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NIPS + FTS = ?: A consideration of the next steps of prenatal screening

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ABSTRACT

Since its introduction less than four years ago, noninvasive prenatal screening (NIPS) has been widely adopted as a screening tool for women at a high-risk for fetal aneuploidy. As use expands into the general population, questions arise concerning the integration of NIPS into preexisting screening routines. We surveyed 208 practicing genetic counselors to assess the current use of NIPS. Genetic counselors were queried as to the advantages/disadvantages of offering NIPS to all patients regardless of a priori risk. Results indicate substantial variation in practice. The majority of participants report offering NIPS in conjunction with another method of screening for fetal aneuploidy, indicating that NIPS is being used as an addition rather than as a replacement. Most offer NIPS with another form of screening, predominantly either first trimester ultrasound, NT, and an MSAFP (45.1%, n=78), or first trimester serum screening, with or without an NT, and an MSAFP (19.7%, n=34). Counselors are evenly split on the merits of expanding the use of NIPS to the general population (con: 55.3%, n=105; pro: 44.7%, n=85). The lack of consensus among respondents suggests that practice guidelines might benefit counselors at this time. In addition, the respondents emphasize the significance of better educating providers about the risks, benefits, and limitations of the test.

KEY WORDS

Noninvasive prenatal screening, Non-invasive prenatal testing, Cell-free DNA, Genetic counseling, Prenatal screening, Aneuploidy

INTRODUCTION

The introduction of noninvasive prenatal screening (NIPS) technology has generated considerable interest, as it promises to be a screen with higher detection rates and lower false positive rates than preexisting screening methods, minimal physical risk to mother and fetus, and information on multiple chromosomal conditions. As centers across the country increase their use of this new technology, it is important to carefully consider the benefits, risks, and limitations of NIPS relative to alternative screening tests to determine how best to integrate this tool into the existing machinery of prenatal screening.

BACKGROUND

Existing guidelines

In December 2012, the American Congress of Obstetricians and Gynecologists (ACOG) and the Society of Maternal-Fetal Medicine (SMFM) approved the use of NIPS in high-risk women. This joint committee opinion did not endorse the use of NIPS in women at a low-risk for fetal aneuploidy due to a lack of adequate performance studies (ACOG, 2012). The American College of Medical Genetics and Genomics (ACMG) took a similar stance in a policy statement published in February 2013 (Gregg et al., 2013), emphasizing that NIPS should not replace a first trimester ultrasound or invasive testing. In addition, the authors underscored that this technology is a screen and not a diagnostic test. A National Society of Genetic Counselors (NSGC) position paper, published in January 2013 reminded providers that this screening should not be considered first-tier testing and highlighted the importance of pre and post-test counseling (Devers et al., 2013). As of now, these position statements have not been revised, and currently none of the major organizations support the use of NIPS in the low-risk population.

Sensitivity and specificity of noninvasive prenatal screening technology in the general population

Four main companies pioneered the clinical use of NIPS, using cell-free DNA (cfDNA) to assess a pregnancy's risk for certain aneuploidies and other chromosomal abnormalities. These four companies are Sequenom, Verinata (since purchased by Illumina), Ariosa Diagnostics, and Natera. Recently, more laboratories have announced that they will offer their own version of NIPS, indicating that the testing may soon become less specialized. The four primary companies all use different methods and the screens vary in terms of what

chromosome abnormalities are covered. For some of the tests, patients must choose to opt in for studies of sex chromosomes and/or microdeletions/microduplications. Each company uses its own methodology for NIPS, and their benefits and limitations vary, though all methods have demonstrated sensitivity and specificity for the identification of Down syndrome superior to that of traditional fetal screening.

There have been several major studies to evaluate the efficacy of NIPS (Bianchi et al., 2014; Chetty, Garabedian, & Norton, 2013; Dar et al., 2014; Gil, Quezada, Bregnant, Ferraro, & Nicolaides, 2013; Nicolaides, Syngelaki, Ashoor, Birdir, & Touzet, 2012; Norton et al., 2012; Norton, Rose, & Benn, 2013; Pergament et al., 2014). Three studies that focused on the use of NIPS in the general population or low-risk population (Bianchi et al., 2014; Nicolaides et al., 2012; Pergament et al., 2014) found that NIPS had comparable sensitivities and specificities in high and low-risk patients.

Nicolaides et al. (2012) and Bianchi et al. (2014) used NIPS technology with a sequencing approach in a population with both low and high-risk patients. Their goal was to see if screening would have the same results in this blended population as had been reported in high-risk populations. Pergament et al. (2014) employed NIPS with a single-nucleotide polymorphism (SNP) approach, which proved to have several advantages. In this study, the authors separated the results by low-risk and high-risk, and then considered them as a whole. All three studies, despite differences in methodology, concluded that NIPS's performance is conserved in the low-risk population.

The Nicolaides et al. (2012) cohort study consisted of 2049 women with a singleton pregnancy presenting for first trimester screening (FTS). These women had both FTS and NIPS, allowing the authors to evaluate their relative merits. Trisomy risk scores were given

for 95.1% (1949 of 2049) of affected cases including all eight fetuses with trisomy 21 and two of the three fetuses with trisomy 18 (Nicolaides et al., 2012, p. 374.e2). In addition, 99.9% (1937 out of 1939) of euploid cases were labeled as having a <1% risk for trisomy 21 and trisomy 18. NIPS identified trisomies 21 and 18 with a false positive rate of 0.1% (Nicolaides et al., 2012, p. 374.e2). However, one of the cases of trisomy 18 failed to generate a result. While this does not match the accuracy of diagnostic testing, it did demonstrate a higher detection rate and lower false positive rate than traditional FTS.

There were some limitations to this study. First, the median maternal weight was 144 pounds, 22 pounds less than the average weight of an American woman. Median maternal weight would be expected to be higher in many patient populations in the United States (Body Measurements, 2012), and higher weight is a major risk factor for low fetal fraction and resulting NIPS failure. Second, for phenotypically normal babies, no cytogenetic testing was done to confirm NIPS results. While it is unlikely that these babies would have trisomy 21 or trisomy 18, they may have had other cytogenetic findings that would have been apparent on a karyotype and/or microarray. Furthermore, the study included seven pregnancies with known abnormal karyotypes that would not be picked up on NIPS. It is possible this number would have been higher if cytogenetic testing had been done on all newborns. Third, the 2049 women include 100 women who received no result from NIPS. These test failures were either due to low fetal fraction (46 cases) or assay failure (54 cases). The 46 cases of low fetal fraction are significant and will also be considered in the context of the findings from Pergament et al. (2014), which are discussed below. The n of 2049 does not include an additional 100 women for whom NIPS could not be run because of laboratory error (70 cases), inadequate sample volume (29 cases), or incorrect labeling (1 case). In

total, there were 200 women who did not have NIPS results. The authors conclude that the detection rate of trisomies is a function of assay precision and fetal fraction, not prevalence, suggesting that the population being tested would not have an effect on the accuracy of the testing.

Bianchi et al. (2014) was based on the CARE (Comparison of Aneuploidy Risk Evaluations) study, a prospective, blinded, multicenter study to analyze the performance of NIPS in comparison to traditional screening. The study enrolled 2042 women that had either already had or planned to have FTS or a second trimester maternal serum screen (quad). Eighteen women, (0.9%) did not get a result because of problems during extraction or sequencing. Of note, 28.5% of the total had NIPS in the third trimester, which represents a drastic deviation from how this screening would typically be used in practice.

In the CARE study, NIPS performed equally well in a general population as it has in the high-risk population, and outperformed standard screening. NIPS had lower false positive rates for trisomy 21 and trisomy 18 than FTS. For trisomy 21, there were six false positives (0.3%) with NIPS compared to sixty-nine (3.6%) with traditional screening (Bianchi et al., 2014, p. 803). For trisomy 18, three patients (0.2%) had a false positive with NIPS while eleven (0.6%) had a false positive with traditional screening (Bianchi et al., p. 803). Of all patients with false positives, none had a false positive on both screens, and both screens detected all eight cases of aneuploidy (five trisomy 21, two trisomy 18, and one trisomy 13. Again, for the false positives, assessment at birth included normal physical exams, but no cytogenetic testing, and confined placental mosaicism or maternal mosaicism cannot be ruled out (Bianchi et al., 2014, 806).

Out of the 1,051 women in the study by Pergament et al (2014), 533 (50.7%) were

considered high-risk and 518 (49.3%) were considered low-risk. Participants were not provided with their NIPS results. NIPS results included risk assessments for trisomy 21, trisomy 18, trisomy 13, and monosomy X (Turner syndrome). In addition, all NIPS results were confirmed with cytogenetic testing, closing another gap from previous studies.

Of the women studied, 966 (91.9%) of the NIPS returned a result. The overall sensitivity (trisomy 21, trisomy 18, trisomy 13, and monosomy X) was 98.1% and the overall specificity was 99.8%. Again, results suggest that the sensitivity and specificity do not suffer in the low-risk population (Pergament et al., 2014, p. 6). A significant difference between the two populations was that NIPS more frequently failed to produce a result in the low-risk population. The authors attribute this to an earlier gestational age at the time of the blood draw in the low-risk population, which increases the chances of low fetal fraction.

When looking at the samples from both populations combined, the authors found that 16% (20/125) of the true aneuploidy samples did not produce a result (Pergament et al., 2014, p. 2). Fifteen of these samples (75%) had low fetal fraction or low fetal fraction and insufficient data clarity, and ten had a fetal fraction below 3.4%, which is considered to be below the 1.5^{th} percentile (Pergament et al., 2014, p. 5). From this, the authors conclude that samples with less than 3.4% fetal fraction were six times more likely to be abnormal than the samples with a fetal fraction greater than 3.4%, highlighting the importance of following-up with patients for whom NIPS failed to provide a result.

Despite increased problems with fetal fraction, NIPS maintains a high sensitivity and specificity in the low-risk population. However, there are issues concerning the positive predictive value (PPV) of the test. Many studies do not consider PPV and, notably, PPV is often missing from the materials produced by the laboratories. In a lecture about the

marketing of NIPS, Stoll (2014a) detailed her analysis of published PPV values, and focused on one particular laboratory whose values were accessible. She used their quoted sensitivity, specificity, and PPV, to determine the incidence of Down syndrome, essentially working backwards. She found that the incidence had to be 1 in 4 in order for the values to be true. While the laboratory does not disclose the incidence of Down syndrome from their "internal data," Stoll was critical of high PPV rates reported by this laboratory, explaining that based on the accessible values, her independent calculation of PPV was much lower.

Several others have noted the failure to discuss, and the importance, of PPV (Begleiter & Finley, 2014; Mennuti, Cherry, Morrissette, & Dugoff, 2013; Mennuti, Cherry, Morrissette, & Dugoff, 2014; Stoll & Lindh, 2015). Begleiter and Finley (2014) highlight the difference in PPV and sensitivity and specificity. They calculated the PPV, for each of the four major commercial versions of NIPS, for a 35-year-old woman with no other risk factors whose screen is positive for Down syndrome. The PPVs ranged from >28% to >80%. These two companies with the lowest and highest calculated PPVs, both claim specificities and sensitivities of at least 99%. In this exercise, they emphasize that false positives are a very real possibility. In a reply to Begleiter and Finley's letter to the editor, Mennuti et al. (2014) state that obstetricians must keep in mind that as NIPS is increasingly used for low-risk women and as other, rarer, conditions are added to the screen, the PPV will drop.

Utility of first trimester screening (FTS) and maternal serum screening in comparison to NIPS

Use of NIPS has grown and continues to grow very rapidly, accompanying and in some cases replacing the use of other prenatal screening modalities. In comparing NIPS to FTS and maternal serum screening, the primary measure is the relative sensitivity and

specificity of each method. However, there are ancillary benefits of FTS and maternal serum screening worth consideration.

The argument has been made that if NIPS becomes the standard screen, there will be no reason to continue taking nuchal translucency measurements (NT) since NT detects only aneuploidy and has not been proven to be clinically useful for detecting fetal heart defects or other anomalies (Shulman, 2014). However, some studies suggest that NT has other utility, and that the first trimester ultrasound screens for more than aneuploidy.

In a comprehensive review, Nicolaides searched PubMed to gather over a decade's worth of studies and articles looking at the utility of nuchal translucency and other first trimester ultrasound findings as screening for chromosome abnormalities (Nicolaides, 2004). Nicolaides concluded that increased NT can be associated with a variety of conditions, including, trisomy 21, Turner syndrome, other chromosome abnormalities, fetal malformations, and genetic syndromes. The cause of the enlarged NT can be cardiac defects, venous congestion, diaphragmatic hernias, skeletal dysplasias, problems with the development of the lymphatic system, and more. These causes may be isolated or syndromic. For example, the fetus could have an isolated heart defect or could have a heart defect as a result of having Down syndrome (Nicolaides, Heath, & Cicero, 2002). From the combined data, Nicolaides found that, "the risk of an adverse outcome, which includes chromosomal and other abnormalities and fetal and postnatal death, increases with NT thickness from approximately 5% for NT between the 95th percentile and 3.4 mm to 30% for NT between 3.5 mm and 4.4 mm to 50% for NT of 4.5 to 5.4 mm and 80% for NT of $\geq$ 5.5 mm" (Nicolaides, 2004, p. 47). While this increased risk does include aneuploidies for

which NIPS is highly sensitive, it demonstrates that increased NT can be a significant indicator of other fetal anomalies.

In addition, Nicolaides pointed to the advantages of an early ultrasound. Many major fetal abnormalities, can be diagnosed at this time, for example, anencephaly, heart defects, and abdominal wall defects. Identifying at risk fetuses earlier provides more time for further testing, decision-making, and the option of earlier termination.

There are two important advantages to FTS that, currently, NIPS cannot replace. One, the use of NIPS has not yet been validated in higher level multiple gestations. Two, an NT is almost instantaneous and, depending on the laboratory, the serum results of an FTS can be returned within days. The turnaround time for NIPS is 7-14 days, depending on the laboratory. In the prenatal setting, this difference in timing can be of great importance to the patient.

Another point to consider is the utility of the analyte analysis from maternal serum screening. Certain analytes levels have been linked with poor obstetrical outcomes, including intrauterine growth restriction, small for gestational age, spontaneous abortion, and preterm birth (Dugoff, 2010; Gagnon et al., 2008; Suskin Kaplan, Neto, Dar, Dolan, & Klugman, 2013). Currently, this information cannot be obtained from NIPS. Despite the correlation between abnormal serum markers and poor obstetrical outcomes, there have not been any randomized trials to evaluate the efficacy of interventions (Norton et al., 2014). Thus, it is unclear if there is a true benefit, other than knowledge, to identifying these women who are at an increased risk for complications.

In addition to the merits of existing screening techniques, it is important to consider the limitations of NIPS. A study from Mary Norton, Robert Currier, and Laura Jelliffe-

Pawlowski (2014), aimed to compare the number of chromosome abnormalities that would be found by traditional prenatal screens and NIPS. They found that out of the screen positive women who had an abnormal invasive testing result (n = 2,993), 16.8% (n=504) had fetal abnormalities that would not be expected to be picked up by NIPS (Norton et al., 2014). In addition, there is also the issue of test failure, necessitating redraws. As demonstrated by the Pergament et al. (2014) study, failures are particularly troubling as these pregnancies may be at higher risk.

In addition, it is very possible that some clinicians may not be willing to forego the information that can be obtained from existing prenatal screening that is not included in NIPS. Therefore the cost of screening may be based on having combinations of these screens, rather than one or the other.

Purpose of the study

Over the past few years, centers across the world have started using cell-free DNA for noninvasive prenatal screening (NIPS). It remains unclear how this technology, will be integrated into existing prenatal screening routines. To date, professional guidelines have not supported utilizing NIPS universally, however, many centers across the country have already started offering NIPS to low-risk women. This paper aims to examine the use of NIPS in current practice, predominantly in the United States and Canada, in order to inform strategies for the optimal use of both new and existing screening techniques.

METHODS

Participants

Genetic counselors seeing at least one prenatal patient per week were eligible to participate.

Instrumentation

The survey consisted of multiple choice and free-response questions that focused on the participant's current use of noninvasive prenatal screening and his or her thoughts regarding how the screening should be used in the near future. The maximum number of questions a participant could answer was twenty-three. It was initially piloted on a group of six genetic counselors who were not otherwise affiliated with the study. The feedback from the pilot was used to improve the language for questions and response choices and ensure that the questions asked had the greatest potential to answer the research questions. The survey was administered through SurveyMonkey. No IP addresses were collected and participants were not asked any identifying questions. Participants were able to return to previous questions to change their answers and no questions were mandatory.

Procedures

The Julia Dyckman Andrus Institutional Review Board approved the study on December 17, 2014. An invitation to participate in the study was distributed through the Student Research Survey Program to the NSGC distribution list on January 13, 2015 (N=3,200). The e-mail briefly described the objectives of the research project and included the link for the survey and contact information for the primary investigators. Recipients were welcome to forward the survey to other counselors. Upon following the link, the participants were directed to the informed consent. A second e-mail sent out to the distribution list on

January 20, 2015 as a reminder. The survey was open until January 27, 2015.

Data Analysis

A total of 208 submissions were received (n = 208). Two respondents who reported seeing less than one patient a week were excluded from the survey (n = 206). Data analysis was performed using SurveyMonkey, Microsoft Excel, and SPSS. The qualitative questions were analyzed by common theme. This was first done by the research team and then by a second coder who was otherwise uninvolved with the study. The inter-rater reliability was calculated for each theme and ranged from 96.7% to 100%, with a mean of 99% (Freelon, 2013).

RESULTS

Demographics

Respondents answered questions regarding where they practice and their typical prenatal patient load. The responses to select demographic questions can be found in Table I.

Current Practice

Participants considered their institution's current use of NIPS. These questions focused on to whom NIPS is offered and how it is used in relation to other forms of prenatal screening. These responses are represented in Figure 1 and Table II.

Universal screening

Respondents reflected on their feelings regarding the implementation of universal NIPS (i.e. offering NIPS to patients both at high and low-risk for fetal aneuploidy). These responses are recorded in Table III. For qualitative questions, themes that appeared in five or more responses are represented in the table.

Table I: Respondent demographic information			
		N = 204	
Variable		n	%
Average number of prenatal patients seen in a week	10−14	61	29.9
	15−19	52	25.5
	5−9	44	21.6
	20 or more	27	13.2
	1-4	20	9.8
Type of institution	University medical center	81	39.7
	Private hospital / medical facility	44	21.6
	Public hospital / medical facility	38	18.6
	Physician's private practice	30	14.7
	Community hospital	8	3.9
	Other	3	1.5
Country of practice	United States	194	94.6
	Canada	9	4.4
	Australia	2	1.0
Region of the United States	East North Central	33	17.2
	Pacific	32	16.7
	Mid-Atlantic	31	16.2
	South Atlantic	28	14.6
	New England	20	10.4
	Mountain	16	8.3
	West South Central	14	7.3
	West North Central	12	6.3
	East South Central	6	3.1

Figure 1: Approximately how many of the patients who get NIPS at your center/institution, are seen by genetics?

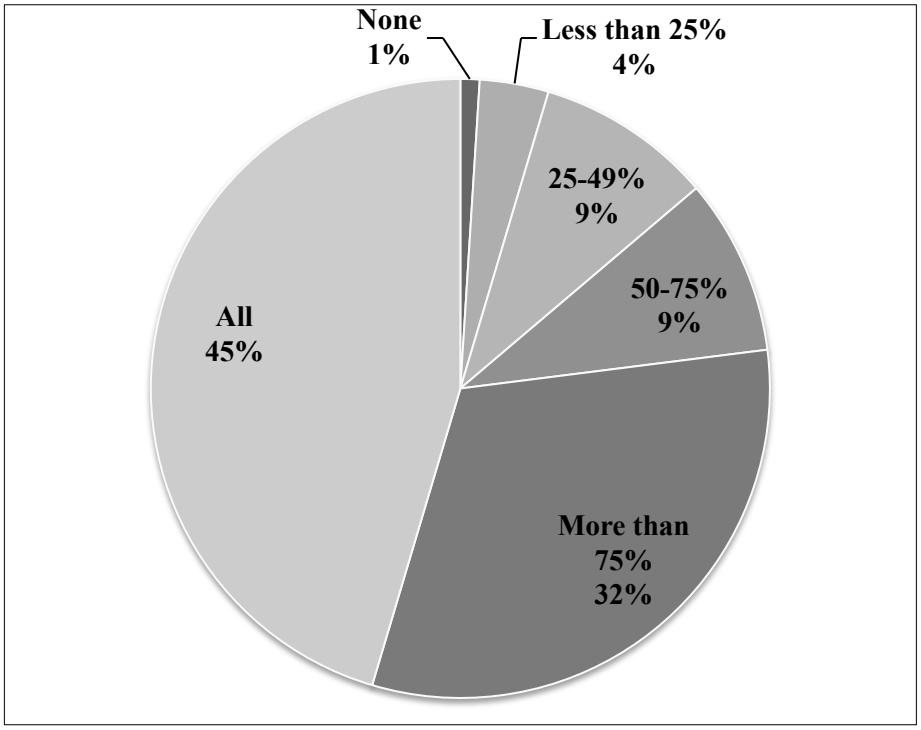

Table II: Current practice		
To whom does your center / practice currently offer NIPS? Please check all that apply.	N = 201	
	n	%
Patients who are high-risk for aneuploidy (35 years or older at time of delivery, positive screen, ultrasound finding, family history)	190	94.5
Low-risk patients who request NIPS	76	37.8
Low-risk patients who present too late for other screening methods or for some reason cannot have other screening	45	22.4
All patients who present for prenatal care	22	11.0
Other	12	5.97
It is not offered to any patient	1	0.5

At your center / practice, how is NIPS typically offered? Please choose the answer that reflects how it is most commonly used.	N = 196	
	n	%
In conjunction with a first trimester ultrasound and NT (no first trimester serum screening), and an MSAFP	78	45.1
In conjunction with first trimester screening (NT and serum screening, or serum only), and an MSAFP	34	19.7
Instead of first and/or second trimester screening	34	19.7
In conjunction with sequential screening or integrated screening	13	7.5
In conjunction with an MSAFP	12	6.9
In conjunction with second trimester serum screening	2	1.2

Which of the following abnormal values would you discuss further with the patient and/or provider, if the patient's first or second trimester screening results are low-risk for aneuploidy and neural tube defects? Please chose all that apply:	N = 194	
	n	%
Increased NT	182	93.8
Elevated or decreased AFP	139	71.7
Elevated or decreased uE3	127	65.5
Elevated or decreased PAPP-A	126	65.0
Elevated or decreased hCG	86	44.3
Elevated or decreased inhibin	62	32.0
None	5	2.6

Table III: Counselors' views on the implementation of universal NIPS

Do you believe that NIPS should be offered universally (i.e. to any pregnant woman, regardless of a priori risk)?	N = 190	
	n	%
No	105	55.3
Yes	85	44.7

	N = 169	
Comments on the universal use of NIPS, by theme:	n	%
Need for more studies / lack of validation in low-risk patients	61	36.1
NIPS is a better than other available screens	56	33.1
The importance of patient education / informed consent	36	21.3
Insurance and cost issues	32	18.9
Lower test performance in low-risk patients	27	16.0
The need for provider education / lack of provider understanding	24	14.2
Concern over NIPS being offered outside of genetics / not enough gc's	15	8.9
Against practice guidelines / no guidelines for implementation	13	7.7
Lack of patient understanding	10	5.9
Concern over loss of information from other screens	7	4.1
Fairness / patient autonomy	7	4.1
Successful validation studies	7	4.1
Availability of other good screens	5	3.0

If NIPS is approved for universal use, how do you think it should be implemented?	N = 189	
	n	%
In conjunction with a first trimester ultrasound and NT (no first trimester serum screening), and an MSAFP	111	58.7
In conjunction with an MSAFP	24	12.7
In conjunction with first trimester screening (NT and serum screening, or serum only), and an MSAFP	20	10.6
Other	17	9.0
Instead of first and/or second trimester screening	9	4.8
In conjunction with sequential screening or integrated screening	6	3.2
In conjunction with second trimester serum screening	2	1.1

Which of the following, if any, would you be concerned about losing in a transition to NIPS (assuming NIPS was done with MSAFP)? Please choose all that apply.	N = 192	
	n	%
NT	164	85.4
PAPP-A	58	30.2
uE3	42	21.9
hCG	31	16.2
None	24	12.5
Inhibin	16	8.3

In pregnancies with no indications / known risk factors (other than general population risk), do you think there should be a gestational age limit for NIPS?	N = 188	
	n	%
No	156	83.0
Yes	32	17.0

Comments on the incorporation of NIPS into prenatal screening routines, by theme:	N = 60	
	n	%
The importance of patient education / informed consent	21	35.0
The need for provider education / lack of provider understanding	21	35.0
Concern over loss of information from other screens	19	31.7
Insurance and cost issues / impact on institutional finances	14	23.3
Concern over NIPS being offered outside of genetics / not enough genetic counselors	11	18.3
Lab transparency / sales representatives as educators	7	11.7
Need for investigation into analytes / no proof pregnancy outcome is improved	6	10.0
Lack of patient understanding	5	8.3

DISCUSSION

Current use

Almost all respondents (94%, n=190) report that NIPS is routinely offered to women at higher risk for aneuploidy (35 years or older at delivery, positive screen, ultrasound finding, family history). Only one respondent (0.5%) said that NIPS is not offered currently offered to any patients.

The majority of respondents report using NIPS in conjunction with another form of screening in the first trimester. It is frequently offered in conjunction with a first trimester ultrasound, NT, and an MSAFP (45.1%, n=78), or in conjunction with first trimester serum screening, with or without an NT, and an MSAFP (19.7%, n=34). A small number of counselors report that it is offered with another form of serum screening alone: 7.5% (n=13) sequential or integrated screening, and 1.2% (n=2) for second trimester serum screening. Only 19.7% (n=34) of participants responded that it is typically performed instead of first or second trimester screening. Responses suggest that in the majority of cases, NIPS is not replacing other screens, but being used in addition.

Current practice is extremely varied, both in terms of what combination of testing is offered and to whom it is offered. While there is consensus around offering NIPS to all high-risk women, there are differences in practice when it comes to the general population. A substantial minority will use NIPS for low-risk patients at the patient's request (37.8%, n=76). Others offer NIPS to low-risk patients who present too late for other screening methods or for some reason cannot have other screening (22.4%, n=45), and 11.0% (n=22) offer it to all patients who present for prenatal care.

UNIVERSAL USE

NIPS in the general population

Currently, centers rarely offer NIPS to all obstetrical patients, thus the extensive use of NIPS in the general population would seem to be a major shift in practice. Respondents were evenly split on the issue of whether or not NIPS should be offered to all women, with 44.7% (n=85) in favor of universal access. In comments, the predominant theme cited in support of universal NIPS was that NIPS is better than other available screens (33.1%, n=56). Counselors touched on the issue of fairness (4.1%, n=7): "Everyone should be offered the best available screen with the highest detection rate and lowest false positive rate." Some respondents also mentioned the existence of successful validation studies (4.1%, n=7): "A number of studies have shown that the efficacy of NIPS for common aneuploidy (PPV, False positive rate etc.) is superior to other available screening tests in both high and low risk populations." In addition, one response served as a reminder that 'traditional' screening programs have not been around forever: "Screening tests are continually evolving so it is a logical next step to move on to the best test."

Among the arguments against universal NIPS, concerns over the lack of validation were the most widespread (36.1%, n=61). One counselor responded: "We do not have validation studies in a low risk population. Without that data, I don't think we can have a meaningful discussion of results with a patient. I can't give them any data on the possibility false-positive or false-negative because the test hasn't been validated for their use."

Respondents in favor and against universal NIPS wrote about education, with 21.3% (n=36) offering comments focused on the importance of patient education and proper informed consent: "…I would also hope NIPS is explained well to a patient. At our center, a

genetic counselor is almost always involved if NIPS is ordered so those patients get good information." The lack of provider understanding and the need for provider education (14.2%, n=24), along with the lack of patient understanding (5.9%, n=10) were frequently used arguments against universal NIPS: "Despite multiple education outreach efforts I'm still getting referrals from outside offices with either confused providers or confused patients (i.e. 'I was told I could come see you guys first before scheduling my termination or just go ahead and schedule the termination'). So until that is a little more under control I hesitate to say everyone should do it."

These concerns were revisited when participants were prompted to share comments on the incorporation of NIPS into prenatal screening routines in general. In response, 35.0% (n=21) wrote about the importance of patient education, 35.0% (n=21) wrote about the importance of provider education and/or expressed concern over a lack of provider understanding, and 8.3% (n=5) expressed concern over a lack of patient understanding. For example, one respondent said, "Every time we have a false positive or false negative they [referring obstetricians] are floored. No matter how many times we reiterate that it is a screening test, they don't hear the message."

Involvement of genetics professionals

Many participants made a case against non-genetics providers offering NIPS. This was raised by 8.3% (n=14) in response to the question of whether or not NIPS should be offered universally, and 18.3% (n=11) included it in their final comments. For example, "Non-genetic providers (OB/GYNs, MFMs) who order the test, in my experience, DO NOT understand the accuracy of the test/the meaning of an abnormal result. If they understood and were willing to properly counsel their patient regarding the results I would be fine

offering it universally. But when the provider says "But the test is 99%" and the actual PPV is 10%, I have a problem."

Although counselors may make a case that use of NIPS in the general population, where PPV is lower, calls for more rather than less participation by genetic professionals, logistical hurdles suggest that expanded use will have the opposite effect. In this study, just under half (45.4%, n=89) of all respondents report that all women who get NIPS are seen by genetics, and 50% (n=98) report that more than 25% are seen by genetics. Assuming no radical change in the availability of genetic services, it would be hard to sustain these numbers if the use of NIPS was expanded. As one respondent noted, "Offering NIPS involves a great deal of upfront counseling to properly inform the patient of the potential results. Our system is not currently equipped to handle this amount of patient volume. There are not enough genetic counselors/ trained health care workers to handle the demand."

Information from other screens

Counselors were very varied in their responses regarding concerns over what would be lost if NIPS was performed without other screens. The majority report that they would be concerned about losing the value of an NT in a complete transition to NIPS (85.4%, n=164). Most counselors report that they currently routinely discuss any abnormal NT or MSAFP (93.8%, n=186; 71.7%, n=139), suggesting that losing these sources of information would negatively impact clinical practice. A smaller number of respondents expressed concern about losing other analyte values. Of these, PAPP-A was highest at 30.2% (n=58). One respondent underscored something else that would be lost: "I also feel that we are losing something important by not having a risk number - when I see a first trimester result that is

abnormal, especially if highly so, I consider and counsel the patient about the possibility of genetic conditions other than the condition tested (like Down syndrome)."

Cost and insurance

Because evidence here suggests that NIPS would be an additional screen rather than a replacement screen, it raises more concerns about cost and insurance coverage. A substantial number of respondents expressed these concerns when commenting on the implementation of universal NIPS (18.9%, n=32). Specific points of concern included insurance coverage for multiple screens, the cost to the patients, the financial impact on the department, and the cost to the overall system. One respondent wrote, "There are very good screens already available for this population at a much lower cost. If NIPS becomes cheaper than other serum screening this may be appropriate to offer. Population screening needs to be as cost effective as possible." Similar anxieties also emerged in the final comments, where 23.3% (n=14) expressed concern about cost and/or reimbursement, such as this: "I think it is a great test, but there needs to be a discussion about expense and who is paying. We don't need to be doing a $2,000 test on a low risk person when a $160 test will do." Investigations into the cost effectiveness of testing as well as practice guidelines will likely have a strong impact on insurance coverage and thus the cost to the patients.

Study limitations

The survey was distributed through the National Society of Genetic Counselors (NSGC) distribution list, which includes only members of NSGC. The experiences and opinions of non-members could not be incorporated into this study. In addition, the "open rate" for the first email was 27.7% and 24.9% for the reminder email. As with any study,

those who are interested in and have strong feelings on the subject are the ones most likely to respond.

Looking forward

Based on this data, there is no consensus among genetic counselors on the best use of NIPS in high-risk or general populations. There is large variability in both current practice and opinions on what should be done going forward. However, the responses suggest that at least when initially implemented, universal NIPS should be offered in conjunction with some form of first trimester screening and an MSAFP. Counselors expressed misgivings about how to proceed with NIPS. This indicates that practice guidelines would be useful to provide consistency, expert review of the costs and benefits, and a standard of care. The careful consideration of revised prenatal screening routines is crucial to ensure patients receive the best possible care.

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