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Current Attitudes and Practices in Genetic Counseling Concerning Noninvasive Prenatal Screening – A Follow Up Study

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ABSTRACT

This study examines the opinions and usage of Noninvasive Prenatal Screening (NIPS) by genetic counselors (GCs). One hundred and three GCs were surveyed regarding their current practice involving NIPS, their opinion on offering it to all patients regardless of a priori risk, and their thoughts on future implications of the screening test. A significantly greater number of GCs are offering NIPS to all patients and believe in the implementation of universal NIPS, or NIPS for any patient no matter their risk, relative to a similar sample surveyed in 2015. Discordance between practice and belief remains an issue. Now more patients are being offered NIPS with a microdeletion panel. Favoring universal NIPS was negatively associated with number of years in practice as well as the percentage of their patients insured through government funding. The most common qualitative response from both those who do and do not believe in the use of NIPS universally concerned the clinical validity of NIPS compared to other screening techniques. There remains no consensus among GCs on how to best utilize NIPS: for what indications, for which conditions, in conjunction with other evaluations of pregnancy.

KEY WORDS
Noninvasive prenatal screening, Non-invasive prenatal testing, Cell-free DNA, Genetic counseling, Prenatal screening, Aneuploidy, NIPS, NIPT, Cell-free fetal DNA, Prenatal testing

INTRODUCTION

Since the introduction of noninvasive prenatal screening into clinical care in 2011, professional organizations have been analyzing and assessing its use to define practice guidelines. In the seven years since its commercialization, opinions about the test's clinical utility have changed rapidly. In 2012, the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) approved of NIPS as a first-line aneuploidy test only for high-risk patients (ACOG and SMFM 2012). Despite these recommendations, the use of NIPS in the general population continued to grow, as did its role in the public eye as the "gender test." In 2015, for her graduate thesis, Emily Suskin surveyed practicing prenatal genetic counselors regarding NIPS. The survey asked about their use of NIPS, their opinions on the universal implementation of NIPS, and their ideal aneuploidy screening. This research was published in the Journal of Genetic Counseling in 2016 and was seen as an extension of research completed by Horsting et al. in 2014 (Horsting et al. 2014; Suskin et al. 2016)

Since the survey completed by Suskin et al. in 2015, the American College of Medical Genetics and Genomics (ACMG) has amended its position statement regarding NIPS, stating that NIPS can be offered to all patients regardless of a priori risk along with all other screening options (Gregg et al. 2016). The proficiency of the technology and the range of conditions screened using NIPS have also evolved. It makes sense, therefore, to revisit the issue in order to assess changes in opinion and practice in the GC community regarding the updated use of NIPS.

Note: Noninvasive prenatal screening for fetal aneuploidy has many names and abbreviations. Noninvasive prenatal testing (NIPT) and cell-free fetal DNA (cffDNA) are other commonly used terms. In keeping with ACMG we will use the term NIPS as it

emphasizes the nature of the test as screening rather than diagnostic, except in the cases of direct quotations.

Current Guidelines

In 2016, the American College of Medical Genetics updated their position statement to propose that regardless of a priori risk, all women, who are not significantly obese, be offered NIPS as the most sensitive screening test available for detecting trisomies 13, 18, and 21 (Gregg et al. 2016). So long as patients are consented with proper pre-test counseling, the ACMG guidelines state all patients should be made aware of the options for expanded NIPS for clinically relevant copy-number variants and sex chromosome abnormalities. Although, ACMG does not recommend screening for other autosomal aneuploidies, genome-wide copy number variants (CNV) screening, or the use of NIPS for sex selection (Gregg et al. 2016). The ACMG recommendations differ from the most recent guidelines published by the National Society of Genetic Counselors (NSGC), which suggested NIPS only be offered to women at high-risk for having babies with chromosomal aneuploidy (Wilson et al. 2013) and conflicts with its own October 2016 position statement recommending that NIPS be offered to all pregnant patients (NSGC 2016). In 2015, the American Congress of Obstetrics and Gynecology (ACOG) and Society for Maternal Fetal Medicine (SMFM), in a joint opinion, said all women can be offered NIPS, with the caveat that it is not the standard of care (ACOG and SMFM 2015). Experts consistently agree that NIPS should not be treated as a substitute for invasive diagnostic techniques.

There are limitations to NIPS as a screening test. A fetal fraction of 4% is generally thought to be the minimum threshold for accurate detection, but both overestimation and underestimation of fetal fraction can be problematic: overestimates of fetal fraction can lead to false positive results and underestimates can lead to sample rejection or no-call results

(Kinnings et al. 2015). NIPS technology is not effective in certain pregnancies, restricting them to traditional screens. Stretches of homozygosity between maternal and fetal genomes render genomic imbalance, copy number detection, and small deletions and duplications undetectable within those regions (Gregg et al. 2016). NIPS is not always made available to women who have had organ transplants from male donors or who have conceived using donor oocytes (Gregg et al. 2016). It is not possible to identify the fetus responsible for an abnormal NIPS result in multiple gestation pregnancies or pregnancies with "vanishing twins" and limited data exists on overcoming this issue. Despite a detection rate argued to be higher than biochemical and sonographic aneuploidy screening methods for twins, the known specificity and sensitivity of NIPS in multiple gestations is still unclear (Sachs et al. 2015).

Comparing Current Screening Options

Many providers, including the majority of genetic counselors that participated in the Suskin et al. study, still see NIPS solely as one part of a stepwise care process. It has been argued that doing NIPS secondarily to traditional first trimester screens, which measure PAPP-A and ß-hCG biochemical marker levels and nuchal translucency, may actually be more problematic than useful. Multiple screens create a lengthier, potentially more expensive, three-step process where the patients' choices may be impacted by timeline (Dondorp et al. 2015).

NIPS is the most accurate method of noninvasive detection available for the classically screened fetal aneuploidies (trisomies 13, 18, and 21). In validation studies of NIPS for Down syndrome caused by true trisomy 21, translocations, and trisomy 21 mosaicism, the screening had a detection rate and clinical specificity, or true negative identification rate, of 99%. Mosaic and translocation-caused Edwards and Patau Syndromes,

trisomies 18 and 13, respectively, had detection and specificity rates between 80-100% (Gregg et al. 2016). With regard to positive predictive value (PPV), NIPS was superior to conventional screens for Down syndrome (80.9 vs. 3.4%, N=15,841), Patau syndrome (33–90% vs. 14%,), and Edwards syndrome (50–70% vs. 3.4%) (Gregg et al. 2016). The negative predictive value for NIPS also has reached nearly 100% for all three trisomies. NIPS, unlike traditional screens, is also clinically available for the detection of trisomies 9, 16, and 22, as well as multiple microdeletion syndromes (Sachs, et al., 2015), including but not exclusive to: 22q11.2 deletion syndrome, cri-du-chat (5p), 1p36 deletion syndrome, Prader-Willi and Angelman (15q) syndromes. All of these have a range of outcomes that are complex and often cause intellectual disability.

Genetic Counselors and NIPS

A 2014 study of 236 genetic counselors provided a baseline for studying the use of NIPS by GCs (Horsting et al. 2014). At that point, few counselors reported offering NIPS to all patients (3.9%) as opposed to high-risk patients only (88.2%), though when asked, 89.4% of respondents agreed, "cffDNA testing will largely replace other screening testing" (Horsting et al., 2014). Between October 2012, when Horsting's data were collected and January 2015, opinions had already begun to change. Suskin reported that 11% of GCs offered NIPS to all prenatal patients, and 37.8% offered the screening to low-risk patients if they requested it (Horsting et al. 2014; Suskin et al. 2016). Barriers to universal access to NIPS, identified by the Suskin study, include perceived lack of provider knowledge, necessity to educate providers, and patient education (Suskin et al. 2016).

A 2016 study by Morrow showed a trend toward offering NIPS regardless of a priori risk, in data collected only eleven months after Suskin's survey, Of all respondents, 36% reported offering NIPS to all patients (Morrow 2016). Additionally, 16% of respondents

stated they were also offering NIPS with microdeletion/microduplications to all patients, and 34% to high-risk patients only (Morrow 2016). While the Horsting and Suskin studies did not specifically ask about offering CNV through NIPS this level of use indicates a further shift towards acceptance of NIPS as a good screening option for all women.

Studies of other professionals

Due to the workflow of most prenatal centers, many patients are not seen by genetic counselors; therefore, the number of low-risk patients offered NIPS will most likely depend on other medical professionals including OB/GYNs, Maternal-Fetal Medicine specialists (MFMs), and Certified-Nurse Midwives. Many recent studies have looked at these providers to examine whether their practice is in line with ACOG/SMFM guidelines and where they see the future of NIPS heading.

A 2014 study looked at 278 MFM physicians to examine three aspects of NIPS: current use, ideal use, anticipated use (Haymon et al. 2014). Data collection occurred in November and December 2012, within two months of the data from GCs in Horsting et al., which makes for some easy comparisons (Haymon et al. 2014; Horsting et al. 2014). At the time of the survey only 5% of MFMs offered NIPS to all patients, compared to 3.9% of GCs. Although a limited number of MFMs reported using NIPS for all patients, a slight majority, 51%, foresaw it replacing maternal serum screening in the future (Haymon et al. 2014).

In another study of prenatal physicians, Brewer et al. also chose to compare current use with ideal use; 72% believed NIPS should be offered to all patients regardless of a priori risk, while in reality only two-thirds were offering it to all patients. An additional question provided a small insight into this discrepancy: "81.5% of providers would use NIPT as a first-line screening for all of their patients if insurance covered it" (Brewer et al. 2017).

Many of these studies bring up concern over providers understanding the test basics of NIPS. One study found that 97.4% of MFMs correctly stated that NIPS should be used as a screening test (Swaney et al. 2016). Yet two other studies showed a self-reported 14.6% and 13% of MFMs offered NIPS as a diagnostic test (Brewer et al. 2017; Haymon et al. 2014). This is especially concerning, if in fact providers are offering NIPS as a diagnostic test, given that the MFMs also reported only 81.6% of their patients are being referred to GCs for post-test counseling (Haymon et al. 2014). These studies demonstrate the necessity of GCs in the patient education process, and the dearth of knowledge some OBs and MFMs have about the tests they offer.

Purpose of the Study

The technology and scope of conditions for which patients are screened using NIPS has continued to evolve since the Suskin et al. study in 2015. Earlier studies suggest that providers have increasingly begun offering NIPS to all prenatal patients, as opposed to only those at higher risk. Yet, the genetics community has not reached consensus on how best to implement this change, or on whether it should be made at all. Concerns over the way the test is being presented to patients have given pause to those who would advocate for NIPS as first-tier testing for fetal aneuploidy (Suskin et al. 2016). Barriers to universal NIPS, including cost, are lessening (Chitty et al. 2016; Fairbrother et al. 2016), but ensuring patients are getting proper education prior to testing and upon return of results is still a top priority. To shed light on the rapidly changing state of clinical care, we undertook an update to the survey by Suskin et al. looking at current and comparative NIPS utilization, opinions on NIPS in the GC community, and ideas for future use.

METHODS

Participants

All genetic counselors whose jobs included prenatal counseling and who were members of NSGC were eligible to participate.

Instrumentation

The survey consisted of 41 multiple-choice, select-all-that-apply, and free-response questions focused on the participants' use of NIPS, their opinions on NIPS, including how their views and practice may conflict, and how, if at all, they believe the usage of NIPS will change in the future. Some of the questions were based on the survey questions by Suskin et al (2016). The survey was administered through SurveyMonkey. No IP addresses were collected, participants were not asked any identifying questions, participants could opt out at any time, and only one question was mandatory.

Procedures

The Institutional Review Board at Sarah Lawrence College approved the study on January 1, 2018. Invitation to participate was distributed through the NSGC Student Research Project Program using the NSGC Listserv (n= 3704 initial) February 13, 2018 with a follow-up invitation on February 27, 2018. The survey remained open until March 6, 2018.

Data Analysis

A total of 105 submissions were received. The data of two respondents were excluded due to non-descriptive answers (n = 103). The open rate was for the first email was 26.8% (967) and 23% (838) for the reminder email. Data analysis was performed independently for each question, as participants were not required to answer all questions. Descriptive statistics were calculated for each quantitative question using SurveyMonkey, Microsoft Excel, and SPSS. The qualitative data were analyzed using an interpretive content

method (Patton 2002). The research team identified emergent themes and sub-themes among the responses. First, each researcher coded responses individually. Matching themes were identified and those themes that were not exact matches were compared and agreed upon by consensus.

RESULTS

Change Over Time

Participants were asked to describe differences, if any, they have noticed corresponding to changes in guidelines. In addition, responses to identical or similar questions as those in the Suskin et al. study were compared to identify any changes in practice and genetic counselors' opinions since 2015. Data regarding these changes are represented in Figures 1 – 3. The study responses suggest a shift toward universal NIPS, in both the opinions on and the use of the screening. Genetic counselors noted both positives and negatives to the continued expansion of NIPS; most of these were in line with qualitative data from the previous study.

Demographics

Participants answered questions regarding their years of experience, practice setting, and patient load. Select demographic data can be seen in Table I and Figure 4. Complete data can be seen in Appendix A.

Current Practice

Respondents were asked about their current use of NIPS and their opinions on best practices in prenatal screening. Survey questions focused on the circumstances under which NIPS is offered at their institution, and GCs' use of alternative prenatal tests. Participants also had the opportunity to reflect upon their use of NIPS and whether or not that reflected their views of best practices. Responses to questions about current use and opinions may be viewed in Tables II – V. Full responses pertaining to current practice question can be seen in Appendix B.

Future Use

Survey respondents were asked under what circumstances they would offer additional types of NIPS (i.e. for other conditions, for whole genome or whole exome

study). A follow-up qualitative question asked participants to expound upon their views on the continued expansion of NIPS, these results may be seen in Table VI and Figure 5. Complete tables can be seen in Appendix C.

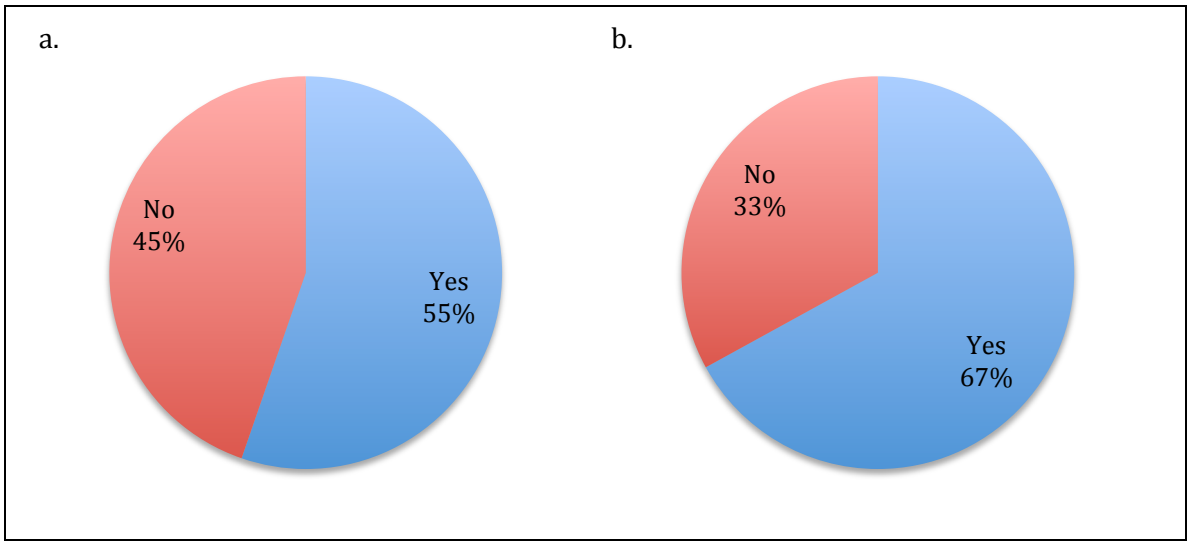

Figure 1. *Do you believe that NIPS should be offered universally (i.e. to any pregnant woman, regardless of a priori risk)?* a. Represents respondents from 2015. b. Represents respondents from 2018.

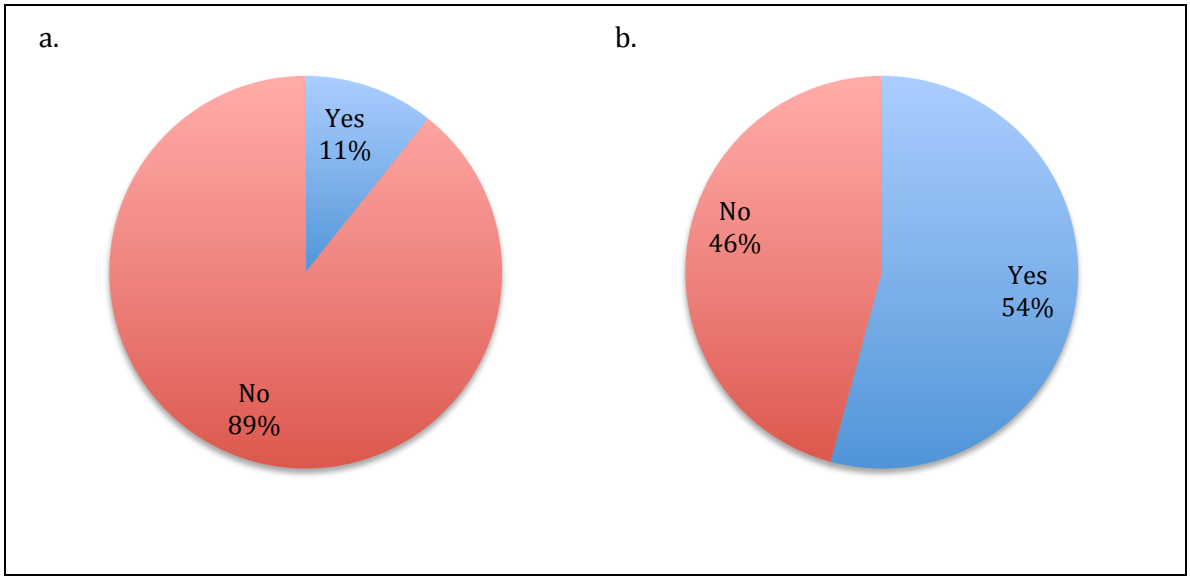

Figure 2. *Do you offer NIPS to ALL patients, regardless of risk?* a. Represents respondents from 2015. b. Represents respondents from 2018.

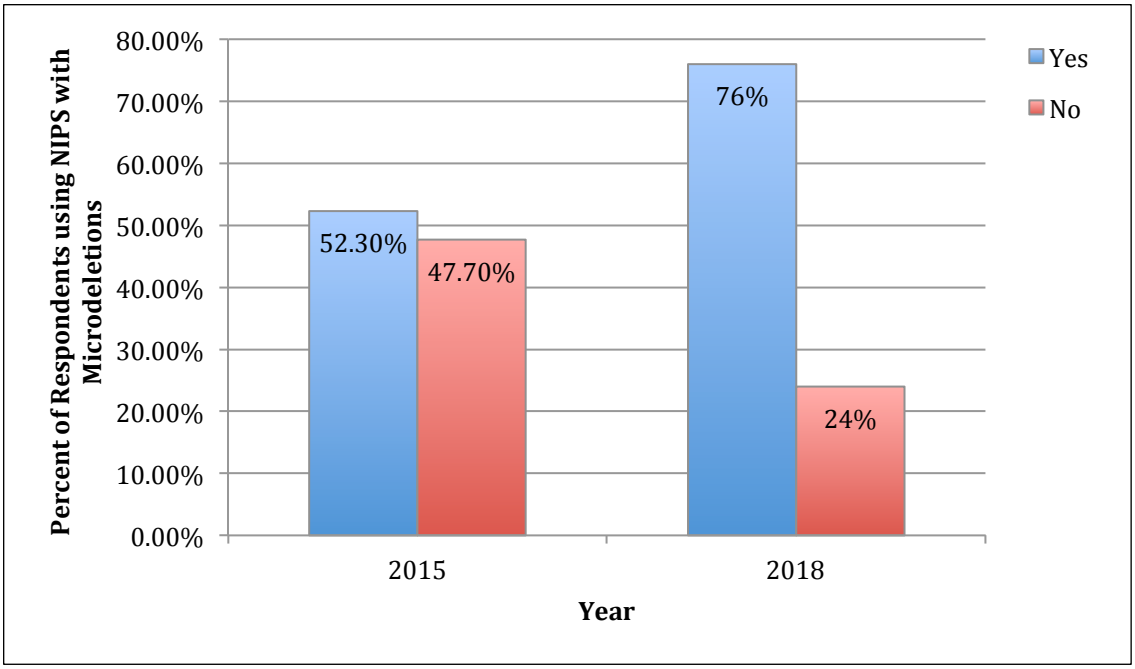

Figure 3. Use of NIPS with microdeletion by year. (Chi-square = 16.89 (df=1), p<.001).

Table I: Demographic Information		
Questions	Answers	n[a] (%)
Are you a certified genetic counselor? (N=103)		
	Yes	103 (100%)
	No	0 (0.00%)
How many years have you been a practicing GC? (In years) (N=103)		
	Less than 3	37 (35.92%)
	3 - 4	6 (5.83%)
	5 - 6	10 (9.71%)
	7 - 10	10 (9.71%)
	11 - 15	7 (6.80%)
	16 - 20	13 (12.62%)
	More than 20	20 (19.42%)
In what country do you work? (N=103)		
	United States	99 (96.12%)
	Canada	3 (2.91%)
	Other (Please Specify) Australia	1 (0.97%)
In which NSGC practice region do you work? [b, c] (N=100)		
	Region 1	11 (11.00%)
	Region 2	18 (18.00%)

Region 3	8 (8.00%)
Region 4	34 (34.00%)
Region 5	6 (6.00%)
Region 6	24 (24.00%)
On average how many prenatal patients do you counsel in a week? (N=103)	
< 5	10 (9.71%)
5 - 9	21 (20.39%)
10 - 14	31 (30.10%)
15 - 19	29 (28.16%)
≥ 20	12 (11.65%)
Which of these best describes your primary work place? (N=100)	
University Medical Center	40 (40.00%)
Private Practice	18 (18.00%)
Private Hospital	18 (18.00%)
Public Hospital	14 (14.00%)
Community Hospital	2 (2.00%)
Diagnostic Laboratory - Commercial	2 (2.00%)
Health Maintenance Organization (HMO)	2 (2.00%)
Government or Military Center	0 (0.00%)
Other (please specify) Non-profit Private MFM office County Hospital and University Private Practice	4 (4.00%) 2 (2.00%) 1 (1.00%) 1 (1.00%)
In what setting do you primarily practice? (N=102)	
Urban	65 (63.73%)
Suburban	33 (32.35%)
Rural	4 (3.92%)
Approximately what portion of your patients have coverage through state or federal insurance programs (Medicaid or Medicare)? (N=100)	
< 25%	22 (22.00%)
25 - 49%	47 (47.00%)
50 - 75%	22 (22.00%)
> 75%	9 (9.00%)
Approximately what percentage of the patients offered NIPS at your center/institution are seen by genetics prior to testing? (N=94)	
< 25%	15 (15.96%)
25 - 49%	5 (5.32%)
50 - 75%	13 (13.83%)

> 75%	61 (64.89%)

[a] Subtotal of respondents. [b] NSGC practice regions are defined as follows:
Region 1: CT, MA, ME, NH, RI, VT, CN Maritime Provinces
Region 2: DC, DE, MD, NJ, NY, PA, VA, WV, PR, VI, Quebec
Region 3: AL, FL, GA, KY, LA, MS, NC, SC, TN
Region 4: AR, IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, OK, SD, WI, Ontario
Region 5: AZ, CO, MT, NM, TX, UT, WY, Alberta, Manitoba, Saskatchewan
Region 6: AK, CA, HI, ID, NV, OR, WA, British Columbia
[c] Responses calculated based on two questions, "In which American state/territory do you primarily work?" and "In which Canadian province/territory do you primarily practice?"

Table II: Current Practices and Opinions		
Questions	Answers	n[a] (%)
Do you believe that NIPS should be offered universally (i.e. to any pregnant woman, regardless of a priori risk)? (N = 100)		
	Yes	67 (67.00%)
	No	33 (33.00%)
Does your institution currently offer NIPS? (N=98)		
	Yes	97 (98.98%)
	No	1 (1.02%)
Do you offer NIPS to ALL patients, regardless of risk? (N=96)		
	Yes	52 (54.17%)
	No	44 (45.83%)
To whom do you offer NIPS? (Select all that apply)[b] (N=46)		
	Patients with a high-risk screen (NT, FTS, Quad, Sequential)	46 (100.00%)
	Patients over 35	44 (95.65%)
	Patients with a previous pregnancy affected with an aneuploidy	44 (95.65%)
	Patients who inquire about the test	24 (52.17%)
	Patients with recurrent miscarriage	8 (17.39%)
	Patients with family history of other genetic conditions	6 (13.04%)
	Patients interested in early detection of fetal sex	5 (10.87%)
	Other (please specify) Abnormal U/S	18 (39.13%) 11 (23.91%)
Do you generally combine the use of NIPS with other aneuploidy screening options? (N=95)		
	Yes	58 (61.05%)
	No	37 (38.95%)
For each sub-type of NIPS, check if you agree with the statement "I offer to all patients" [c]		
	Classic Aneuploidy Screening (Trisomy 13, Trisomy 18, Trisomy 21) (N=91)	45 (49.45%)

Sex Chromosomes (N=91)	55 (60.44%)
Early Pregnancy Loss Chromosomes (Trisomy 9, Trisomy 16, Trisomy 22) (N=85)	8 (9.41%)
Microdeletion Syndromes (limited panel) (N=89)	16 (17.98%)
Whole Genome Copy Number Variant Screening (N=88)	1 (1.14%)
Single gene conditions (N=89)	0 (0.00%)
For each sub-type of NIPS, check if you agree with the statement "Not currently offered at this center" [c]	
Classic Aneuploidy Screening (Trisomy 13, Trisomy 18, Trisomy 21) (N=91)	0 (0.00%)
Sex Chromosomes (N=91)	0 (0.00%)
Early Pregnancy Loss Chromosomes (Trisomy 9, Trisomy 16, Trisomy 22) (N=85)	53 (62.35%)
Microdeletion Syndromes (limited panel) (N=89)	23 (25.84%)
Whole Genome Copy Number Variant Screening (N=88)	50 (56.82%)
Single gene conditions (N=89)	55 (61.80%)
Approximately what percent of patients have diagnostic testing? (Amniocentesis or CVS) (N=86)	
< 25%	66 (76.74%)
25 - 49%	14 (16.28%)
50 - 74%	4 (4.65%)
> 75%	2 (2.33%)

[a] Subtotal of respondents. [b] This question was only asked to those who stated they do not offer NIPS to all patients. [c] Responses compiled from matrix question "*Please explain your current use of NIPS for each category of conditions?*"

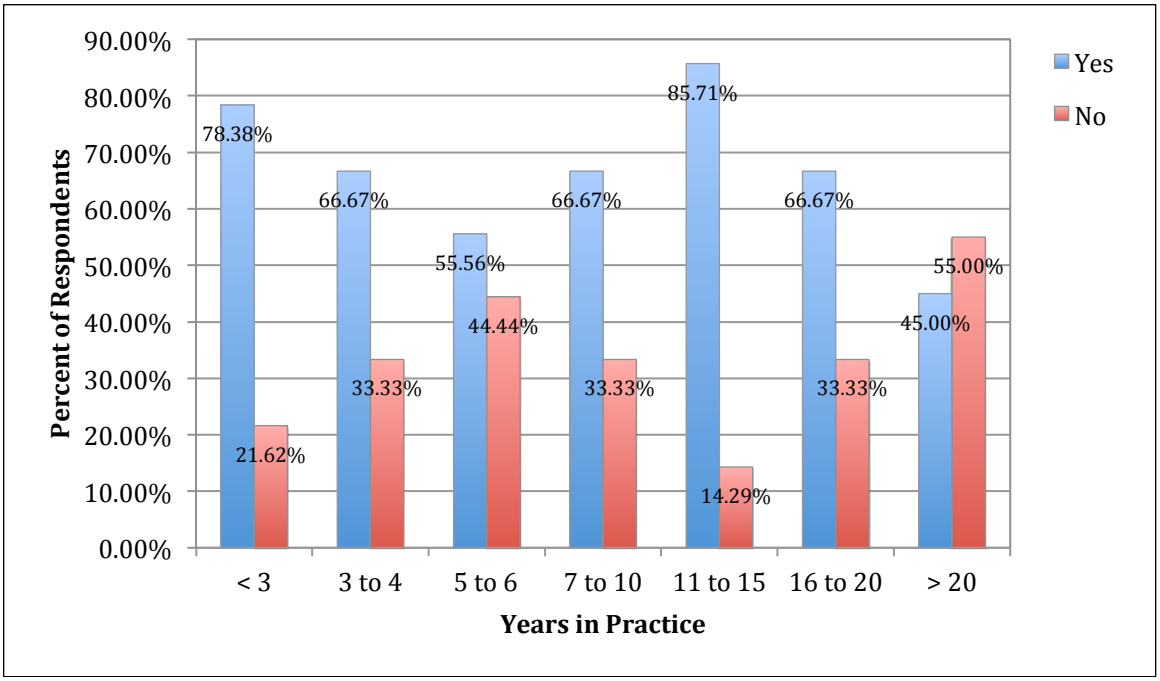

Figure 4. Response to *"Do you believe that NIPS should be offered universally (i.e. to any pregnant woman, regardless of a priori risk)?"* based on years in practice (N = 100). (r (99) = -.21, p<.05).

Table III: Opinion on Universal NIPS by Those Who Offer NIPS to All Patients Regardless of Risk		
Do you think NIPS should be offered universally?	Currently Offer NIPS to All Regardless of Risk	Do Not Offer NIPS to All
Yes	92.3% (48)	36.4% (16)
No	7.7% (4)	63.6% (28)
Total	100.0% (52)	100.0% (44)

Chi-Square = 33.57, (df=1), p <.001

Table IV: Subtypes of NIPS Offered To All Patients Compared to Opinion On Universal NIPS		
NIPS Subtype	NIPS Should Be Offered Universally	NIPS Should Not Be offered Universally
Classic aneuploidy (N=91)*	36 (60%) (n=60)	9 (29.03%) (n=31)
Sex Chromosomes (N=91)***	45 (75%) (n=60)	10 (32.26%) (n=31)
Early Pregnancy Loss (N=85) n.s.	7 (12.28%) (n=57)	1 (3.57%) (n=28)
Microdeletions (N=89)*	15 (25.42%) (n=59)	1 (3.33%) (n=30)
Copy Number Variants (N=88) n.s.	1 (1.69%) (n=59)	0 (0.00%) (n=29)
Single Gene Conditions (N=89) n.s.	0 (0%) (n=59)	0 (0%) (n=30)

*p<.05, **p<.01, ***p<.001, n.s.: not significant

Table V: Free Response on Opinions and Use of NIPS		
Question	Theme	n[a] (%)
Please explain why you think NIPS should be offered universally … (N=58) [Comments by theme]		
	NIPS is superior to traditional screening options	44 (74.58%)
	Offer all screening choices	11 (18.64%)
	Need for pre-test counseling by GC	7 (11.86%)
	Emphasis placed on limitations of NIPS	7 (11.86%)
Please explain why you think NIPS should not be offered universally…(N=19) [Comments by theme]		
	Data does not show superior test validity in low-risk populations	13 (68.34%)
	Use of test to detect gender/sex	5 (26.32%)
	Lack of insurance coverage, cost is prohibitory	4 (21.05%)
	Want values from other screening	3 (15.79%)
	Providers do not have sufficient or accurate knowledge about NIPS	3 (15.79%)
	NIPS will be universal in the future, inevitable	3 (15.79%)
Please explain the difference in your practice of offering NIPS and your opinion on whether it should be offered to all patients … (N=20)[b] [Comments by theme]		
	Decision was made by others are the institution/practice	10 (50.00%)
	Cost of test is prohibitory, lack of insurance coverage	6 (30.00%)
	Limitation on counselor – time or patient load	4 (20.00%)
What benefits, if any, have you noticed or perceived since the implementation of Universal NIPS into the ACMG screening guidelines, in 2016? (N=47) [Comments by theme]		
	None or N/A	16 (34.04%)
	Better insurance coverage	9 (19.15%)
	Increased test validity	7 (14.89%)
	Improved access	6 (12.77%)
	Anxiety reduction for patients	5 (10.64%)
	More options	5 (10.64%)
	Patient awareness of NIPS has increased	5 (10.64%)
	Increase in use by providers and knowledge about test specifics	5 (10.64%)
What issues, if any, do you feel have arisen since the implementation of Universal NIPS into the ACMG screening guidelines, in 2016? (N=57) [Comments by theme]		
	Inadequate or incorrect pre-test counseling	15 (26.32%)

No issues or N/A	13 (22.81%)
Lack of insurance coverage or cost is prohibitory	13 (22.81%)
Providers lack sufficient or accurate understanding of test specifics	12 (21.05%)
Miss traditional screening info-analytes or ultrasound	7 (12.28%)
Test being used to determine sex/gender	7 (12.28%)
MFM agreement about practice guidelines	6 (10.53%)

[a] Subtotal of respondents. [b] Responses compiled from two questions, "*Please explain the difference between your practice of not offering NIPS universally and your opinion that it should be offered to all patients …*" and "*Please explain the difference between your practice of offering NIPS universally and your opinion that it should not be offered to all patients…"*

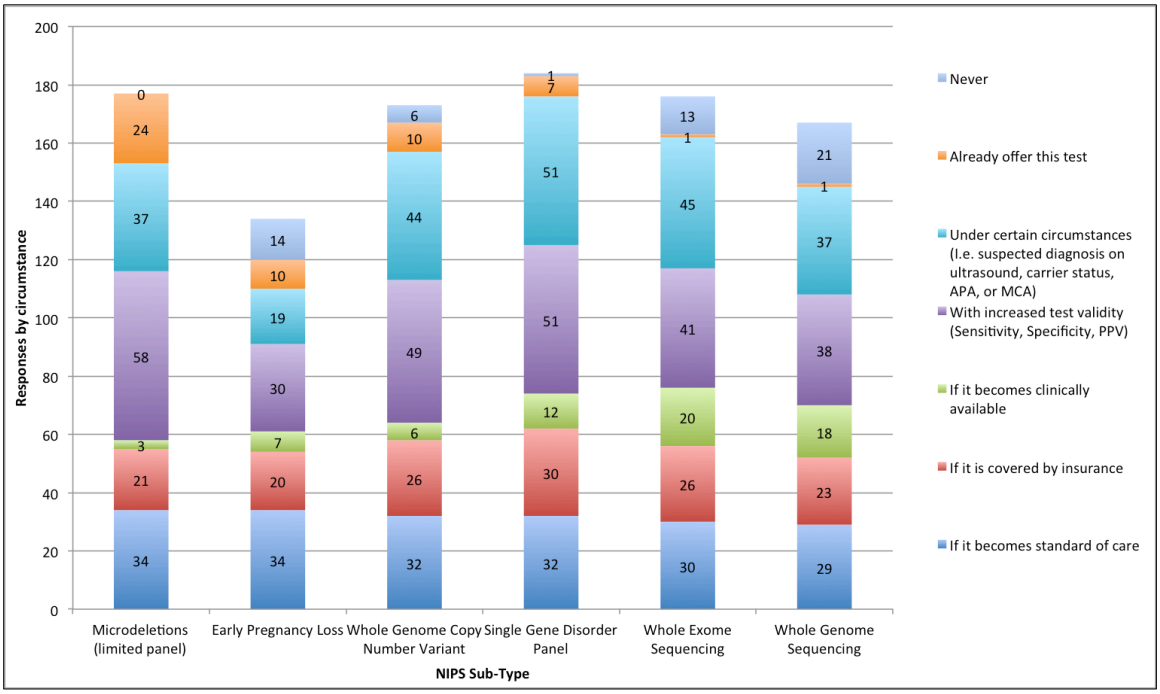

Figure 5. *Under what circumstances, in the future, would you choose to offer NIPS for these conditions?*

Table VI: Opinions on Future Uses of NIPS		
Question	Theme	n[a](%)
What additional comments or concerns, if any, do you have with the continued expansion of NIPS into new patient populations and conditions? (N=25)		
	Patient education needs to improve	12 (48.00%)
	Test validity needs to increase	9 (36.00%)
	Provider education needs to be improved	8 (32.00%)
	Test utility needs to be better established	5 (20.00%)
	Insurance coverage needs to improve, cost of test needs to be reduced	3 (12.00%)

[a] Subtotal of respondents.

DISCUSSION

Changes over time

As we had hypothesized, the opinion of genetic counselors concerning universal NIPS has significantly shifted since the 2015 survey by Suskin et al. (Chi-square = 13.02 (df=1), p<.001). When *asked "Do you believe that NIPS should be offered universally (i.e. to any pregnant woman, regardless of a priori risk)?"* 44.74% (85) of genetic counselors in 2015 stated yes, while 67% (67) chose yes in 2018 (Figure 1). Practice has also changed in the last three years. Since the Suskin et al. 2015 study, significantly more genetic counselors were offering NIPS universally (Chi-Square = 66.94, (df=1), p <.001). Only 10.7% (22) of the genetic counselors in the previous study reported offering NIPS to any pregnant woman regardless of risk, while 54.2% of the counselors in the current study offered universal NIPS (Figure 2). As per our study, a greater number of GCs are also offering NIPS with microdeletions. When asked how they currently use NIPS with microdeletion panels 24.0% stated they do not currently offer it, this number is down significantly from 2015 when 47.7% reported not offering NIPS with microdeletions (Figure 3, Chi-square = 16.89 (df=1), p<.001). One area of minimal change was to whom NIPS is offered. Responses were similar for all categories of patients except that low-risk patients were more likely to be offered NIPS if they inquired about it. The rate increased from 36.9% in the previous study to 49.0% in the current study. This change was in line with the trends noted in this study, but was not statistically significant (Chi-square = 2.43 (df=1), p = .12).

Analysis of coded qualitative data revealed a few significant changes between the two studies. When asked about why they support universal NIPS, fewer respondents reported feeling the need to emphasize the limitations of NIPS: 11.9% (7) in 2018 versus 27.5% (19)

in 2015 (Chi-square = 4.63 (df=1), p<.05). No other codes showed significant difference over time vis-à-vis those who support universal NIPS.

On the other hand qualitative data on those who do not support universal NIPS showed several significant differences. Interestingly, the expressed desire for additional prenatal screening test values increased from 3.1% (3) in 2015 to 15.8% (3) in 2018 (Fisher's Exact probability <.05). So despite many studies on NIPS offering proof of its validity and accuracy, GCs are increasingly concerned about the loss of other screening values with an increased use of NIPS. One respondent echoed concerns regarding skipped MSAFP screening and NT measurements, saying the following, "we have an office that has had a couple of patients with anencephaly that were missed until 20 weeks and multiples not diagnosed until 20 weeks. Our office still recommends an NT regardless of which blood test a patient chooses." There was a significant difference in concerns expressed about gender and sex, 26.5% (5) in 2018 versus only 1.0% (1) in 2015 (Fisher's Exact probability, .001). Our results also documented increased public awareness of the test, including its ability to detect fetal sex. One respondent wrote: "Most [patients] do [NIPS] for gender. We have had couples terminate for gender. NIPT gets them results early enough they can act without people knowing they are pregnant..."

Demographic information versus Study Question

Demographic data identified some trends. Years in practice were negatively correlated with the belief that NIPS should be offered to any pregnant woman regardless of a priori risk (Figure 4, r (99) = -.21, p<.05). Genetic counselors practicing for fewer years were more open to the idea of NIPS being offered universally. In fact, 78.4% (29) of those practicing less than 3 years were in favor of universal NIPS, while only 45.0% (9) of those practicing over 20 years favored universal NIPS.

The belief that NIPS should be offered universally was also significantly related to the portion of patients GCs see who have coverage through state or federal insurance programs (e.g., Medicaid or Medicare) (Chi-square = 8.25 (df=3), $p<.05$). Counselors practicing in institutions where fewer patients were covered by these insurance programs were more likely to believe NIPS should be offered to all pregnant women. Comparatively, 86.4% (19), of respondents with less than 25% of their patients insured through federal or state programs, were in favor of universal NIPS, while only 58.97% (46) of those with 25% or more of their patients covered under Medicaid, favored universal NIPS. Another note about Medicaid coverage, respondents from the same state did not necessarily report Medicaid covering the test in the same way. This may indicate that certain labs have policies where they absorb any cost associated with a patient on Medicaid, regardless of whether they receive reimbursement in order to increase the number of tests ordered. There was no correlation between the percentage of patients who elect to pursue diagnostic testing and whether or not respondents think NIPS should be offered universally (Chi-square = 3.09 (df=2) $p=.08$). However, GCs who reported less than 25% of their patients pursue diagnostic testing, were more likely to report being in favor of universal NIPS [71.2% (47)] than those with greater than 25% of patients doing invasive testing [50% (10)].

Current Practices versus Study Question

Genetic counselors who work in institutions where NIPS is offered to all patients regardless of risk were more likely to believe in offering NIPS universally (Table III, Chi-square = 33.57 (df=1), $p<.001$). While 92.3% (48) of those who currently offer NIPS to all patients believe in universal NIPS, 36.4% (16) of those who do not offer NIPS to all reported that they are in favor of universal access. Data reflects significant dissonance remaining between counselors' beliefs and actions.

"*To whom do you offer NIPS? (Select all that apply),"* was asked of all respondents who reported not offering NIPS universally. Almost all stated that they offer NIPS to patients over 35, patients with a high-risk screen, and patients with a previous pregnancy affected with an aneuploidy. Very few reported offering NIPS to patients with a family history of other genetic conditions, patients interested in early detection of fetal sex, or patients with recurrent miscarriage. These trends did not correlate with opinion of offering NIPS universally.

An additional question inquired about which subtypes of NIPS GCs offer to all patients. In comparing responses from participants who believe in universal NIPS against those who do not, significant differences were identified. The difference was significant in regards to those offering sex chromosomes (Table IV, Chi-square=15.61, $p<.001$), with 75.00% of those who support universal NIPS and 32.26% who do not support universal NIPS offering sex chromosomes to all patients. It is also significant for those offering limited microdeletion panels (Table IV, Chi-square=6.58, $p<.05$), with 25.42% and 3.33% of those who do and do not support universal NIPS respectively offering these panels to all patients.

Discordance between practice and opinion

Two questions were drafted in an attempt to parse out the differences between the 20.83% (20) of genetic counselors whose beliefs and practices do not align. One question was asked of those who support universal NIPS, but do not offer it to all patients, the other was asked to those who do not support universal NIPS, but offer it universally. Qualitative responses revealed themes including that the decision was made by other people (50%, n=10), the cost of the test and lack of insurance coverage (30%, n=6), and the inability for genetic counselors to accommodate all patients (20%, n=4) (Table V). In comparing the

2015 and the 2018 studies, the majority of counselors reported their beliefs aligning with the practice at their institution, 64.73% (123), in 2015, and 79.17% (76), in 2018 (Table III). However, there was a significant change in the number of counselors who believe that the universal use of NIPS is appropriate and worked in institutions in which all prenatal patients are offered NIPS. The number of respondents jumped from 23.5% (20) in the previous study to 75.0% (48) in the current study (Chi-square = 39.00 (df=1), $p<.001$). In 2018, a greater number of GCs reported believing NIPS should not be offered universally and working in an institution that offers NIPS to all patients, 12.5% (4) than in 2015 when only 1.9% (2) of respondents reported this.

Support of Universal NIPS

The 58 qualitative responses to the question "*Please explain why you think NIPS should be offered universally …"* were coded by consensus identifying four major and three minor themes (Table V). An additional question of "*What benefits, if any, have you noticed or perceived since the implementation of Universal NIPS into the ACMG screening guidelines, in 2016?*" had 47 responses which were also analyzed for common themes; eight major and two minor themes were identified (Table V).

Those who supported the use of universal NIPS often made statements about how NIPS has superior validity than traditional screening, including higher specificity, higher sensitivity, and lower false positive rate. Of those who said NIPS should be offered to all patients regardless of risk, 74.58% (44) discussed the superiority of NIPS to other available screening tests. One GC stated, "... studies suggest that the sensitivity/specificity of the testing in average-risk populations is likely very similar to that in high-risk populations, and it's a far superior test to conventional serum screening," while another succinctly stated, "It's the best screen available. It has the highest detection rate and the lowest false positive- why

not offer it everyone [sic]?" This theme illustrates genetic counselors' comfort with relying on the data in order to determine which screening test to offer. This theme also emerged in another question that asked respondents to discuss benefits they have noticed since the implementation of universal NIPS screening into ACMG guidelines with 14.89% (7) of GCs saying improvements have been made in test analytical validity. An example of this opinion "Fewer false positive than other serum screens, this change has been FABULOUS!" demonstrates the excitement some genetic counselors feel about the changes NIPS have brought about.

Of GCs who supported the use of NIPS for all patients in the current study, 18.64% (11) advocated that offering the screening to all women should be our way of presenting options in an unbiased manner and expanding access to care. One participant pointed out "[NIPS] will expand high quality screening access to individuals who don't have access to first trimester ultrasounds with accurate NT/NB measurements." Another noted, "By not offering it to everyone we become more paternalistic." In describing the benefits, 23.4% (11) genetic counselors expressed having more choices and improved access for patients. One wrote, "I love how even patients who miss our '1st tri window' can still get the best screening and not have to settle for a Quad with an increased risk for false positive."

Pre-test counseling was mentioned by a minority 11.86% (7) of GCs offering comments. One respondent stated, "It should be offered and carefully explained by a genetic counselor. There are nuances to the data on low risk groups, multiples, egg donor pregnancies. Also, insurance coverage is an issue for some patients, especially those in the low risk category," which emphasized the way genetic counselors are uniquely equipped to discuss these diverse topics and provide accurate information.

Genetic counselors who believe NIPS should be offered to all patients, 11.86% (7) commented on perceived limitations of the test and how that affected their opinions of its use. For example, one respondent said, "Less false positives than first trimester or quad screening. However I don't think that NIPS with microdeletions should be offered to everyone due to the low PPVs." This exemplifies the common idea that NIPS should be provided universally for the traditional trisomies, though in the opinions of these GCs, not for every condition. Another counselor similarly said, "I believe it is one of the best screening tools we have currently for the common aneuploidies, and we should approach it in the same way we have approached first trimester screening. However, it is worth noting that I only feel that universal screening for Trisomy 13, Trisomy 18, and Trisomy 21 should be offered - NOT microdeletions/duplications, genome-wide copy number variants, or single gene disorders."

Do not support universal NIPS

Responses to "*Please explain why you think NIPS should not be offered universally …*" were analyzed for common themes. From the nineteen answers, coded by consensus, six themes were identified (Table V). Other qualitative responses that were critical to universal NIPS were in response to "*What issues, if any, do you feel have arisen since the implementation of Universal NIPS into the ACMG screening guidelines, in 2016?*" This question was also coded by consensus, and from the 57 responses ten common themes were identified (Table V).

In a striking comparison to supporters of universal access, GCs who do not believe NIPS should be offered to all patients stated that NIPS is not better than other screens or data does not suggest its universal expansion is beneficial, with 73.68% (14) raising such concerns. One stated, "PPV for most conditions is still very low with low risk patients," demonstrating concern with clinical utility. Others did not state that the values are too low,

but rather that there are "Limited studies in low risk population Limited PPV in low risk population Limited sensitivity for microdels, sex chromosome aneuploidy."

Gender and sex, or the use of NIPS for detecting it, were a popular point of contention for GCs who do not believe in universal NIPS. This was brought up by 26.32% (5) of respondents against universal NIPS, including one who wrote: "I have no problem with it being offered to everyone if people are choosing it for the real reason of aneuploidy screening and not for determining gender." This theme was also identified by 12.28% (7) of respondents when asked about issues that have arisen since the ACMG inclusion of universal NIPS into their guidelines, despite specification the test should not be used for sex selection (Gregg et al. 2016).

Hesitation about the expansion of NIPS to all patients and for a larger range of conditions was at least partially related to cost. GCs who do not believe in offering NIPS to all patients indicated insurance coverage was a concern in 21.05% (4) of responses. This reasoning was often combined with other issues, much as it was here: "For women under 35, a first trimester screen has almost as high detection rate as NIPS at half the cost...Test utilization is important in the grand scheme of healthcare. Unnecessarily spending thousands of dollars adds to the system in general and compounds the problem. The difference between a 96% detection rate and 99.99% one is there, but I don't believe it's big enough for me to consider doing NIPS on all patients. Not unless the cost of NIPS drastically reduces." Willingness of insurance to cover testing was a frustration expressed by 22.81% (13) of those who identified issues since the ACMGs inclusion of universal NIPS. In the case of this second question, some respondents explained that "despite the ACMG guideline, ACOG does not concur and insurance does not cover this testing," showing there is still work that must be done before insurance coverage will cover universal NIPS.

Desire for values from non-NIPS screening tests was brought up by 15.79% (3) of respondents. An example that reflects this was, "I ultimately think we should move to genome wide NIPS for all pregnant patients but still think biochemical screening (AFP, uE3, hCG) has usefulness if it would be incorporated with NIPS for screening for adverse outcome or specific conditions (ONTD [open neural tube defects], SLO [Smith-Lemli-Opitz], abdominal wall defects, etc)." The survey also identified that 61.05% (58) of genetic counselors combine NIPS with other aneuploidy screening. Of those that use additional screening, 98.83% (55) combine NIPS with NT. While the survey did not include level 2 anatomy scan as a type of aneuploidy screening, several respondents included it under the "other" option.

Of those who do not believe in the use of universal NIPS, 15.79% (3) plainly stated concerns, such as, "Lack of knowledge of offering providers". In discussing issues associated with the shifting 2016 ACMG guidelines, GCs specifically referenced a lack of understanding and inaccurate knowledge provision by obstetricians and gynecologists. Specifically, this counselor explained their experience: "Doctors tell their patients that the screening is INSTEAD of amnio/cvs. Or at least that's what patients are hearing. And I have actually heard MDs say, 'This blood draw will tell us if everything is okay with the baby's chromosomes' or 'There's now a blood test that tells us the same thing the amnio does.' VERY DANGEROUS. MDs need to be properly educated. Or be willing to explain to pts why an aneuploidy was missed." More succinctly, another counselor gave this opinion, "I also think that most general OB providers don't understand the concepts of sensitivity, specificity, positive predictive value."

A few of the genetic counselors, 15.79% (3), included in their responses, statements about universal NIPS being an inevitable fact of the future. Quotes such as "[universal

NIPS] will likely be the case within a few years …," often included stipulations about how they wish universal NIPS would be implemented, and were linked with provider knowledge and other screening values.

Future

Participating GCs were asked under what circumstances they would be willing to offer different methods of genetic information analysis by NIPS in the future. The question gave genetic counselors the option of stating they would never use a specific subset of NIPS. Of the test options, which included microdeletions (limited panel), early pregnancy loss, whole genome copy number variant screening, single gene disorder panel, whole exome, and whole genome, the only test type which no respondents reported they would never use was the limited microdeletion panel (Figure 5). In relation to the limited microdeletion panel, the majority of respondents (73.42%) stated they would be willing to offer it in the future if there were increased test validity (sensitivity, specificity, PPV).

Study Limitations

This survey was distributed through the NSGC listserv. The open rate was 26.8% (967) and 23% (838) for the reminder email; as with any study the people who respond are the most interested in the topic. One error in our survey logic may have resulted in a drop off of responses by asking respondents a question that did not apply to them, only qualitative data was affected. Another survey logic error had a number of GCs skip a question, resulting in a lower number of responses for a qualitative question. Of note both errors were corrected within a half hour of the survey being released, and no quantitative data was affected. Also in general, self reported data may result in skewed results due to the respondents answering how they think they should, instead of what they actually do and think, or interpreting the question in a way that was different than it was intended when

written. Also quantitative data collected by self-reporting may be subject to misperceptions by the GC such as overestimation or underestimation of a fact. In future studies, question design should be undertaken with care in order to better analyze the data, especially in asking about current use of NIPS. A more effective way to ask would be to first ask if they offer the type of test, then whether they offer it to everyone, followed by to whom do they offer it, as to avoid conflicting responses.

CONCLUSION

Although a majority of genetic counselors believe that NIPS should be offered to all patients, and our study suggests significantly more GCs are offering NIPS universally than in 2015, we still do not see a consensus on how and when to offer it. Especially in relation to whether NIPS is offered in isolation or in conjunction with additional screening tests, as only about 60% of respondents reported offering it with other screening methods. NIPS technology can now be used to detect a wider range of genetic abnormalities. However, counselors are still not in agreement as to what constitutes the appropriate use of these expanded NIPS panels. Guidelines put forth by the ACMG support offering NIPS as a choice for all pregnant women, but this is change has not been mirrored by other professional organizations. Until practice guidelines are in agreement and use is in alignment with practice guidelines, the issues of how and who best to offer NIPS will most likely remain unsettled. Research on genetic counselors practice and opinions should continue to help inform standard of care implementation for prenatal screening.

CONFLICT OF INTEREST

Carla Bennett and Abigail Whiting declare that they have no conflict of interest.

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APPENDIX A

Demographic Information		
Questions	Answers	n[a](%)
Are you a certified genetic counselor? (N=103)		
	Yes	103 (100%)
	No	0 (0.00%)
How many years have you been a practicing GC? (in years) (N=103)		
	Less than 3	37 (35.92%)
	3 - 4	6 (5.83%)
	5 - 6	10 (9.71%)
	7 - 10	10 (9.71%)
	11 - 15	7 (6.80%)
	16 - 20	13 (12.62%)
	More than 20	20 (19.42%)
In what country do you work? (N=103)		
	United States	99 (96.12%)
	Canada	3 (2.91%)
	Other (Please Specify) Australia	1 (0.97%)
In which NSGC practice region do you work? [b, c] (N=100)		
	Region 1	11 (11.00%)
	Region 2	18 (18.00%)
	Region 3	8 (8.00%)
	Region 4	34 (34.00%)
	Region 5	6 (6.00%)
	Region 6	24 (24.00%)
On average how many prenatal patients do you counsel in a week? (N=103)		
	< 5	10 (9.71%)
	5 - 9	21 (20.39%)
	10 - 14	31 (30.10%)
	15 - 19	29 (28.16%)
	≥ 20	12 (11.65%)
Which of these best describes your primary work place? (N=100)		
	University Medical Center	40 (40.00%)
	Private Practice	18 (18.00%)
	Private Hospital	18 (18.00%)
	Public Hospital	14 (14.00%)

Community Hospital	2 (2.00%)
Diagnostic Laboratory - Commercial	2 (2.00%)
Health Maintenance Organization (HMO)	2 (2.00%)
Government or Military Center	0 (0.00%)
Other (please specify) Non-profit Private MFM office County Hospital and University Private Practice	4 (4.00%) 2 (2.00%) 1 (1.00%) 1 (1.00%)
In what setting do you primarily practice? (N=102)	
Urban	65 (63.73%)
Suburban	33 (32.35%)
Rural	4 (3.92%)
Approximately what portion of your patients have coverage through state or federal insurance programs (Medicaid or Medicare)? (N=100)	
< 25%	22 (22.00%)
25 - 49%	47 (47.00%)
50 - 75%	22 (22.00%)
> 75%	9 (9.00%)
Approximately what percentage of the patients offered NIPS at your center/institution are seen by genetics prior to testing? (N=94)	
< 25%	15 (15.96%)
25 - 49%	5 (5.32%)
50 - 75%	13 (13.83%)
> 75%	61 (64.89%)

[a] Subtotal of respondents. [b] NSGC practice regions are defined as follows:
Region 1: CT, MA, ME, NH, RI, VT, CN Maritime Provinces
Region 2: DC, DE, MD, NJ, NY, PA, VA, WV, PR, VI, Quebec
Region 3: AL, FL, GA, KY, LA, MS, NC, SC, TN
Region 4: AR, IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, OK, SD, WI, Ontario
Region 5: AZ, CO, MT, NM, TX, UT, WY, Alberta, Manitoba, Saskatchewan
Region 6: AK, CA, HI, ID, NV, OR, WA, British Columbia
[c] Responses calculated based on two questions, "In which American state/territory do you primarily work?" and "In which Canadian province/territory do you primarily practice?"

APPENDIX B

Current Practices and Opinions		
Questions	Answers	n[a] (%)
Do you believe that NIPS should be offered universally (i.e. to any pregnant woman, regardless of a priori risk)? (N = 100)		
	Yes	67 (67.00%)
	No	33 (33.00%)
Please explain why you think NIPS should be offered universally … (N=58) [Comments by theme on the belief that NIPS should be offered universally]		
	NIPS is superior to traditional screening options	44 (74.58%)
	Offer all screening choices	11 (18.64%)
	Need for pre-test counseling by GC	7 (11.86%)
	Emphasis placed on limitations of NIPS	7 (11.86%)
	Women <35 are still at risk of having affected pregnancy	4 (6.78%)
	NIPS should be provided with NT and/or LII	3 (5.08%)
	NIPS provides flexibility of timing	3 (5.08%)
Please explain why you think NIPS should not be offered universally…(N=19) [Comments on disagreement with offering NIPS universally by theme]		
	Data does not show superior test validity in low-risk populations	13 (68.34%)
	Use of test to detect gender/sex	5 (26.32%)
	Lack of insurance coverage, cost is prohibitory	4 (21.05%)
	Want values from other screening	3 (15.79%)
	Providers do not have sufficient or accurate knowledge about NIPS	3 (15.79%)
	NIPS will be universal in the future, inevitable	3 (15.79%)
Does your institution currently offer NIPS? (N=98)		
	Yes	97 (98.98%)
	No	1 (1.02%)
Do you offer NIPS to ALL patients, regardless of risk? (N=96)		
	Yes	52 (54.17%)
	No	44 (45.83%)
Please explain the difference between your practice of not offering NIPS universally and your opinion that it should be offered to all patients … (N=16) [Responses by theme]		
	Decision was made by others are the institution/practice	7 (43.75%)
	Lack of insurance coverage, cost prohibitory	6 (37.50%)
	Limitation of counselor - time or patient load	3 (18.75%)
	Doctor's decision, some offer universally, others do not	2 (12.50%)
	Disagree with practice, but did not state whose decision it was	2 (12.50%)

Other screening values wanted	1 (6.25%)
Please explain the difference between your practice of offering NIPS universally and your opinion that it should not be offered to all patients…(N=4) [Responses by theme]	
Fear of inadequate patient education and consenting	3 (75.00%)
Traditional Screening is effective as a first line test	3 (75.00%)
Cost of test is prohibitory	2 (50.00%)
Knowledge gap of doctors and other providers	2 (50.00%)
To whom do you offer NIPS? (Select all that apply)[b] (N=46)	
Patients with a high-risk screen (NT, FTS, Quad, Sequential)	46 (100.00%)
Patients over 35	44 (95.65%)
Patients with a previous pregnancy affected with an aneuploidy	44 (95.65%)
Patients who inquire about the test	24 (52.17%)
Patients with recurrent miscarriage	8 (17.39%)
Patients with family history of other genetic conditions	6 (13.04%)
Patients interested in early detection of fetal sex	5 (10.87%)
Other (please specify) Abnormal U/S	18 (39.13%) 11 (23.91%)
Do you generally combine the use of NIPS with other aneuploidy screening options? (N=95)	
Yes	58 (61.05%)
No	37 (38.95%)
What additional screening do you offer to patients who pursue NIPS? (Select all that apply)[c] (N=58)	
Nuchal Translucency (NT)	55 (98.83%)
AFP maternal serum screen	39 (67.24%)
First trimester screening of analytes	18 (31.03%)
Quad screen	12 (20.69%)
Sequential screen	9 (15.52%)
Other (Please Specify) Anatomy scan	11 (18.97%) 10 (17.24%)
Assuming NIPS was performed with MSAFP, which of the following would you be concerned about losing in a transition to NIPS as primary screening? (Please select all that apply) (N=95)	
NT (Nuchal Translucency)	78 (82.11%)
PAPP-A (pregnancy associated plasma protein A)	31 (32.63%)
uE3 (unconjugated estriol)	27 (28.42%)
hCG (free beta human chorionic gonadotropin or intact/total human chorionic gonadotropin)	15 (15.79%)
Inhibin-A	7 (7.37%)

None	14 (14.74%)
What do you recommend first to patients who receive no-call results on NIPS? (N=87)	
Redraw sample with the same lab	43 (49.43%)
Offer diagnostic testing	18 (20.69%)
Redraw sample to send to a different lab	0
Increased ultrasound/early anatomy scan	0
No action taken/Do not recommend further testing	0
Other (please specify) Two or more options Patient specific Lab choice Additional counseling No-call results not received	26 (29.89%) 17 (19.54%) 5 (5.74%) 2 (2.30%) 1 (1.15%) 1 (1.15%)
Please explain your current use of NIPS for each category of conditions? Classic Aneuploidy Screening (Trisomy 13, Trisomy 18, Trisomy 21) (N=91)	
Must be performed if test is ordered	47 (51.65%)
Offered to all patients	45 (49.45%)
Offered to high-risk patients (AMA, positive screen)	54 (59.34%)
Offered to patients with u/s findings	53 (58.24%)
Offered to patients with family history of condition	40 (43.96%)
Only offered if patient asks	11 (12.09%)
Offered to patients with history of multiple miscarriage	11 (12.09%)
Offered for research purposes	0 (0.00%)
Not currently offered at this center	0 (0.00%)
Please explain your current use of NIPS for each category of conditions? Sex Chromosomes (N=91)	
Must be performed if test is ordered	15 (16.48%)
Offered to all patients	55 (60.44%)
Offered to high-risk patients (AMA, positive screen)	47 (51.65%)
Offered to patients with u/s findings	43 (47.25%)
Offered to patients with family history of condition	34 (37.36%)
Only offered if patient asks	12 (13.19%)
Offered to patients with history of multiple miscarriage	6 (6.59%)
Offered for research purposes	0 (0.00%)
Not currently offered at this center	0 (0.00%)
Please explain your current use of NIPS for each category of conditions? Early Pregnancy Loss Chromosomes (Trisomy 9, Trisomy 16, Trisomy 22) (N=85)	
Must be performed if test is ordered	1 (1.18%)
Offered to all patients	8 (9.41%)

Offered to high-risk patients (AMA, positive screen)	6 (7.06%)
Offered to patients with u/s findings	13 (15.29%)
Offered to patients with family history of condition	15 (17.65%)
Only offered if patient asks	8 (9.41%)
Offered to patients with history of multiple miscarriage	12 (14.12%)
Offered for research purposes	0 (0.00%)
Not currently offered at this center	53 (62.35%)
Please explain your current use of NIPS for each category of conditions? Microdeletion Syndromes (limited panel) (N=89)	
Must be performed if test is ordered	1 (1.12%)
Offered to all patients	16 (17.98%)
Offered to high-risk patients (AMA, positive screen)	11 (12.36%)
Offered to patients with u/s findings	42 (47.19%)
Offered to patients with family history of condition	33 (37.08%)
Only offered if patient asks	22 (24.72%)
Offered to patients with history of multiple miscarriage	2 (2.25%)
Offered for research purposes	0 (0.00%)
Not currently offered at this center	23 (25.84%)
Please explain your current use of NIPS for each category of conditions? Whole Genome Copy Number Variant Screening (N=88)	
Must be performed if test is ordered	0 (0.00%)
Offered to all patients	1 (1.14%)
Offered to high-risk patients (AMA, positive screen)	4 (4.55%)
Offered to patients with u/s findings	31 (35.23%)
Offered to patients with family history of condition	16 (18.18%)
Only offered if patient asks	7 (7.95%)
Offered to patients with history of multiple miscarriage	7 (7.95%)
Offered for research purposes	0 (0.00%)
Not currently offered at this center	50 (56.82%)
Please explain your current use of NIPS for each category of conditions? Single gene conditions (N=89)	
Must be performed if test is ordered	0 (0.00%)
Offered to all patients	0 (0.00%)
Offered to high-risk patients (AMA, positive screen)	1 (1.12%)
Offered to patients with u/s findings	24 (26.97%)
Offered to patients with family history of condition	20 (22.47%)
Only offered if patient asks	11 (12.36%)
Offered to patients with history of multiple miscarriage	0 (0.00%)

Offered for research purposes	1 (1.12%)
Not currently offered at this center	55 (61.80%)
Approximately what is the uptake of patients who are offered this type of testing? Classic Aneuploidy Screening (Trisomy 13, Trisomy 18, Trisomy 21) (N=89)	
< 25%	2 (2.25%)
25 - 49%	7 (7.87%)
50 -74%	21 (23.60%)
> 75%	59 (66.29%)
N/A - not offered	0 (0.00%)
Approximately what is the uptake of patients who are offered this type of testing? Sex Chromosomes (N=89)	
< 25%	4 (4.49%)
25 - 49%	5 (5.62%)
50 -74%	29 (32.58%)
> 75%	50 (56.18%)
N/A - not offered	1 (1.12%)
Approximately what is the uptake of patients who are offered this type of testing? Early Pregnancy Loss Chromosomes (Trisomy 9, Trisomy 16, Trisomy 22) (N=89)	
< 25%	14 (15.73%)
25 - 49%	4 (4.49%)
50 -74%	6 (6.74%)
> 75%	5 (5.62%)
N/A - not offered	60 (67.42%)
Approximately what is the uptake of patients who are offered this type of testing? Microdeletion Syndromes (limited panel) (N=87)	
< 25%	20 (22.99%)
25 - 49%	13 (14.94%)
50 -74%	11 (12.64%)
> 75%	12 (13.79%)
N/A - not offered	31 (35.63%)
Approximately what is the uptake of patients who are offered this type of testing? Whole Genome Copy Number Variant screening (N=89)	
< 25%	21 (23.60%)
25 - 49%	7 (7.87%)
50 -74%	3 (3.37%)
> 75%	5 (5.62%)
N/A - not offered	53 (59.55%)

Approximately what is the uptake of patients who are offered this type of testing? Single gene conditions (N=89)	
< 25%	22 (24.72%)
25 - 49%	3 (3.37%)
50 -74%	2 (2.25%)
> 75%	4 (4.49%)
N/A - not offered	58 (65.17%)
Under what circumstances does Medicaid cover NIPS for these conditions? Classic Aneuploidy Screening (N=78)	
Coverage of all patients	15 (19.23%)
Coverage of patients over 35	40 (51.28%)
Coverage only if family history or history of previous affected pregnancy	21 (26.92%)
Coverage only if ultrasound findings	25 (32.05%)
Coverage if high-risk by screening	34 (43.59%)
No Coverage	12 (15.38%)
N/A	8 (10.26%)
Under what circumstances does Medicaid cover NIPS for these conditions? Sex Chromosomes (N=76)	
Coverage of all patients	15 (19.74%)
Coverage of patients over 35	27 (35.53%)
Coverage only if family history or history of previous affected pregnancy	14 (18.42%)
Coverage only if ultrasound findings	16 (21.05%)
Coverage if high-risk by screening	21 (27.63%)
No Coverage	19 (25.00%)
N/A	13 (17.11%)
Under what circumstances does Medicaid cover NIPS for these conditions? Microdeletion Syndromes (limited panel) (N=76)	
Coverage of all patients	7 (9.21%)
Coverage of patients over 35	10 (13.16%)
Coverage only if family history or history of previous affected pregnancy	11 (14.47%)
Coverage only if ultrasound findings	11 (14.47%)
Coverage if high-risk by screening	10 (13.16%)
No Coverage	28 (36.84%)
N/A	26 (34.21%)
Under what circumstances does Medicaid cover NIPS for these conditions? Early Pregnancy Loss (N=74)	
Coverage of all patients	1 (1.35%)
Coverage of patients over 35	2 (2.70%)

Coverage only if family history or history of previous affected pregnancy	1 (1.35%)
Coverage only if ultrasound findings	1 (1.35%)
Coverage if high-risk by screening	1 (1.35%)
No Coverage	27 (36.49%)
N/A	42 (56.76%)
Under what circumstances does Medicaid cover NIPS for these conditions? Whole Genome Copy Number Variant Screening (N=77)	
Coverage of all patients	1 (1.30%)
Coverage of patients over 35	2 (2.60%)
Coverage only if family history or history of previous affected pregnancy	4 (5.19%)
Coverage only if ultrasound findings	5 (6.49%)
Coverage if high-risk by screening	3 (3.90%)
No Coverage	29 (37.66%)
N/A	40 (51.95%)
Under what circumstances does Medicaid cover NIPS for these conditions? Single gene conditions (N=75)	
Coverage of all patients	0 (0.00%)
Coverage of patients over 35	0 (0.00%)
Coverage only if family history or history of previous affected pregnancy	4 (5.33%)
Coverage only if ultrasound findings	2 (2.67%)
Coverage if high-risk by screening	1 (1.33%)
No Coverage	28 (37.33%)
N/A	42 (56.00%)
Approximately what percent of patients have diagnostic testing? (Amniocentesis or CVS) (N=86)	
< 25%	66 (76.74%)
25 - 49%	14 (16.28%)
50 - 74%	4 (4.65%)
> 75%	2 (2.33%)
How frequently is diagnostic testing pursued for the following reason? Positive or high-risk NIPS results (N=86)	
Never	0 (0.00%)
Rarely	2 (2.33%)
Sometimes	14 (16.28%)
Often	70 (81.40%)
How frequently is diagnostic testing pursued for the following reason? Positive or high-risk aneuploidy screen (FTS or Quad) (N=86)	
Never	3 (3.49%)
Rarely	32 (37.21%)

Sometimes	42 (48.84%)
Often	9 (10.47%)
How frequently is diagnostic testing pursued for the following reason? Conflicting screening results (N=85)	
Never	6 (7.06%)
Rarely	22 (25.88%)
Sometimes	39 (45.88%)
Often	18 (21.18%)
How frequently is diagnostic testing pursued for the following reason? Advanced Maternal Age (N=86)	
Never	6 (6.98%)
Rarely	45 (52.33%)
Sometimes	32 (37.21%)
Often	3 (3.49%)
How frequently is diagnostic testing pursued for the following reason? Desire for microarray testing (N=86)	
Never	9 (10.79%)
Rarely	30 (34.88%)
Sometimes	28 (32.56%)
Often	19 (22.09%)
How frequently is diagnostic testing pursued for the following reason? Parental Anxiety (N=85)	
Never	12 (14.12%)
Rarely	46 (54.12%)
Sometimes	24 (28.24%)
Often	3 (3.53%)
How frequently is diagnostic testing pursued for the following reason? Ultrasound findings (N=86)	
Never	1 (1.16%)
Rarely	3 (3.49%)
Sometimes	26 (30.23%)
Often	56 (65.12%)
How frequently is diagnostic testing pursued for the following reason? Family history of condition / parent is carrier of condition (N=86)	
Never	1 (1.16%)
Rarely	13 (15.12%)
Sometimes	40 (46.51%)
Often	32 (37.21%)
How frequently is diagnostic testing pursued for the following reason? Residual risk of aneuploidy after negative NIPS result (N=86)	

Never	26 (30.23%)
Rarely	55 (63.95%)
Sometimes	5 (5.81%)
Often	0 (0.00%)
How frequently is diagnostic testing pursued for the following reason? No call or Inconclusive results on NIPS (N=86)	
Never	6 (6.98%)
Rarely	40 (46.51%)
Sometimes	37 (43.02%)
Often	3 (3.49%)
What is the most common reason patients pursue diagnostic testing (N=86)	
Ultrasound findings	41 (47.67%)
Positive or high-risk NIPS results	38 (44.19%)
Positive or high-risk aneuploidy screen (FTS or Quad)	3 (3.49%)
Advanced maternal age	2 (2.33%)
Parental anxiety	1 (1.16%)
Desire for microarray testing	1 (1.16%)
Conflicting screening results	0
Residual risk of aneuploidy with negative NIPS results	0
Family history of condition/ parent is carrier of condition	0
No-call or inconclusive NIPS	0
Other (please specify)	0
In your experience, how has the prevalence of the following changed since the implementation of NIPS? Invasive diagnostic procedures (CVS/Amniocentesis) (N=85)	
Decreased	58 (68.24%)
Stayed the Same	9 (10.59%)
Increased	4 (4.71%)
Unable to Judge	14 (16.47%)
In your experience, how has the prevalence of the following changed since the implementation of NIPS? Abortion or Selective Termination (N=85)	
Decreased	4 (4.71%)
Stayed the Same	51 (60.00%)
Increased	4 (4.71%)
Unable to Judge	26 (30.59%)
In your experience, how has the prevalence of the following changed since the implementation of NIPS? Children born at specialized care facility (N=85)	
Decreased	0 (0.00%)

Stayed the Same	29 (34.12%)
Increased	20 (25.53%)
Unable to Judge	36 (42.35%)
What benefits, if any, have you noticed or perceived since the implementation of Universal NIPS into the ACMG screening guidelines, in 2016?…(N=47) [Comments on perceived benefits with the implementation of Universal NIPS into the ACMG screening guidelines by theme]	
None or N/A	16 (34.04%)
Better insurance coverage	9 (19.15%)
Increased test validity	7 (14.89%)
Improved access	6 (12.77%)
Anxiety reduction for patients	5 (10.64%)
More options	5 (10.64%)
Patient awareness of NIPS has increased	5 (10.64%)
Increase in use by providers and knowledge about test specifics	5 (10.64%)
Fewer diagnostic tests	3 (6.38%)
Guideline discrepancy, ACOG/SMFM do not support universal NIPS	3 (6.38%)
Earlier detection rate	2 (4.26%)
What issues, if any, do you feel have arisen since the implementation of Universal NIPS into the ACMG screening guidelines, in 2016? (N=57) [Comments on issues that have arisen since the implementation of Universal NIPS into the ACMG screening guidelines by theme]	
Inadequate or incorrect pre-test counseling	15 (26.32%)
No issues or N/A	13 (22.81%)
Lack of insurance coverage or cost is prohibitory	13 (22.81%)
Providers lack sufficient or accurate understanding of test specifics	12 (21.05%)
Miss traditional screening info-analytes or ultrasound	7 (12.28%)
Test being used to determine sex/gender	7 (12.28%)
MFM agreement about practice guidelines	6 (10.53%)
Increased Patient Anxiety	5 (8.77%)
Increase in patient load	3 (5.26%)
Reduced diagnostic testing	2 (3.51%)
More diagnostic tests	1 (1.75%)

[a] Subtotal of respondents. [b] This question was only asked to those who stated they do not offer NIPS to all patients. [c] This questions was only asked to those who stated they do combine NIPS with other aneuploidy screening.

APPENDIX C

Future Uses and Opinions		
Question	Answers	n[a](%)
Under what circumstances, in the future, would you choose to offer NIPS for these conditions? Microdeletions (Limited Panel) (N=79)		
	If it becomes standard of care/is integrated into screening guidelines	34 (43.04%)
	If it is covered by insurance	21 (26.58%)
	Test becomes clinically available	3 (3.80%)
	Increased test validity (Sensitivity, Specificity, PPV)	58 (73.42%)
	Under certain circumstances (i.e. suspected diagnosis on ultrasound, carrier status, APA, or MCA)	37 (46.84%)
	Already offer this test	24 (30.38%)
	Never	0 (0.00%)
Under what circumstances, in the future, would you choose to offer NIPS for these conditions? Early Pregnancy Loss (N=77)		
	If it becomes standard of care/is integrated into screening guidelines	34 (44.16%)
	If it is covered by insurance	20 (25.97%)
	Test becomes clinically available	7 (9.09%)
	Increased test validity (Sensitivity, Specificity, PPV)	30 (38.96%)
	Under certain circumstances (i.e. suspected diagnosis on ultrasound, carrier status, APA, or MCA)	19 (24.68%)
	Already offer this test	10 (12.99%)
	Never	14 (18.18%)
Under what circumstances, in the future, would you choose to offer NIPS for these conditions? Whole Genome Copy Number Variant screening (N=79)		
	If it becomes standard of care/is integrated into screening guidelines	32 (40.51%)
	If it is covered by insurance	26 (32.91%)
	Test becomes clinically available	6 (7.59%)
	Increased test validity (Sensitivity, Specificity, PPV)	49 (62.03%)
	Under certain circumstances (i.e. suspected diagnosis on ultrasound, carrier status, APA, or MCA)	44 (55.70%)
	Already offer this test	10 (12.66%)
	Never	6 (7.59%)
Under what circumstances, in the future, would you choose to offer NIPS for these conditions? Single Gene Disorder Panel (N=80)		
	If it becomes standard of care/is integrated into screening	32 (40.00%)

guidelines	
If it is covered by insurance	30 (37.50%)
Test becomes clinically available	12 (15.00%)
Increased test validity (Sensitivity, Specificity, PPV)	51 (63.75%)
Under certain circumstances (i.e. suspected diagnosis on ultrasound, carrier status, APA, or MCA)	51 (63.75%)
Already offer this test	7 (8.75%)
Never	1 (1.25%)
Under what circumstances, in the future, would you choose to offer NIPS for these conditions? Whole Exome (N=79)	
If it becomes standard of care/is integrated into screening guidelines	30 (37.97%)
If it is covered by insurance	26 (32.91%)
Test becomes clinically available	20 (25.32%)
Increased test validity (Sensitivity, Specificity, PPV)	41 (51.90%)
Under certain circumstances (i.e. suspected diagnosis on ultrasound, carrier status, APA, or MCA)	45 (56.96%)
Already offer this test	1 (1.27%)
Never	13 (16.46%)
Under what circumstances, in the future, would you choose to offer NIPS for these conditions? Whole Genome (N=79)	
If it becomes standard of care/is integrated into screening guidelines	29 (36.71%)
If it is covered by insurance	23 (29.11%)
Test becomes clinically available	18 (22.78%)
Increased test validity (Sensitivity, Specificity, PPV)	38 (48.10%)
Under certain circumstances (i.e. suspected diagnosis on ultrasound, carrier status, APA, or MCA)	37 (46.84%)
Already offer this test	1 (1.27%)
Never	21 (26.58%)
What additional comments or concerns, if any, do you have with the continued expansion of NIPS into new patient populations and conditions? (N=25) [Additional comments on the continued expansion of NIPS to new patient populations and conditions by theme]	
Patient education needs to improve	12 (48.00%)
Test validity needs to increase	9 (36.00%)
Provider education needs to be improved	8 (32.00%)
Test utility needs to be better established	5 (20.00%)

Insurance coverage needs to improve, cost of test needs to be reduced	3 (12.00%)
Lab secrecy should be ended	2 (8.00%)
Miss traditional screening value(s)	2 (8.00%)
Future usefulness	1 (4.00%)

[a] Subtotal of respondents.