

NIPT: Current Utilization and Implications for the Future of Prenatal Genetic Counseling

Master's Thesis

Presented to

The Faculty of the Graduate School of Arts and Sciences
Brandeis University
Graduate Program in Genetic Counseling
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In Partial Fulfillment
of the Requirements for

Master's Degree

by
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May 2013

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ACKNOWLEDGEMENTS

I would like to thank my primary thesis advisor, Judith Tsipis, for her valuable insight and dedication to my project. I would also like to thank my committee members, Amy Sachs and Tomi Toler, who provided excellent advice and feedback during the project. Thank you all for taking the time to be part of my thesis advisory committee and for being very supportive during the whole process.

I would also like to thank Liz and Ted Cross who provided their wisdom and guidance during data analysis. Thank you also to the Graduate School of Arts and Sciences as well as the Genetic Counseling Program for funding this project.

Many thanks to Beth Rosen-Sheidley, Gretchen Schneider, and Missy Goldberg for their ongoing encouragement and guidance throughout my entire time in the Brandeis Genetic Counseling Program.

Finally, I would like to extend a sincere thank you to my family, classmates and friends for always providing love and support.

ABSTRACT

NIPT: Current Utilization and Implications for the Future of Prenatal Genetic Counseling

A thesis presented to the Graduate Program in Genetic Counseling

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Non-invasive prenatal testing (NIPT) for select fetal trisomies became clinically available in 2011. When it was introduced, there were no formal recommendations regarding how healthcare providers should incorporate NIPT into the prenatal genetic counseling setting. We sought to identify how genetic counselors have incorporated NIPT, how they obtain informed consent from their patients, and their opinions regarding the informed consent process for NIPT. We distributed an anonymous online survey to NSGC members through an e-blast to the NSGC listerv. We directed our recruitment toward prenatal genetic counselors in late October 2012, which was approximately one year after NIPT became clinically available. Two hundred and six prenatal genetic counselors responded to the survey, and 181 indicated they had incorporated NIPT into their practice with the majority offering this testing to patients whose pregnancies are high risk. Respondents indicated that genetic counselors, as well as other healthcare providers, obtain informed consent from patients, and most do so verbally. Most respondents indicated that there

should be a separate informed consent form for NIPT and that a discussion about NIPT with a patient should highlight that it is a screening test, it has a detection rate superior to that of maternal serum screening, an explanation of the specific conditions that NIPT screens for, and recommendations for invasive testing following a positive NIPT result. Following data collection for our study, the American College of Obstetricians and Gynecologists (ACOG), the National Society of Genetic Counselors (NSGC), and the American College of Medical Genetics and Genomics (ACMG) released practice guidelines for offering NIPT. Our results demonstrate that most genetic counselors have been offering NIPT in a manner consistent with the guidelines that the major governing bodies in prenatal genetics have since published. Future research should investigate patient understanding following NIPT to determine the best method for obtaining informed consent.

Key Words: non-invasive prenatal testing, cell free fetal DNA, informed consent, genetic counseling

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INTRODUCTION

The discovery that cell free fetal DNA exists in maternal blood and is quantifiable (Lo et al., 1997) set the stage for the development of a new prenatal screening method. By means of massively parallel shotgun sequencing (Chiu et al., 2010; Ehrich et al., 2011; Palomaki et al., 2012), selective sequencing of chromosomes (Bianchi et al., 2012) and detection via single nucleotide polymorphisms (Zimmermann et al., 2012), non-invasive prenatal testing (NIPT) can detect select fetal aneuploidies.

Prior to the clinical availability of NIPT, healthcare providers expressed concern over the potential replacement of maternal serum screening by NIPT (de Jong, 2011), as well as the potential increase in the number of women wishing to pursue NIPT and requiring education by healthcare professionals (Schmitz, Netzer, & Henn, 2009). A more recent study (Sayres, 2011) of healthcare providers regarding the future integration of NIPT also found that most obstetrics providers thought their patients would desire as much diagnostic information as could be available to them and that if a patient asked for a test it should be provided. Though most providers surveyed felt they did not have a lot of knowledge of NIPT at the time, the majority felt it could be offered to test for trisomy 21 and other aneuploidies.

Possible psychological benefits arising from the introduction of NIPT into clinical practice were predicted to include: less negative psychological impact for parents who terminate a pregnancy earlier based on NIPT results obtained early in the pregnancy;

more time for parents to contemplate a decision to terminate while it is still an option; or more time to prepare mentally and physically for the birth of a child with a genetic condition (Hall, Bostanci, & Wright, 2010). Providers have also expressed concern that with the ease and simplicity of NIPT for aneuploidy, NIPT may lead to non-invasive testing for late-onset and non-medical traits of the fetus (Benn & Chapman, 2009). Furthermore, the Down syndrome community has expressed fears that this earlier test in pregnancy could lead to an increase in the number of patients choosing to terminate pregnancies found to have Down syndrome (King, 2012; Rochman, 2012).

As prenatal clinics implement NIPT for aneuploidy, an important factor to consider is the informed consent process. In terms of test structure, NIPT is a blood draw similar to maternal serum screening. However, the results of these two tests provide very different degrees of insight into the genetic makeup of the pregnancy and concern exists regarding patient perception of potential test results (Newson, 2008). A study conducted in France investigated women who were counseled about maternal serum screening and whether they understood the information they were given in order to make a truly informed decision. They found that patients' perceptions on issues surrounding the test, including risks to have a child with Down syndrome and the meaning of a false positive result, were not well understood. The study quotes that 12% of patients felt completely uninformed and 47% felt partially uninformed of the specifics of the test (Favre et al., 2007). Though NIPT is different from maternal serum screening, this study shows that patients already feel they are uninformed in one type of prenatal screening.

The first clinical non-invasive prenatal test became available in October 2011 by Sequenom (SequenomInc., 2011) and since then there are a number of laboratories that

offer NIPT, including Ariosa Diagnostics Inc. (AriosaDiagnostics, 2012), Verinata Health (VerinataHealth, 2012), and most recently Natera Inc. (NateraInc., 2013). During data collection for this study, there were no formal recommendations for incorporating NIPT into clinical practice other than the International Society for Prenatal Diagnosis (ISPD) rapid response in October 2011 (ISPD, 2011). Following data collection, the American Congress of Obstetricians and Gynecologists (ACOG), the National Society of Genetic Counselors (NSGC), and the American College of Medical Genetics and Genomics (ACMG) published position statements on NIPT (ACOG, 2012; Gregg et al., 2013; Wilson et al., 2013). All three statements recognize NIPT as a screening tool. ACOG and NSGC specifically recommend it for patients whose pregnancies are at increased risk for certain chromosome abnormalities because of advanced maternal age, family history, or positive serum and/or ultrasound screening tests. All three position statements include the recommendation for pre-test counseling and that positive NIPT results should be confirmed with either chorionic villus sampling (CVS) or amniocentesis.

The additional discussion needed to explain NIPT raises the possibility that patients will experience information overload which can undermine informed consent (Schmitz, 2012). The purpose of informed consent is to provide all relevant information in order to allow the patient to maintain autonomy and make decisions in the absence of deceit and coercion. As NIPT becomes part of routine medical care for high-risk patients, it is possible that women will feel obligated to undergo testing, which challenges informed decision-making (Deans & Newson, 2011). Healthcare providers should not assume that all women would opt for this testing simply because it is available. A thoughtful discussion about NIPT should highlight the benefit of the test being non-invasive

when compared to CVS or amniocentesis as well as the idea that since it is nearly diagnostic for the conditions tested, it has the potential to provide powerful information and not all patients may wish to receive this information prenatally. This is especially important as more healthcare providers begin offering NIPT to all patients, rather than only to those considered high risk.

The purpose of the present study was to identify how genetic counselors have incorporated NIPT into their clinical setting and how NIPT has changed the landscape of prenatal genetic counseling in their practice with special attention paid to the informed consent process.

METHODS

STUDY DESIGN

We invited genetic counselors to complete an online anonymous survey pertaining to the integration of NIPT into their clinical practice. They were asked to provide statistics on the number of patients, types of patients, and circumstances in which they offer NIPT. We queried participants regarding their experience with NIPT results, both positive and negative. Furthermore, we asked participants to share information on their current practices for informed consent regarding NIPT as well as their thoughts for the future of NIPT in clinical practice.

SAMPLE AND RECRUITMENT

Brandeis University Committee for Protection of Human Subjects approved this study. An e-blast was sent to all NSGC members on the NSGC listserv. A reminder e-blast was emailed approximately three weeks after the initial invitation to participate. We directed the recruitment notice (Appendix A) towards prenatal genetic counselors practicing in a prenatal clinic setting. Only those that indicated they were currently practicing as a prenatal genetic counselor were eligible to complete the survey.

DATA COLLECTION AND DATA ANALYSIS

We developed and distributed the research tool as an online anonymous survey using Qualtrics®. It was available from October 10, 2012 until November 14, 2012. The

survey contained multiple choice questions in the form of single and multiple selections, as well as open-ended responses (Appendix B). The survey consisted of a demographics section followed by a question asking whether respondents had incorporated NIPT into their clinical practice. Only those who had integrated NIPT into their practice at the time of the survey were eligible to complete the entire survey. We asked participants who indicated they had not integrated NIPT a series of questions pertaining to potential future integration of NIPT and then they exited the survey. The majority of the information obtained came from participants who indicated they had already incorporated NIPT into their clinical practice.

We completed data analysis using SPSS 19.0.0 for calculating descriptive statistics and correlations among the data.

RESULTS

DEMOGRAPHICS

There were 206 survey respondents spanning all six NSGC regions (Table 1). The largest number of participants (43.2%) had 0-5 years of experience as a prenatal genetic counselor. Many participants indicated they worked in a university medical center (36.8%), private medical facility (22.4%), or public medical facility (20.4%). Of all participants, 21 (10.2%) indicated they had not integrated NIPT into their clinical practice. Approximately half (55%) of the participants who had not integrated NIPT into clinical practice indicated they intend to incorporate NIPT into their clinical practice in the future.

Table 1. Demographics of Survey Respondents^a

NSGC Region	N=200	
	%	n
1 (CT, MA, ME, NH, RI, VT, CN, Maritime Provinces)	13.0	26
2 (DC, DE, MD, NJ, NY, PA, VA, WV, PR, VI, Quebec)	21.5	43
3 (AL, FL, GA, KY, LA, MS, NC, SC, TN)	12.0	24
4 (AR, IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, OK, SD, WI, Ont.)	22.0	44
5 (AZ, CO, MT, NM, TX, UT, WY, Alberta, Manitoba, Sask.)	16.5	33
6 (AK, CA, HI, ID, NV, OR, WA, British Columbia)	15.0	30
Years as a Prenatal Genetic Counselor	N=176	
0-5	43.2	76
6-10	21.4	43
11-15	15.9	28
16-20	6.8	12
21-25	6.3	11
>26	3.4	6
Work Setting	N=201	
University medical center	36.8	74
Private hospital/medical facility	22.4	45
Public hospital/medical facility	20.4	41
Private Clinic (OB/GYN, MFM, Perinatologist, Geneticist)	16.4	33
HMO	3.0	6
Commercial Lab	1.0	2

^a Participants were not required to answer each question to continue with the survey

INCOPORATION OF NIPT

A total of 181 participants indicated they had incorporated NIPT into their clinical practice. The largest percentage of participants indicated they began using NIPT in their clinical practice between January 2012 and the end of April 2012 (Figure 1). Participants specified they usually refer to the technology of utilizing cell free DNA to detect aneuploidies non-invasively as NIPT (53.7%). Another 37.7% of participants routinely refer to this testing as cell-free fetal DNA testing, 4.6% refer to it by the brand name of the test, 2.9% refer to it as non-invasive prenatal diagnosis (NIPD), and 1.1% use more than one of the above-mentioned terms to describe the test to patients. Most participants (61.5%) revealed that the NIPT discussion has made genetic counseling sessions longer, whereas 28.4% said that it varies, and 10.1% indicated session length has not changed. For those who reported longer sessions, respondents attributed the longer session time to a combination of contrasting maternal serum screening, NIPT, and invasive diagnostic testing (95.0%), explanation of NIPT (90.1%), patient decision-making (74.3%), and ensuring patient comprehension (47.5%).

The number of NIPT samples sent for testing each week ranged from 0 to 30 samples. Over half of respondents (58.6%) indicated they send between 0 and 5 samples per week, 28.0% indicated they send between 6 and 10 samples, 8.3% send between 11 and 16 samples, and 5.1% indicated they send between 16 and 30 samples per week. Respondents who indicated they began using NIPT between November 2011 and the end of April 2012 were significantly more likely to send more samples per week than respond-

ents who indicated they began offering NIPT in their clinic after May 2012 ($\chi^2=20.165$, $p=.003$)(Figure 2).

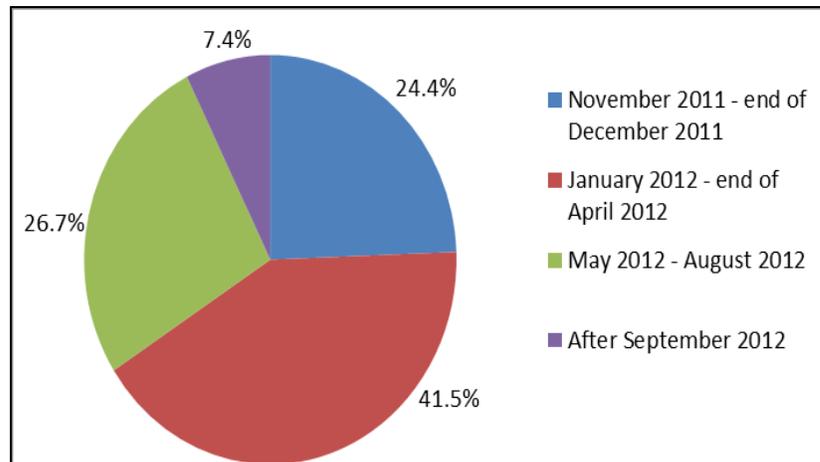


Figure 1. Time of NIPT Incorporation (N=176)

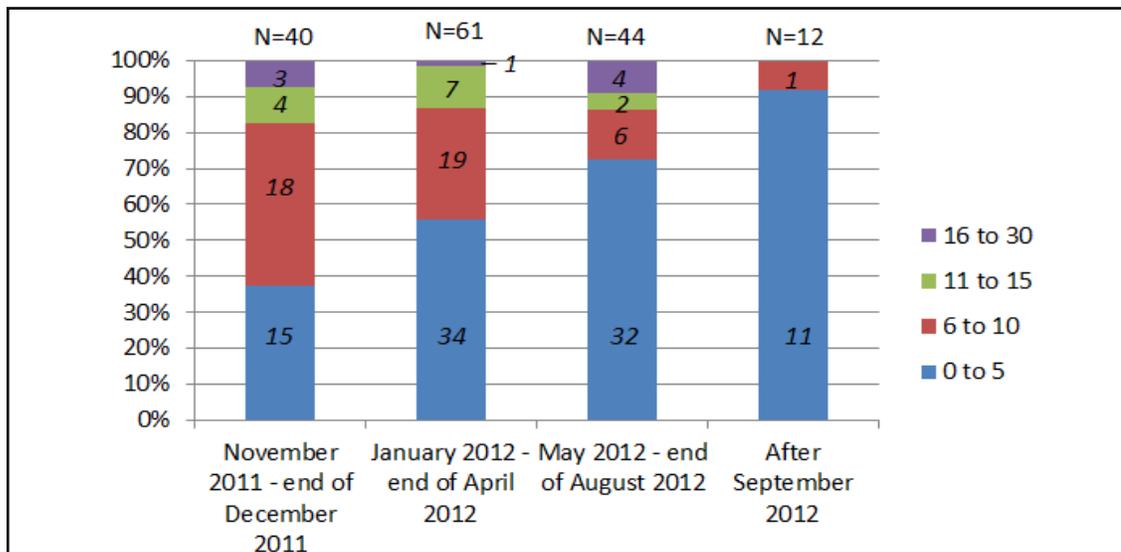


Figure 2. Time NIPT incorporated into clinical practice compared to number of samples sent each week. Number of respondents for each time period is indicated above each bar. Number of respondents in each category indicated in italics.

Respondents were able to select more than one lab they use for NIPT and the majority of respondents (67.4%) indicated they use Sequenom. Similar numbers of respondents selected Verinata (42.0%) and Ariosa/Labcorp (38.7%). Genetic counselors whose

clinics incorporated NIPT between November 2011 and April 2012 were significantly more likely to use Sequenom ($\chi^2=17.43$, $p<.001$) and Verinata ($\chi^2=6.79$, $p=.034$) than genetic counselors whose clinics incorporated NIPT after May 2012 (Figure 3).

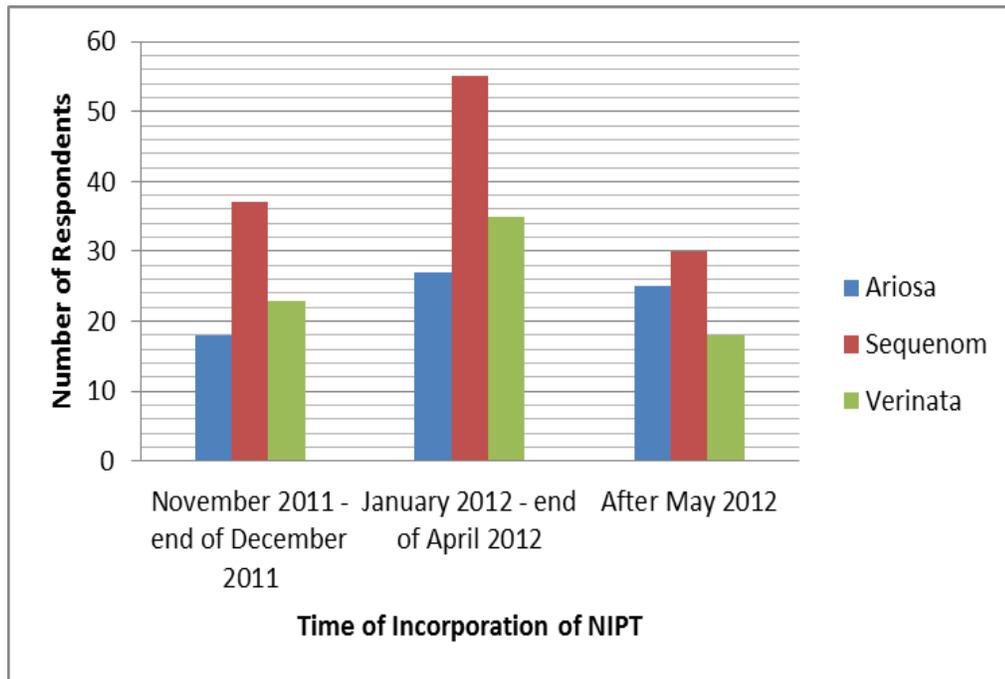


Figure 3. Labs used for NIPT compared to time of clinical incorporation

Currently, the majority of genetic counselors (94.1%) who offer NIPT indicated they offer NIPT to patients considered high risk, which included women of advanced maternal age (AMA), abnormal ultrasounds, positive maternal serum screen, and women with a personal or family history of chromosome abnormalities. Only 1.7% offer to patients that request the test specifically and 1.7% offer to all pregnant patients, regardless of risk factors (Figure 4).

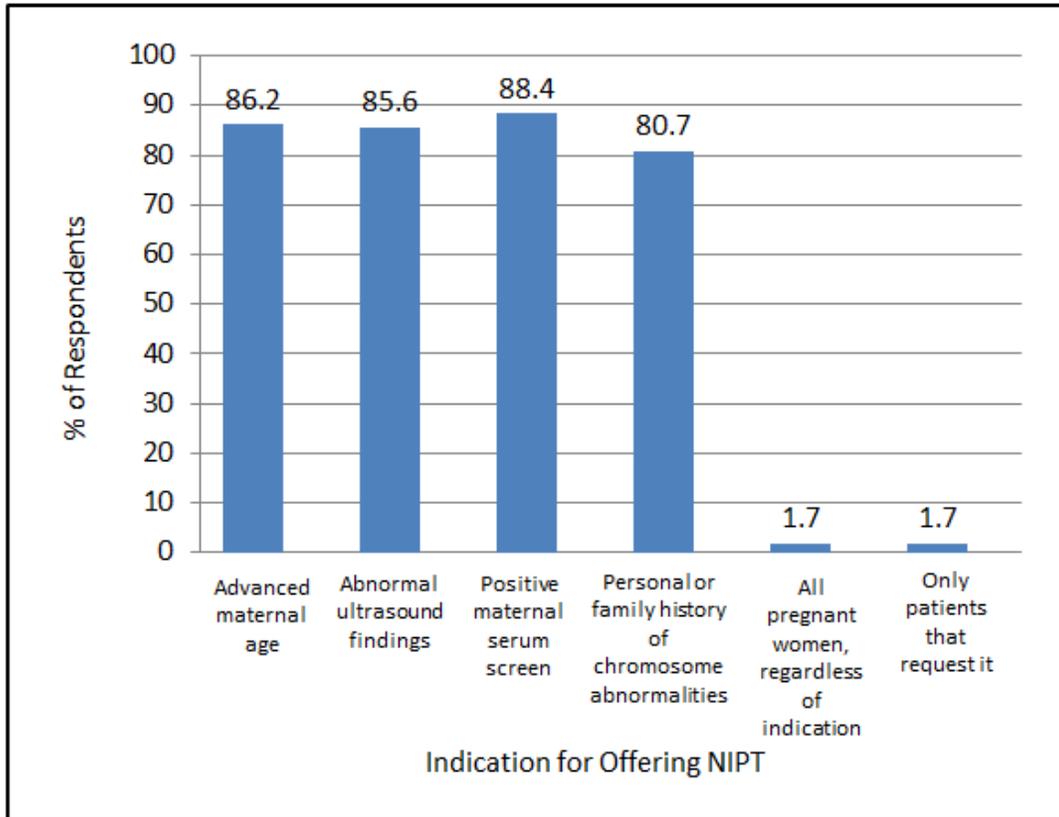


Figure 4. Indications for Which NIPT is Offered.

We asked respondents to assume a patient was AMA and then indicate if they would discuss NIPT in a number of different scenarios (Table 2). We then asked respondents to assume a patient was non-AMA and then indicate if they would discuss NIPT in the same clinical scenarios. Regardless of clinical scenario, fewer counselors indicated they would discuss NIPT with non-AMA patients compared to AMA patients. Counselors were significantly less likely to discuss NIPT with non-AMA patients than with AMA patients in the following scenarios: referred for first trimester screening; referred for diagnostic testing; maternal serum screening result is negative; a negative first trimester screen with at least one ultrasound marker, but together do not increase the risk

for aneuploidy above the lab cut-off; any structural fetal anomaly on ultrasound; nuchal translucency >3.0mm; and family history of trisomy.

Table 2. Scenarios in which respondents would offer NIPT to AMA and non-AMA patients

Scenario	Patients of AMA		Patients of non-AMA		Significance
	% of cases	n	% of cases	n	<i>P</i> ^a
Referred for first trimester screening	81.2	147	6.6	12	<.001 (133.007)*
Referred for diagnostic testing	82.3	149	29.3	53	<.001 (92.092)*
Maternal serum screen result is negative	56.9	103	1.7	3	<.001 (98.101)*
Maternal serum screen result is positive	89.5	162	89.0	161	1.00 ^b
Negative first trimester screen plus one or more soft markers on ultrasound ^c that when combined with first trimester screen results does not increase the risk for aneuploidy to above the lab cut-off	80.7	146	62.4	113	<.001 (31.03)*
Negative first trimester screen plus one or more soft markers on ultrasound ^c that when combined with first trimester screen results does increase the risk for aneuploidy to above 1:270	83.4	151	81.8	148	.549 ^b
Multiple soft markers found on ultrasound regardless of maternal serum screen result	86.7	157	84.5	153	.289 ^b
Nuchal translucency is >3.0mm	78.5	142	73.5	133	.049 ^{b*}
Nuchal translucency is >3.5mm	77.3	140	76.2	138	.727 ^b
Cystic hygroma found on ultrasound	73.5	133	72.4	131	.625 ^b
Presence of any structural fetal anomaly on ultrasound	68.5	124	63.0	114	.013 ^{b*}
History of previous pregnancy with a trisomy (T13, T18, T21)	85.1	154	82.9	150	.125 ^b
Family history of trisomy (T13, T18, T21) other than a previous pregnancy	58.0	105	39.2	71	<.001 (82.658)*

Results in significance column are written as: p value (Chi square value); ^aSignificance calculated using McNemar Chi-square test; ^bSignificance calculated using exact significance tests; ^ci.e., echogenic focus, choroid plexus cysts, echogenic bowel, thickened nuchal fold, hydronephrosis; * indicates significance

When asked about the frequency with which they had seen patients with a positive NIPT result, 24 respondents (19.2%) had never had a patient with a positive NIPT result, 68 respondents (54.4%) had 1-5 patients with positive NIPT results, 26 respondents (20.8%) had 6-10 patients, and 7 respondents (5.6%) had 11 or more patients with a positive NIPT result. To gain more insight into pregnancy outcomes following positive NIPT results, we asked respondents to indicate what their experiences had been (Table 3). We found that 70.3% of respondents had had one or more patients in their clinic elect to continue their pregnancy without confirming the positive NIPT result with invasive testing. An additional 14.6% of respondents indicated they had had at least one patient terminate a pregnancy in their clinic based on NIPT results only. Further, 36.1% of respondents indicated they worked in a clinic that had had one or more patients whose invasive testing did not confirm the positive NIPT result they had previously received.

Table 3. Outcomes following a positive NIPT result

Scenario	N	Number of Patients							
		0		1-5		6-10		11 or greater	
		%	n	%	n	%	n	%	n
Did not confirm with invasive testing and continued the pregnancy	91	29.7	27	63.7	58	6.6	6	0	0
Terminated the pregnancy based only on NIPT	89	85.4	76	14.6	13	0	0	0	0
Confirmed result with amnio/CVS and continued the pregnancy	87	55.2	48	42.5	37	2.3	2	0	0
Confirmed result with amnio/CVS and terminated the pregnancy	89	28.1	25	59.6	53	11.2	10	1.1	1
Had an amnio/CVS result that did not confirm the NIPT result	83	63.9	53	36.1	30	0	0	0	0

Forty-five respondents (28.1%) indicated they had a patient in their clinic with a false positive NIPT result discovered after invasive diagnostic testing. When asked to comment on the clinical and psychosocial issues that accompanied the situation, common responses included feelings of anxiety, confusion, and anger expressed by patients as well as relief when a normal result was uncovered through invasive techniques. Six respondents (3.8%) indicated they had a false negative NIPT result discovered upon invasive diagnostic testing and one respondent (0.6%) revealed they had a patient who had a negative NIPT result that was later found to be incorrect upon the birth of the child. In this instance, the baby had Down syndrome at birth following a positive maternal serum screen and a negative NIPT result.

INFORMED CONSENT PROCESS

We asked participants to share their current clinical practices for consenting patients for NIPT as well as their thoughts for the future. Participants could choose all responses that applied, and all respondents (100%) indicated that genetic counselors consent for NIPT in their clinic. Maternal fetal medicine specialists (31.8%) are also consenting patients for NIPT. We asked respondents to select which health care provider(s) is/are appropriate to consent for NIPT. Again, participants could choose all that applied and 97.7% selected genetic counselors, 60.3% selected maternal fetal medicine specialists, 9.8% chose obstetricians, 8.0% chose nurse practitioners, and 5.2% selected midwives. Most respondents (62.2%) indicated they obtain consent for NIPT verbally (Figure 4).

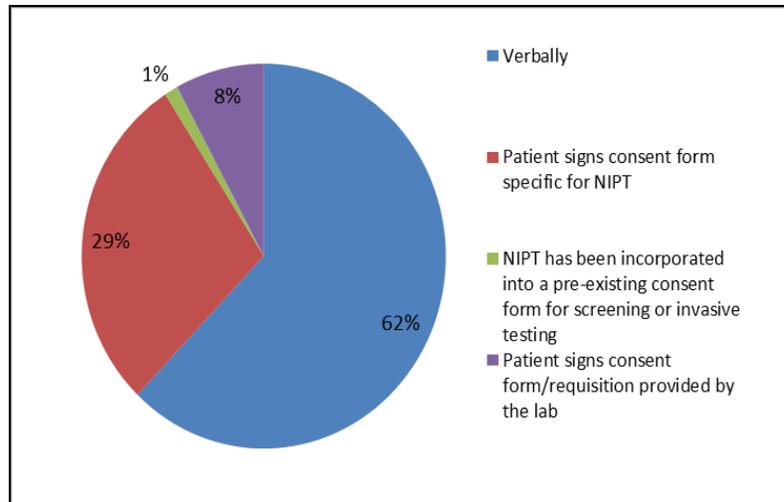


Figure 4. Informed consent process for NIPT.

Slightly less than half of respondents (45.1%) indicated that there should be a separate informed consent form specific to NIPT, whereas 22.0% did not think there should be a separate consent form, and 32.9% were undecided. In addition, when respondents were asked how well they felt their patients understood the difference in detection rates between NIPT and maternal serum screening for chromosomal aneuploidies, most respondents (61.3%) felt that their patients fully understand the difference, 9.2% of respondents believed that patients do not really understand the difference, and 29.4% said it was hard to assess. In order to judge patient understanding, respondents indicated they do one or more of the following: take note of questions the patient asks (93.9%); ask the patient directly if they understand (76.7%); observe facial expressions (70.6%); and observe patient body language (60.7%). There was no significant difference between how well genetic counselors felt their patients understood NIPT and how they obtained informed consent.

We asked respondents to list the four most important points they believe should be included in a discussion about NIPT with patients. The following themes emerged

from their responses: if they get a positive NIPT result then follow up with a CVS or amniocentesis is recommended; NIPT is a screening test and is not diagnostic; NIPT only detects certain chromosome aneuploidies; cost and insurance coverage should be mentioned; NIPT has a superior detection rate compared to other types of prenatal screening tests; and there is a possibility for false positives and false negatives (Table 4).

Table 4. Points to include in a discussion with patients about NIPT.

Discussion Point	Number of Respondents	Sample Quotation
Positive result should be confirmed with amniocentesis	81	“the test is not diagnostic, and therefore decisions regarding continuation/termination should not be made based on these results alone...”
Not diagnostic	80	“...it is still just a better screen, not diagnosis...”
Only detects T13, T18, T21, monosomy X	76	
Cost/insurance coverage	60	“...this is a new technology and not yet [considered] “standard of care” by most insurance carriers”
Superior detection rate	53	“...best noninvasive detection possible (quote sensitivity and specificity)...”
False positive/false negative	51	“...the possibility exists for a false positive or false negative...”
Considered a screening test	48	“It’s advanced screening, not diagnostic...”
Not as comprehensive as karyotype	32	
Turnaround time for results	25	
Description of technology	15	
Non-invasive	12	
Potential need for blood re-draw	12	
Parents should consider what they would do with results	12	
Test is new and not validated for use in general population	10	
Cannot detect open neural tube defects	9	

FUTURE INTEGRATION OF NIPT

Finally, in an open-ended question, we asked survey participants to provide their thoughts on the future of sex determination and whole exome sequencing (WES) in the context of NIPT (Table 5). Some respondents expressed support for sex determination when there is a question of a sex chromosome disorder, which is illustrated by the following quote:

“ I find sex determination is useful for detecting sex chromosome abnormalities, mostly Turner syndrome, in the presence of a cystic hygroma...”

Other respondents had no reservations regarding sex determination regardless of clinical circumstance. Some respondents expressed concern over patients terminating an otherwise healthy pregnancy based on sex alone, as illustrated by a respondent who said,

“I worry that sex determination will lead to termination based on sex, which I feel is ethically objectionable.”

With respect to WES, common responses included that the knowledge required to fully interpret results from WES is not currently at a level that is clinically useful in a prenatal setting. This is demonstrated by the following quote:

“...I don't think it is scientifically responsible. There are still so many uncertainties about exome sequencing that it's difficult to interpret results, and that's in patients who have clinical symptoms or relevant family histories. I feel that having a clinical assessment is necessary in the accurate [interpretation] of exome sequencing results.”

Some respondents stated that there will be many variants of unknown significance uncovered with this type of testing. Overall, there were an equal number of genetic counselors who expressed excitement about WES in the context of prenatal genetic counseling and who were undecided on how they felt. Another trend, that was not specific for sex

determination or WES, was the need for genetic counseling and obtaining informed consent.

Table 5. Respondents' thoughts on the future of NIPT pertaining to sex determination and whole exome sequencing.

Respondents' Thoughts	Number of Respondents
Sex Determination	
Support for sex determination in the context of disorders involving sex chromosomes in the fetus	22
Worry that patients will terminate an otherwise healthy pregnancy based on sex alone	22
No reservations	12
Whole Exome Sequencing	
Knowledge required to fully interpret results is not at a clinically useful level	20
Many variants of unknown significance	7
Excitement for WES	8
Undecided over feelings of WES in a prenatal setting	9
Both Sex Determination and WES	
Need for genetic counseling and obtaining informed consent	15

DISCUSSION

This was the first study to look at the integration of NIPT into clinical practice, particularly in the context of genetic counseling. We queried prenatal genetic counselors regarding their current use of NIPT, including their informed consent process, and their thoughts for the future of NIPT in prenatal genetic counseling. We had a 26% response rate of prenatal genetic counselors based on the most recent NSGC Professional Status Survey (NSGC, 2011). We found that the largest group of respondents incorporated NIPT into their clinical practice between January and April 2012. At the time of this study, those who began offering NIPT earlier were significantly more likely to send a larger volume of samples per week. These counselors may be more comfortable with NIPT having offered it for longer, and subsequently they may be offering it to patients with a wider range of indications, resulting in a larger volume of samples. Alternatively, larger and/or busier clinics may be more likely to adopt new types of testing as they become available which would also explain why counselors who began offering the test earlier tend to send more samples per week.

The majority of respondents indicated they most frequently offer NIPT to pregnancies considered high risk and that incorporation of this new test has made pre-test genetic counseling sessions longer. Among the most important points they identified as needing to be added when counseling a patient about NIPT are: the test is not diagnostic; the detection rate is superior to other prenatal screening tests; diagnostic testing is recommended to confirm a positive NIPT result; and this test is not as comprehensive as a

karyotype. Fewer respondents than expected noted the importance for a discussion surrounding the significance of a positive result. However, many included general statements relating to a higher detection rate which could have been meant to include a discussion of the significance of a positive result.

When asked about obtaining consent for NIPT, all respondents indicated that genetic counselors, often in addition to other healthcare professionals, obtain informed consent from their patients. A number of respondents indicated that a separate informed consent form should be developed for NIPT, however the majority indicated that they obtain informed consent verbally. Of note is that there is a requisition form for each lab that some providers have the patient sign prior to NIPT testing. When we asked how the patient gives informed consent, respondents were able to select “other” and fill in a text response in which some participants indicated the patient signs the lab requisition/consent form provided by the NIPT lab as a means of obtaining informed consent. Had this option been available in the list of potential responses we speculate that respondents may have selected this option more frequently, and therefore the group who chose verbal consent may not have been quite as large. A study conducted before NIPT was clinically available showed that providers, specifically obstetricians and midwives, viewed consent for NIPT differently than for invasive techniques for prenatal diagnosis. Specifically, most providers (96.1%) thought that invasive testing required written informed consent as compared to 68.3% for NIPT and 75.4% for maternal serum analyte Down syndrome screening (van den Heuvel et al., 2010). These findings suggest that for some providers, it is the risk of miscarriage following an invasive procedure that influences the need for written consent rather than the sensitivity of the diagnostic test itself. This, and the

findings by Favre et al. (2007) that a majority of patients felt either partially or fully uninformed following a discussion of maternal serum screening, highlights the importance of effectively educating patients to help facilitate informed decision-making. Genetic counselors are trained specifically in these areas and will continue to play a vital role in patient education and obtaining informed consent, especially when NIPT becomes more widely available.

At this time, NIPT can only be used clinically to detect certain aneuploidies and for sex determination. However, whole genome sequencing by NIPT of the fetus has recently been demonstrated in the research setting (Fan et al., 2012). Opinions of genetic counselors from this study regarding the future integration of NIPT revealed concern over the fact that technology is advancing much more rapidly than knowledge of genes, their variants, and the implications of those variants for patients. Respondents acknowledged the increasing need for genetic counselors in settings where healthcare providers offer patients these types of tests.

After we completed data collection for this study, ACOG and the Society for Maternal-Fetal Medicine released a committee opinion statement pertaining to the incorporation of NIPT into clinical practice. The recommendation from this group as of December 2012 is to offer NIPT as a first screening option to patients that are considered high risk for having a fetus with an aneuploidy, and also to offer NIPT as a second screening option if a patient receives a positive maternal serum screening result. Upon receipt of a positive NIPT result, ACOG recommends confirmation of results with CVS or amniocentesis since false positive results are possible with this testing (ACOG, 2012). ACMG also released guidelines, which recommend pre-test counseling for NIPT as well as post-test

counseling for screen positive individuals (Gregg, et al., 2013). Furthermore, NSGC recommends that only patients at increased risk for a chromosome aneuploidy should be offered NIPT and diagnostic testing is recommended to confirm positive results (Wilson, et al., 2013). In this study, we queried genetic counselors as to whom they offer testing prior to any of these statement releases. Consistent with these recommendations, we found that most genetic counselors offered NIPT to women of AMA and did not offer it to women who were not AMA and who present to clinic for first trimester screening. This is not surprising, considering that this is how the test is marketed to medical professionals (SequenomInc., 2012). Of note is we found that 14.6% of respondents indicated that they had had at least one patient who terminated a pregnancy based only on NIPT results. We did not ask if there were any ultrasound findings in these cases, and so we cannot assume that the NIPT result was the only factor in decision-making.

STUDY LIMITATIONS

The number of study participants was 206 total respondents, 181 of which indicated they had incorporated NIPT and therefore were responsible for the bulk of the data analyzed. There may have been a sample bias because the subject of the e-blast included the term “NIPT”, and genetic counselors may have been more likely to complete the survey if their clinic had already incorporated NIPT. Furthermore, we recruited through NSGC and therefore only NSGC members received the e-blast recruitment email, though it was possible for colleagues to forward the recruitment email to non-members.

We did find some discrepancy in number of respondents for two questions that essentially asked the same thing. Respondents were not required to answer every question

in the survey, which caused this inconsistency. In particular, we asked respondents about positive NIPT results on two occasions, however in the second question pertaining to positive NIPT results, participants could only fill in a number if they selected a certain answer for the question immediately before (Appendix B).

CONCLUSION

We surveyed prenatal genetic counselors to determine how they have incorporated NIPT into prenatal genetic counseling since the launch of the first test in 2011. We found that those who had incorporated NIPT into their clinic have mostly offered it to women at increased risk for aneuploidy, which is consistent with the newly released recommendations of ACOG, ACMG, and NSGC with regard to NIPT prenatal genetic screening. Respondents mostly gathered informed consent for NIPT verbally and indicated genetic counselors obtain informed consent from patients. Nearly half of respondents believe there should be a separate informed consent for NIPT and the discussion surrounding this test should highlight its screening nature, its superior detection rate compared to other screening methods, the limited number of conditions it can screen for, and the recommendations for diagnostic testing following a positive result. Future studies should address patient understanding of NIPT following genetic counseling to determine the best method for obtaining true informed consent as well as verify that informed consent for NIPT is being obtained as a wider array of healthcare providers begin to order this test.

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APPENDIX A. Recruitment Notice

Subject: Student Research Project – NIPT: Current Utilization and Implications for the Future of Prenatal Genetic Counseling

Are you Currently Practicing as a Prenatal Genetic Counselor in a Prenatal Clinic?

If you are, I invite you to participate in a research study investigating the **current integration and future directions of non-invasive prenatal testing (NIPT)**.

The purpose of this research study is to learn how genetic counselors in all parts of the United States and Canada are currently incorporating NIPT into clinical practice in the hopes of defining a direction for the future integration of NIPT.

Participation in this study is available to all prenatal genetic counselors who are currently working in a prenatal clinic setting. This study consists of an anonymous online survey that will take approximately 20-30 minutes to complete. Participation is anonymous and voluntary. You may discontinue participation at any time.

Participants will have the option to enter a draw to win one of two \$50 gift cards to Amazon.com upon completion of the survey.

If you are interested in answering questions pertaining to your current experience with NIPT with the aim of establishing a standard of care for the future, please follow the link to the survey below.

[Link to survey](#)

If you have any comments or questions, please feel free to contact me by email at abuchana@brandeis.edu, or the Brandeis University faculty sponsor, Judith Tsipis, at tsipis@brandeis.edu. Thank you in advance for your participation.

Sincerely,

Amanda Buchanan

Brandeis University Genetic Counseling Program, Class of 2013

APPENDIX B. Survey

NIPT: Current Utilization and the Future Implications for Prenatal Genetic Counseling

Thank you for choosing to participate in my survey. Your responses are anonymous. You may choose to discontinue participation at any time during the survey.

Non-invasive prenatal testing (NIPT) involves measuring cell free fetal DNA in maternal blood to detect fetal aneuploidies. This test became clinically available in November 2011 for measuring trisomy 21. Since this time, other tests have emerged that also detect trisomies 13 and 18, and monosomy X. Currently there are no clear guidelines for how NIPT should be integrated into clinical practice. The purpose of this research study is to determine the current integration of NIPT and the future direction of NIPT in the hopes of establishing a standard of care for genetic counseling. Your insight on this topic will help to delineate current practices as well as directions for the future of NIPT in clinical practice.

For the purpose of consistency throughout the survey, “NIPT” will be used to describe the technology of measuring cell free fetal DNA in maternal blood to predict fetal aneuploidies.

Upon completion of the survey, you will have the option to enter a draw to receive one of two \$50 gift cards for Amazon.com.

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

Q1 Are you currently practicing as a prenatal genetic counselor?

- Yes (1)
- No (2)

If No Is Selected, Then Skip To End of Survey

Q2 What region do you practice in?

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

Q3 How many years have you been working as a prenatal genetic counselor?

Q4 What type of setting do you work in?

- University medical center (1)
- Private hospital/medical facility (2)
- Public hospital/medical facility (3)
- HMO (4)
- Private OB/GYN office (5)
- Government hospital/medical facility (6)
- Other, please specify: (7) _____

Q5 Has NIPT been incorporated into your clinical practice?

- Yes (1)
- No (2)

If yes Is Selected, Then Skip To When did your practice begin offering NIPT to patients?

Answer If Has NIPT been incorporated into your clinical practice? No Is Selected

Q6 Please briefly explain why NIPT has not been incorporated into your clinical practice.

Answer If Has NIPT been incorporated into your clinical practice? No Is Selected

Q7 Does your clinic intend to incorporate NIPT into your clinical practice?

- Yes (1)
- No (2)

If No Is Selected, Then Skip To Thank you for your participation.

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

Q8 Please describe when you expect NIPT to be incorporated your into clinical practice.

If Please describe when you expect NIPT to be incorporated into your clinical practice. Is Not Empty, Then Skip To Thank you for your participation. If Please describe when you expect NIPT to be incorporated NIPT into your clinical practice? Is Empty, Then Skip To Thank you for your participation.

Q9 When did your practice begin offering NIPT to patients?

- November 2011 - end of December 2011 (1)
- January 2012 – end of April 2012 (2)
- May 2012 – August 2012 (3)
- After September 2012 (4)

Q10 In your clinic, how do you refer to the method of testing cell free fetal DNA for aneuploidy in maternal serum when you are talking to patients?

- NIPT (Non-invasive prenatal testing) (1)
- NIPD (Non-invasive prenatal diagnosis) (2)
- Cell-free fetal DNA testing (3)
- other, please specify: (4) _____

Q11 Approximately how many samples per week does your practice currently send for NIPT?

Q12 Who consents the patient for NIPT in your practice setting? (Check all that apply)

- Maternal-fetal Medicine Specialist (1)
- Nurse Practitioner (2)
- Midwife (3)
- Genetic Counselor (4)
- Obstetrician (5)
- Other, please specify: (6) _____

Q13 At present, which health care provider(s) do you think is/are appropriate to consent patients for NIPT? (Check all that apply)

- Maternal-fetal Medicine Specialist (1)
- Nurse Practitioner (2)
- Midwife (3)
- Genetic Counselor (4)
- Obstetrician (5)
- Other, please specify: (6) _____
- No preference (7)

Q14 Have you received any referrals from outside OB clinics for women with positive NIPT results without having had genetic counseling prior to testing?

- Yes (1)
- No (2)

Answer If Have you received any referrals from outside OB clinics from outside OC clinics for women with positive NIPT results without having had genetic counseling prior to testing? Yes Is Selected

Q15 How many total?

Q16 To whom do you currently offer NIPT?

- Only patients that request it (1)
- All pregnant patients, regardless of indication (2)
- Only high-risk patients (check all that apply) (3)

If To whom do you currently offer NIPT? Only high-risk patients (check all that apply) Is Selected

- Advanced maternal age (4)

If To whom do you currently offer NIPT? Only high-risk patients (check all that apply) Is Selected

- Abnormal ultrasound findings (5)

If To whom do you currently offer NIPT? Only high-risk patients (check all that apply) Is Selected

- Positive maternal serum screen (6)

If To whom do you currently offer NIPT? Only high-risk patients (check all that apply) Is Selected

- Personal or family history of chromosome abnormalities (7)

Q17 If you offer NIPT following abnormal ultrasound findings, are there any abnormal ultrasound findings for which you do not offer NIPT?

- Yes, Please describe: (1) _____
- No (2)

Q18 For women of advanced maternal age, in which of the following scenarios do you discuss NIPT with the patient? (Check all that apply):

- Referred for first trimester screening (1)
- Referred for diagnostic testing (2)
- Maternal serum screen result is negative (3)
- Maternal serum screen result is positive (4)
- Negative first trimester screen plus one or more soft markers on ultrasound (I.e., echogenic focus, choroid plexus cysts, echogenic bowel, thickened nuchal fold, hy-

- dronephrosis) that when combined with first trimester screen results does not increase the risk for aneuploidy to above the lab cut-off (5)
- Negative first trimester screen plus one or more soft markers on ultrasound (I.e., echogenic focus, choroid plexus cysts, echogenic bowel, thickened nuchal fold, hydronephrosis) that when combined with first trimester screen results does increase the risk for aneuploidy to above 1:270 (6)
 - Multiple soft markers found on ultrasound regardless of maternal serum screen result (7)
 - Nuchal translucency is >3.0mm (8)
 - Nuchal translucency is >3.5mm (9)
 - Cystic hygroma found on ultrasound (10)
 - Presence of any structural fetal anomaly on ultrasound (11)
 - History of a previous pregnancy with a trisomy (T13, T18, T21) (12)
 - Family history of trisomy (T13, T18, T21) other than a previous pregnancy (13)
 - Other, please specify: (14) _____

Q19 For pregnant women that are not AMA, in which of the following scenarios do you discuss NIPT with the patient? (Check all that apply):

- Referred for first trimester screening (1)
- Referred for diagnostic testing (2)
- Maternal serum screen result is negative (3)
- Maternal serum screen result is positive (4)
- Negative first trimester screen plus one or more soft markers on ultrasound (I.e., echogenic focus, choroid plexus cysts, echogenic bowel, thickened nuchal fold, hydronephrosis) that when combined with first trimester screen results does not increase the risk for aneuploidy to above the lab cut-off (5)
- Negative first trimester screen plus one or more soft markers on ultrasound (I.e., echogenic focus, choroid plexus cysts, echogenic bowel, thickened nuchal fold, hydronephrosis) that when combined with first trimester screen results does increase the risk for aneuploidy to above 1:270 (6)
- Multiple soft markers found on ultrasound regardless of maternal serum screen result (7)
- Nuchal translucency is >3.0mm (8)
- Nuchal translucency is >3.5mm (9)
- Cystic hygroma found on ultrasound (10)
- Presence of any structural fetal anomaly on ultrasound (11)
- History of a previous pregnancy with a trisomy (T13, T18, T21) (12)
- Family history of trisomy (T13, T18, T21) other than a previous pregnancy (13)

Other, please specify: (14)

Q20 Have you offered NIPT in pregnancies with multiple gestations?

- Yes (1)
- No (2)

Q21 Overall, approximately what percent of your patients offered NIPT choose the test?

- less than 25% (1)
- 26-50% (2)
- 51-75% (3)
- 76-100% (4)

Q22 Has the amount of time it takes to complete a genetic counseling session changed with the introduction of NIPT?

- yes, it has become longer (1)
- yes, it has become shorter (2)
- no change (3)
- It varies (4)

Answer If Has the amount of time it takes to complete a genetic counseling session changed with the introduction of NIPT? yes, it has become longer Is Selected

Q23 If it has become longer, what is taking more time? (Check all that apply)

- Patient decision making (1)
- NIPT explanation (2)
- Contrasting maternal serum screening, NIPT, and invasive, diagnostic testing (3)
- Patient comprehension (4)
- Other, please specify: (5) _____

Answer If Has the amount of time it takes to complete a genetic counseling session changed with the introduction of NIPT? yes, it has become shorter Is Selected

Q24 If it has become shorter, please explain why you think it is taking less time:

Q25 What do you think are the four most important points that should be included in a discussion of NIPT to patients?

Q26 How is informed consent obtained for NIPT at your clinic?

- Verbally (1)
- There is an informed consent form that patients sign specifically for NIPT (2)
- We have incorporated NIPT into a pre-existing informed consent form for screening (3)
- We have incorporated NIPT into a pre-existing informed consent form for invasive diagnostic testing (4)
- Other, please specify: (5) _____

Q27 Do you think there should be a separate informed consent form for NIPT?

- Yes (1)
- No (2)
- Unsure (3)

Q28 At what point in the conversation of NIPT do you first give information on T13, T18, and T21 to patients?

- During the description of NIPT, prior to the patient opting for testing (1)
- When negative NIPT results are given (2)
- When positive NIPT results are given (3)
- I do not give patients information on T13, T18, T21 (4)
- Other, please specify: (5) _____

Q29 How well do you feel your patients comprehend the detection rates of NIPT versus maternal serum screening for chromosomal aneuploidies?

- In general, patients fully understand the difference (1)
- In general, patients do not really understand the difference (2)
- Hard to assess (3)

Q30 How do you assess your patient's understanding of the differences in detection rates of trisomies for NIPT compared to other available screening options? (Check all that apply)

- Observe body language (1)
- Observe facial expressions (2)
- Observe questions they are asking (3)
- Ask them directly if they understand (4)

Q31 What specificity (false-positive rate) do you quote for NIPT for trisomy 21?

Q32 What sensitivity (detection rate) do you quote for NIPT for trisomy 21?

Q33 What specificity (false-positive rate) do you quote for NIPT for trisomy 18?

Q34 What sensitivity (detection rate) do you quote for NIPT for trisomy 18?

Q35 What specificity (false-positive rate) do you quote for trisomy 13?

Q36 What sensitivity (detection rate) do you quote for NIPT for trisomy 13?

Q37 Amongst your patients with positive maternal serum screens for aneuploidy and negative NIPT results, approximately what percent continue on to invasive diagnostic procedures?

- 0-25% (1)
- 26-50% (2)
- 51-75% (3)
- 76-100% (4)
- N/A - I have never had a patient screen positive for an aneuploidy on maternal serum screening who tests negative for aneuploidies with NIPT (5)

Q38 Approximately how many patients in your clinic have had positive NIPT results?

Answer If Approximately how many patients in your clinic have had positive NIPT results? Text Response Is Greater Than 0

Q39 Of the patients in your clinic with a positive NIPT result, approximately how many:

Did not confirm with invasive diagnostic testing and continued the pregnancy (1)

Terminated the pregnancy based only on NIPT (2)

Confirmed result with amniocentesis or CVS and continued the pregnancy (3)

Confirmed the result with amniocentesis or CVS and terminated the pregnancy (4)

Had an amniocentesis or CVS result that did not confirm the NIPT result (5)

N/A - I have never had a patient with a positive NIPT result (6)

Q40 In your clinic, have you received a positive test result from NIPT that was later found to be negative by invasive diagnostic testing?

- Yes (1)
- No (2)

Answer If In your clinic, have you received a positive test result from NIPT that was later found to be negative by invasive diagnostic testing? yes Is Selected

Q41 Please describe the clinical and psychosocial issues that accompanied the situation(s).

Q42 In your clinic, have you received a negative result from NIPT that was found to be incorrect by follow-up invasive diagnostic testing?

- Yes (1)
- No (2)

Answer If In your clinic, have you received a negative result from NIPT that was later found to be incorrect by follow-up invasive diagnostic testing? yes Is Selected

Q43 Please describe the clinical and psychosocial issues that accompanied the situation(s).

Q44 In your clinic, have you received a negative result from NIPT that was found to be incorrect upon birth of the child?

- Yes (1)
- No (2)

Answer If In your clinic, have you received a negative result from NIPT that was found to be incorrect upon birth of the child? yes Is Selected

Q45 Please describe the clinical and psychosocial issues that accompanied the situation(s).

Q46 Which lab(s) does your clinic currently use for NIPT? (Check all that apply)

- Ariosa/Labcorp (1)
- Sequenom (2)
- Verinata (3)
- Natera (4)
- Other, please specify: (5) _____

Q47 What are your thoughts for the future of NIPT regarding sex determination and exome sequencing?

Q48 Thank you for your participation.

If you are interested in entering a draw to win one of two \$50 Amazon.com gift cards, please email abuchana@brandeis.edu stating you wish to be entered into the draw. Your email address will in no way be connected to your responses to this survey.