT? (Select all that apply)

- Laboratory Director where NIPT was performed
- Genetic Counselor from the NIPT Laboratory
- Pediatric Genetic Counselor
- Cancer Genetic Counselor
- Websites of the testing laboratories/companies
- NSGC Prenatal SIG forum
- OMIM/PubMed—peer reviewed literature search
- Guidelines from professional societies
- Genome Browsers (DECIPHER, ECARUCA, Genecards, Toronto Database, UCSC)
- Other, please specify: ______________________

**Q52.** How often do you review the current published literature or case reports regarding incidental findings from NIPT? (Approximately)

- ○ Rarely
- ○ 2-3 Times a Year
- ○ Once a Month
- ○ 2-3 Times a Month
- ○ Once a Week
- ○ 2-3 Times a Week

**Survey Block: Open-Ended Question**
Q53. If you were part of a committee writing a national guideline for the follow-up clinical evaluation for incidental findings identified through NIPT, what recommendations would you make?

Survey Block: Demographics Questions

Q54. In which NSGC region are you currently practicing?
- Region 1: CT, MA, ME, NH, RI, VT, CN, Maritime Provinces
- Region 2: DC, DE, MD, NJ, NY, PA, VA, WV, PR, VI, Quebec
- Region 3: AL, FL, GA, KY, LA, MS, NC, SC, TN
- Region 4: AR, IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, OK, SD, WI, Ontario
- Region 5: AZ, CO, MT, NM, TX, UT, WY, Alberta, Manitoba, Saskatchewan
- Region 6: AK, CA, HI, ID, NV, OR, WA, British Columbia

Q55. What is the setting of your practice? (Select all that apply)
- Community Hospital
- Government Organization/Medical Facility
- Health Maintenance Organization (HMO)
- Laboratory/Industry
- Outreach/Satellite/Field Clinic
- Private Clinic/Practice
- Private Hospital/Medical Facility
- Public Hospital/Medical Facility
- University Medical Center
- Other, please specify: ______________________

Q56. Which of the following best describes the location of the institution where you primarily practice?
- Urban
- Suburban
- Rural
- Not applicable

Q57. How many years total have you been practicing as a genetic counselor in any setting? (Approximately)

Q58. Of these, how many years have you spent in a clinical prenatal setting? (Approximately)