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Obstetrician and Gynecologist Utilization of the NIPT Expanded Testing Option

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NIPT EXPANDED TESTING OPTION

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OBSTETRICIAN AND GYNECOLOGIST UTILIZATION OF THE NIPT EXPANDED TESTING OPTION

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Noninvasive prenatal testing (NIPT) enables the detection of common fetal aneuploidies such as trisomy 21, trisomy 18, trisomy 13, and sex chromosome abnormalities via analysis of cell-free fetal DNA circulating in maternal serum. Although the accuracy of NIPT for fetal aneuploidy is expected to be higher than that of currently available alternative maternal serum screening options, the implications of results are not straight forward. In October 2013, the option to screen for additional trisomies and select microdeletion syndromes, such as 22q11.2 deletion syndrome and 5 p- syndrome, became clinically available. Due to this rapidly evolving prenatal screening technology, clinicians must make a conscious effort to keep abreast of the current options; however, the complexity of the testing methods, oftentimes unclear clinical utility of results, and current lack of professional guidelines for its use renders this task challenging. To assess physicians' awareness of, utilization of, and attitudes toward the expanded NIPT option, 85 Houston, Texas area Obstetrician/Gynecologists (Ob/Gyns) were surveyed. While all respondents indicated they were aware of NIPT in its traditional form, 75% were aware of the expanded testing option. Of these respondents, 17% report having elected the expanded testing option when ordering NIPT. Thirty-nine percent of those surveyed indicated they would feel at least somewhat uncomfortable explaining the expanded testing option to a patient and, accordingly, 91% expressed that practitioners need more information regarding the screen. The responding Ob/Gyns indicated that this new screening option will be increasingly applicable to their future practice, with 28% indicating that they plan to incorporate the NIPT expanded testing option into their practice in the future. Based on these findings and the quickly evolving landscape of prenatal screening, education and reeducation of healthcare professionals is imperative to ensure responsible patient counseling, informed consent, and appropriate management following test results.

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BACKGROUND

Rapidly evolving prenatal screening technology necessitates that clinicians make a conscious effort to keep abreast of the evolving testing options. In October 2011, noninvasive prenatal testing (NIPT) became clinically available. NIPT analyzes cell-free fetal DNA circulating in maternal blood in order to identify fetuses with chromosomal abnormalities. NIPT in its traditional form screens for trisomy 21, trisomy 18, trisomy 13, and sex chromosome aneuploidies. NIPT technology was originally validated in singleton pregnancies at high risk for trisomy 21 due to advanced maternal age, abnormal serum screen, personal or family history of aneuploidy, and/or abnormal ultrasound.[1,2,3] Additional studies have demonstrated a high detection rate for not only trisomy 21 (98-100%), but also trisomy 18 (97-100%), trisomy 13 (79-92%), monosomy X (94%), and sex chromosome aneuploidies [47,XXX], [47,XXY], and [47,XYY] (96.2%) in high-risk pregnancies.[3,4,5,6] A recent study determined that NIPT has significantly lower false positive rates and higher positive predictive values for detection of trisomy 21 and trisomy 18, not only in high-risk pregnancies, but also in average-risk pregnancies when compared to alternative screening options.[7] NIPT has been widely accepted by professional societies as a clinically valid prenatal screen. However, guidelines and opinions implore healthcare professionals to employ good clinical judgment and ensure proper informed consent when offering NIPT to their patients.[8,9,10,11]

In October 2013, two years after the launch of NIPT, the option became available to screen for several additional conditions, including other select trisomies and specific syndromes caused by chromosomal microdeletions, such as 22q deletion syndrome (DiGeorge syndrome) and 5p- syndrome (Cri-du-chat syndrome). This expanded testing option utilizes the same technology as NIPT for aneuploidy, but targets more specific chromosome regions in the case of microdeletion syndromes. Whether the expanded option is offered as an opt-out or opt-in option is laboratory dependent.

As of April 2015, eighteen months after the expanded testing option became clinically available, there have been no large, prospective studies that address the ability of this technology to detect additional trisomies and select microdeletion syndromes in maternal serum. However, several proof of concept studies have demonstrated the technology's ability to detect subchromosomal abnormalities [12,13,14,15,16,17,18] In March 2015, a study by Wapner et al. attempted to better assess the ability of single nucleotide polymorphism (SNP) technology to detect microdeletion syndromes using a cohort of 358 maternal serum samples and 111 samples generated by PlasmArt, a technology that utilizes artificial DNA mixtures. Based on these assays, positive predictive values for the examined microdeletion syndromes range from 3.8% to 17.0%.[19] This study illustrates the difficulty in determining clinical performance of the expanded testing option for many of these rare conditions.

While this new expanded testing option is currently clinically available and easily accessible, the accuracy and precision of the testing as well as the correct interpretation of results remains uncertain. This gap between available information and informed interpretation presents physicians and other healthcare providers with the difficult decision of whether to offer this testing to patients and how to clinically utilize results. Moreover, position statements on the NIPT expanded testing option have not been issued by professional societies such as the American Congress of Obstetricians and Gynecologists (ACOG) or the National Society of Genetic Counselors (NSGC), perhaps due to the absence of informative data. In the meantime, the Society for Maternal-Fetal Medicine (SMFM) has advised its members to take caution with expanded NIPT due to the high false-positive rate, specifying that these tests ideally should be offered only after counseling by a genetic counselor.[20]

The methods by which physicians receive accurate information regarding the newly available expanded testing option of NIPT have yet to be determined; however, many physicians presumably learn about testing options directly from testing laboratories. The influence of pharmaceutical marketing on physician perception and utilization of prescription drugs has been well established, as educational presentations and promotional materials sponsored by competing laboratories are

effective strategies to increase uptake of products.[21,22] With regard to NIPT, marketing materials from laboratories advertise sensitivity as high as 100% and specificity as high as 99.9% for certain trisomies and microdeletion syndromes without offering further counseling information, such as the positive predictive value.[23] Although a study that specifically evaluates the effects of marketing for expanded NIPT has not been identified, the established laboratory marketing influence in other realms of healthcare suggests that these materials likely impact physician perception and use of expanded NIPT. It is concerning that physicians may be more inclined to order the expanded NIPT option as a result of laboratory marketing, possibly without having the opportunity to appreciate the complex nuances of expanded NIPT.

The apparent uncertainty surrounding the use and interpretation of the expanded testing option of NIPT is reminiscent of the initial reception of NIPT in its traditional form. During the 2011 interim between the clinical launch of NIPT and professional society endorsement, studies revealed that many clinicians reported a lack of comprehensive knowledge about NIPT, as well as a desire for clinical and regulatory guidance.[24] Allyse et al. urgently called for validation studies and regulation on NIPT in clinical practice in order for clinicians to comfortably and appropriately integrate the new technology.[25] Even after professional organizations released guidelines for clinical utilization of NIPT only in the context of high-risk patients, a study by Musci, et al. reported that 97% of Ob/Gyns offer NIPT to high-risk patients and 91% offer NIPT to average-risk patients.[26] This suggests that even in the absence of professional organization endorsement, the availability of testing allows for potential implementation. Healthcare professional education and reeducation to ensure responsible facilitation of prenatal care for patients is of paramount importance as we proceed in a world where technical ability outpaces technical knowledge. The objective of this study was to characterize current practices regarding the expanded NIPT option. This knowledge is necessary in order to determine what, if any, education is needed and desired by those implementing this new testing option in their practices.

METHODS

Eligibility included English-speaking physicians who attend Houston area Obstetrical departmental meetings from September 2014 – February 2015. In order to be included in this study, respondents must have indicated their primary practice setting to be General Obstetrics and Gynecology. Information was collected by an anonymous survey, which contained three sections: demographic information, assessment of awareness of the expanded NIPT option, and description of Ob/Gyns' attitudes towards the expanded NIPT option. The survey was distributed either via intra-office mail or in-person at the beginning of Ob/Gyn section meetings at 12 sites (University of Texas Health, Baylor College of Medicine, and Kelsey-Seybold Clinic).

Data collected from the surveys was analyzed for all applicable variables using the statistical analysis software program, STATA (v.13.0, College Station, TX). Descriptive charts and graphs were created using Microsoft Excel. A comparison between groups was performed using contingency tests (Chi-squared analysis or Fisher's exact test) or Kruskal-Wallis tests where appropriate. Statistical significance was assumed at a Type I error rate of 0.05.

RESULTS

A total of 118 surveys were distributed, 88 of which were given in-person, and 30 of which were distributed via intra-office mail. Ninety-two surveys were returned. Seven individuals did not meet the inclusion criteria of practicing primarily in general Obstetrics and Gynecology and were excluded from all analysis. Therefore, 111 surveys were distributed to eligible individuals, and the final sample size for analysis was 85, producing a response rate of 76.6%. The survey questions were selective in terms of which respondents were eligible to answer each, which resulted in varying numbers of total responses. Of the 85 general Ob/Gyns, 58% (n=49) were female and 58.3% were non-Hispanic white. The majority of these (8%, n=68) indicated that they practiced primarily in a private setting, while the remainder practiced in either an academic (17%, n=14) or a hospital-based setting (4%, n=3). See Table 1 for complete demographic data. The median time participants reported practicing in the indicated setting was 12 years (range = 0.13 – 40 years).

Table 1 Demographics of eligible respondents (n=85)

	n (%)
Gender	
Male	35 (41)
Female	49 (58)
No response	1 (1)
Race	
White (non-Hispanic)	49 (58)
Hispanic or Latino	10 (12)
Black or African American	8 (9)
Asian or Pacific Islander	12 (14)
Other	5 (6)
No response	1 (1)
Primary Practice Setting	
Private practice	68 (80)
Academic/University Medical Center	14 (16)
Hospital-based	3 (4)

NIPT knowledge and awareness

All participants indicated that they were aware of NIPT, with only 75% (n=64) reporting that they were aware of the expanded testing option of NIPT. The majority of those who have ordered NIPT reported that they were aware of the expanded testing option of NIPT (80%, n=55). This is compared to those who did not report having ordered NIPT, of whom only 64% (n=7) indicated that they were aware of the expanded testing option ($p = 0.046$). As expected, those who order NIPT are significantly more likely to be aware of the expanded testing option. The majority of participants (82%, n=69) indicated having ever ordered NIPT and an additional 5% (n=4) responded that they always refer to an MFM or genetic counselor for NIPT. The median number of NIPT orders per month was 4 (range = 1-30 orders). Just under half of the participants (49%, n=35) reported never seeing a positive result. Among the remaining participants, about half had seen only 1 positive result (51%, n=19) with nearly all (97%, n=36) having seen no more than 5 positive results. Increased risk for fetal aneuploidy was the most common indication for which Ob/Gyns report ordering NIPT (59%, n=50). Many physicians also reported ordering NIPT upon patient request (33%, n=28) and/or for all pregnant patients (15%, n=13). Although not all physicians had seen a positive NIPT result, all who indicated that they have ordered NIPT provided their first recommendation following a positive result. Of Ob/Gyns surveyed, 3% (n=2) selected only targeted ultrasound as their first recommendation. The question instructs participants to choose their first recommendation, yet five individuals selected multiple responses. All responses were included in analysis, yet some individuals may make more recommendations than they indicated here since they were instructed to select only one. Overall, Ob/Gyns report making appropriate recommendations following a positive NIPT result by offering diagnostic testing (32%, n=22) and/or referrals to specialists (71%, n=49). A summary of participants' clinical utilization of NIPT is included in Table 2.

Table 2 Ob/Gyn responses to questions about clinical utilization of NIPT

	n (%)
Before today, were you aware of the expanded testing option of NIPT? (n=85)	
Yes	64 (75)
No	12 (14)
I am unsure	9 (11)
If yes, how did you initially learn about the expanded testing option? Check all that apply. (n=64)	
Medical literature	31 (48)
Professional society/conference	15 (23)
Colleague	10 (16)
Marketing from labs that offer it	30 (47)
Educational lecture	12 (19)
Other	2 (3)
If you order NIPT, what lab do you order from? Check all that apply. (n=69)	
Sequenom/MaterniT21 Plus	34 (49)
Natera/Panorama	26 (38)
Verinata/Verifi/Illumina	20 (29)
Ariosa/Labcorp/Harmony	30 (44)
Other	7 (10)
I am unsure	4 (6)
It depends on:	10 (15)
No response	1 (2)
For which patients do you order/refer for NIPT? Check all that apply. (n=85)	
All patients at increased risk for fetal aneuploidy (maternal age, ultrasound finding, etc)	50 (59)
Only patients at increased risk for fetal aneuploidy who decline invasive testing	15 (18)
Patients who request it	28 (33)
All pregnant patients	13 (15)
Other	3 (4)
No response	12 (14)
If a patient had a positive NIPT result, what would be your first recommendation? Please select the best answer. (n=69)	
I would offer CVS/amniocentesis	22 (32)
I would recommend a targeted ultrasound	2 (3)
I would refer the patient to a specialist, such as an MFM or genetic counselor	49 (71)
Other	2 (3)

Expanded NIPT knowledge and awareness

Twelve individuals (14%) reported that they order the expanded testing option when ordering NIPT; therefore, 17% of respondents who have ordered NIPT have also ordered the expanded testing option. Only one participant reported having seen a positive expanded NIPT result. Table 3 includes a summary of the clinical utilization of expanded NIPT. When asked about the indications for which they order expanded NIPT, half (50%, n=6) of those who do order it reported that they order upon patient request. When asked what factors prompt Ob/Gyns who do order expanded NIPT to be selective about the patients for whom they order it, the most common response was insurance coverage/consideration of whether the patient can afford it (58%, n=7). No participants selected "running out of time to discuss testing options with the patient," "feeling that this testing is not in the best interest of the patient," or "lack of convenient access to the testing" as factors that influence their decision not to order expanded NIPT for certain patients. Although participants were instructed to select their first recommendation for a positive expanded NIPT result, one respondent selected two answers. All responses were included, but other participants may not have selected all that apply because they were instructed not to do so. Similarly, only participants who reported ordering expanded NIPT were instructed to indicate the timing of a referral for expanded NIPT. However, 17 participants who do not currently order expanded NIPT also responded to this question, and their responses were included. Respondents who order expanded NIPT tended to refer only after receiving a positive result (83%, n=10) rather than prior to ordering (17%, n=2). Finally, half (50.0%, n=6) of the respondents who do order expanded NIPT report that they tell patients that the testing is 99-100% accurate. No respondents selected accuracies lower than 90% or indicated that they do not tell patients this information.

Table 3 Ob/Gyn responses to questions about clinical utilization of expanded NIPT

	n (%)
For which patients do you order the expanded testing option when ordering NIPT? Check all that apply. (n=12)	
Family history of trisomy 16, trisomy 22, or a microdeletion syndrome	7 (58)
Ultrasound indicative of trisomy 16, trisomy 22, or a microdeletion syndrome	5 (42)
Those who request it	6 (50)
All pregnant patients who pursue NIPT	4 (33)
For those patients for whom you do **not** order the expanded testing option, what factors influence your decision not to order it? Check all that apply. (n=12)	
Lack of interest from my patient	3 (25)
My patient cannot afford it/it is not covered by their insurance	7 (58)
Not enough published data regarding accuracy	1 (8)
My professional society(ies) have not published guidelines	1 (8)
I order this testing for all of my patients	2 (17)
Other	1 (8)
No response	2 (17)
If a patient had a positive NIPT expanded testing result, what would be your first recommendation? Please select the best answer. (n=12)	
I would offer CVS/amniocentesis	3 (25)
I would refer the patient to a specialist, such as an MFM or genetic counselor	10 (83)
With regard to the NIPT expanded testing option, when do you refer patients to an MFM/genetic counselor? (n=29)	
Prior to ordering the test	13 (45)
Only when patients have a positive result	16 (55)
I am unsure	2 (7)
What do you tell your patients the accuracy is for the NIPT expanded testing option? (n=12)	
99-100%	6 (50)
90-98%	3 (25)
I am unsure	2 (17)
No response	1 (8)

Participants were also asked about their perceptions of expanded NIPT in terms of whether the expanded testing option is in an opt-in or opt-out format, whether they were aware of professional guidelines for this testing, and whether they plan to incorporate it into their practice in the future (Table 4). Participants who indicated that they were aware of the expanded testing option of NIPT

were asked whether they were aware of professional guidelines concerning expanded testing. Nearly one-third (31%, n=20) responded that they were aware of such guidelines. All participants who indicated that they have ordered/referred for NIPT were asked whether their laboratory of choice offers the expanded portion of NIPT in the opt-in or the opt-out format, and the majority (68%, n=50) indicated that they were unsure. This is in accordance with the fact that many labs offer certain conditions within the expanded NIPT option in the opt-in format and certain conditions in the opt-out format. Finally, half of participants (50%, n=42) reported that they were unsure of whether they plan to incorporate NIPT expanded testing into their practices in the future.

Table 4 Ob/Gyn responses to questions about perceptions of expanded NIPT

	n (%)
Are you aware of professional guidelines concerning the expanded testing option of NIPT? (n=64)	
Yes	20 (31)
No	19 (30)
I am unsure	18 (28)
No response	7 (11)
Does your laboratory of choice offer the expanded testing option in the opt-in or opt-out format? (n=73)	
Opt-in	19 (26)
Opt-out	2 (3)
I am unsure	50 (68)
No response	2 (3)
Do you plan on incorporating the NIPT expanded testing option into your practice in the future? (n=85)	
Yes	24 (28)
I currently order NIPT expanded testing	11 (13)
I am unsure	42 (50)
No	8 (9)

Attitudes toward expanded NIPT

Participants were asked to share their attitudes toward the expanded testing option of NIPT by indicating their comfort level explaining the testing to patients using a Likert scale ranging from very uncomfortable to very comfortable, and by selecting whether they consider expanded testing a screen or a diagnostic test (Table 5). Participants were divided into those who reported ordering the expanded testing option of NIPT and those who did not. Only 34% (n=25) of those who did not report ordering expanded NIPT indicated that they felt at least somewhat comfortable explaining the testing to patients, whereas the majority (83%, n=10) of those who reported ordering expanded NIPT indicated that they felt at least somewhat comfortable explaining it to patients ($p = 0.012$). Additionally, the majority of participants (68%, n=58) correctly identified that expanded NIPT is a screen rather than a diagnostic test. When divided into groups based on whether or not they order expanded NIPT, 14% (n-10) of those who reported that they do not order the expanded testing option incorrectly identified it as a diagnostic test, compared to 33% (n=4) of those who reported that they have ordered expanded NIPT who incorrectly identified it as a diagnostic test ($p = 0.004$). Therefore, individuals who have ordered expanded NIPT were significantly more likely to inappropriatelyperceive that it is a diagnostic test rather than a screen.

Table 5 Ob/Gyn responses to questions about comfort with expanded NIPT (n=85)

	n (%)
How comfortable are you with explaining the expanded testing option of NIPT to your patients?	
Very uncomfortable	10 (12)
Somewhat uncomfortable	23 (27)
Neutral	13 (15)
Somewhat comfortable	26 (30)
Very comfortable	9 (11)
No response	4 (5)
Which do you consider the NIPT expanded testing option to be?	
A screen	58 (68)
A diagnostic test	14 (17)
Neither	1 (1)
I am unsure	10 (12)
No response	2 (2)

Participants were also asked to react to a series of statements by indicating whether they agree, disagree, or were unsure (Table 6). In order to further characterize the attitudes of Ob/Gyns who were previously aware of the expanded testing option of NIPT, the responses were compared to those of individuals who were not previously aware of the expanded testing option of NIPT. Of those who were previously aware of the expanded testing option of NIPT, about one-fifth (19%, n=12) agreed that it provides little added benefit. This was in comparison to those who reported that they were not aware of expanded NIPT, none of whom agreed that expanded NIPT provides little added benefit ($p = 0.048$). Therefore, those who were previously aware of expanded NIPT are more likely to be wary of its benefit. Additionally, of respondents who were aware of expanded NIPT, about half (49%, n=31) disagreed with a statement that the testing will replace invasive testing, whereas 18% (n=2) of those who were not aware of expanded NIPT disagreed with this statement ($p = 0.005$). Therefore, those who were previously aware of expanded NIPT were significantly more likely to perceive that expanded NIPT is not a replacement for diagnostic invasive prenatal testing. Despite

comfort level and utilization, an overwhelming majority of participants (91%, n=77) agreed that practitioners need more information/education about expanded NIPT. This desire for more information is consistent across all groups of physicians, including those who reported that they have ordered expanded NIPT and those who have not. Finally, 40% (n=25) of those who were aware of expanded NIPT agreed that it will become standard of care, whereas over half (56%, n=5) of those who were not previously aware of expanded NIPT agreed with this statement ($p = 0.048$). Thus, those who had previously learned of the expanded testing option of NIPT are less likely to think that it will become standard of care.

Furthermore, comfort level with explaining expanded NIPT was a significant predictor of respondents' attitudes toward expanded NIPT. Of those who were at least somewhat comfortable with explaining the expanded testing option of NIPT to patients, 37% (n=13) agree that expanded NIPT will replace invasive procedures. This is compared to just over one quarter (22%, n=7) of those who reported being either somewhat uncomfortable or very uncomfortable with explaining the testing to patients and agreed that expanded NIPT will replace invasive testing ($p = 0.029$). Thus, those who are more comfortable explaining expanded NIPT to patients are more likely to report that they view expanded NIPT as a replacement for invasive procedures. Similarly, 41% (n=14) of those who are either somewhat comfortable or very comfortable explaining expanded NIPT to patients agreed that clinical utility and validity have been established for NIPT expanded testing. In comparison, only 7% (n=2) of those who are somewhat uncomfortable or very uncomfortable explaining expanded NIPT agree that clinical utility and validity have been established for expanded NIPT ($p = 0.026$). As expected, those who report more comfort explaining expanded NIPT are more likely to perceive that the testing has been validated.

Finally, the source from which Ob/Gyns learn about the expanded testing option of NIPT is suggestive of whether they anticipate incorporating this testing option into their practice in the future. Although several participants selected multiple sources of information for learning about expanded

NIPT, those who selected a single source of academic nature, including medical literature, a professional society/conference, a colleague, or an educational lecture, were compared to those whose sole source of information was marketing from labs. Of those who selected a single source of information about expanded NIPT, the majority (71%, n=10) of those who had learned from only laboratory marketing were unsure of whether they would incorporate it into their practice in the future. In comparison, only 19% (n=5) of those who learned from only academic sources were unsure ($p = 0.005$). Thus, those who gained information from academic sources were more likely to report that they had an idea of whether they would incorporate expanded NIPT into their future practices.

Table 6 Ob/Gyn attitudes toward expanded NIPT (n=85)

	Agree (%)	Unsure (%)	Disagree (%)	No response (%)
The NIPT expanded testing option provides little added benefit	12 (14)	30 (35)	41 (48)	2 (3)
The conditions included in the expanded testing option were chosen arbitrarily	5 (6)	34 (40)	43 (51)	3 (3)
The NIPT expanded testing option will affect my practice	29 (34)	28 (33)	25 (29)	3 (4)
The NIPT expanded testing option will replace invasive procedures	25 (30)	23 (27)	35 (41)	2 (2)
Practitioners need more information/education about the test/technology	77 (91)	3 (3)	2 (2)	3 (4)
Clinical utility and validity have been established for NIPT expanded testing	19 (22)	47 (55)	15 (18)	4 (5)
NIPT expanded testing is going to simplify prenatal diagnosis	32 (38)	33 (39)	15 (17)	5 (6)
Prenatal diagnosis of microdeletion syndromes reduces lifetime medical costs	29 (34)	41 (48)	12 (14)	3 (4)
The technology used in the NIPT expanded testing option is applicable to any microdeletions/duplications in the genome	11 (13)	48 (56)	22 (26)	4 (5)
The NIPT expanded testing option will eventually be standard of care	30 (35)	45 (53)	6 (7)	4 (5)

DISCUSSION

To date, this is the first known study to examine Ob/Gyns' awareness of, clinical utilization of, and attitudes toward the novel expanded NIPT option, based on a systematic search of medical literature using the search engine PubMed and the search terms "NIPT," "microdeletion," "cell free," and/or "utilization" in April 2015. This study identified that the majority of Ob/Gyns surveyed were aware of the expanded NIPT option, yet few actually have utilized it in clinical practice. Physicians surveyed have expressed a strong desire for more information regarding the expanded NIPT option. Given the lack of published large validation studies and professional guidelines, ethical controversy and apprehension surround the widespread utilization of the expanded testing option.[27] Proof of concept studies using no more than 16 affected pregnancy plasma samples to demonstrate the technical ability to detect subchromosomal abnormalities in maternal serum, and larger studies using artificial DNA mixtures have attempted to characterize the validity of expanded NIPT.[1,19,28] However, the low incidence of each condition renders the positive predictive value extremely low, despite projected high sensitivity and specificity rates.

This study demonstrated that almost half (46.9%) of those who reported awareness of the expanded NIPT option had heard about it from marketing from labs. While education from labs can benefit ordering physicians and encourage them to learn more about prenatal testing options, currently available marketing materials from labs may not provide a full picture of the implications of this screen. For example, laboratory pamphlets cite an up to 99.5% sensitivity and >99% specificity for 22q11 deletion syndrome, but they do not include information explaining that by factoring in a population prevalence of 1/2,000, the positive predictive value is low (less than 5%).[23] This study revealed that although many Ob/Gyns are receiving information about expanded NIPT from labs, participants were more likely to plan to incorporate expanded NIPT into their practices in the future if they had learned about it from an academic source. The survey did not ask what sources physicians prefer to receive information from, but these results would support the hypothesis that physicians

prefer to learn about the expanded testing option from academic sources, such as medical literature, professional societies, colleagues, or educational lectures.

Although no professional guidelines specific to expanded NIPT have been published, guidelines for similar screening should be relied upon for direction when new testing becomes available. A joint statement by the American College of Medical Genetics (ACMG), the Perinatal Quality Foundation (PQF), ACOG, NSGC, and SMFM on expanded carrier screening cautions that if residual risk information has not been determined, lab reports should clearly communicate the limitations of interpretation of screening.[29] This guideline calls upon laboratories and healthcare professionals to communicate the results of carrier screening to patients in a realistic manner. It is reasonable to think that discussion surrounding expanded NIPT should follow suit with the same urgency. Because communication between physicians and patients is crucial, this study investigated Ob/Gyns' understanding of the expanded NIPT option. When asked about the accuracy of the expanded testing option that they quote to patients, the majority of participants who have ordered expanded NIPT quote 90% or greater. The word "accuracy" was used in this question in order to prevent confusion between mores specific terms such as sensitivity or positive predictive value. Although the term "accuracy" was intentionally ambiguous in order to capture a number that Ob/Gyns may realistically discussed with patients, this question is limited to the participants' interpretations of the term "accuracy." This study provided further insight into Ob/Gyns' confidence in expanded NIPT results, revealing that seventeen percent of respondents incorrectly indicated that expanded NIPT is a diagnostic test. This finding parallels a finding from Benn, et al., which reported that nearly half of Ob/Gyns view traditional NIPT as a full substitute for invasive testing.[30]

However, the majority of physicians report making proper recommendations following a positive result, including offering invasive, diagnostic testing and/or a referral to a specialist such as an MFM or genetic counselor. Even if patients eventually receive the recommended care, it is preferable that patients receive accurate and appropriate information prior to testing for purposes of

both informed consent and prevention of psychological harm. This concept of knowledgeable pre-test counseling is particularly pertinent to expanded NIPT due to the complex nature of the technology and the often unfamiliar information it can produce. The model in which comprehensive information is provided only following a positive result is consistent with a trend in which technological ability to perform tests surpasses understanding of its validity, utility, and best practices. For this reason, the education of healthcare professionals who provide information about expanded NIPT to patients is crucial. Practitioners must consider whether the ability to prenatally screen for subchromosomal abnormalities, or other genetic conditions, is sufficient basis for performing the testing.

A strength of this study is that during the study period, no major publications regarding the clinical utility or validity of expanded NIPT were published, nor were professional guidelines published during the study period. No new major laboratories began offering expanded NIPT, and no new types of genetic conditions were added to testing panels during the study period. Thus, the information and testing options available to participants was consistent. Furthermore, responses from particular respondents indicated consistent representation of knowledge and awareness. Few individuals skipped questions to which they were instructed to respond. This suggests that the responses gathered from the survey accurately represent the perceptions and attitudes of participants.

Limitations to this study include the fact that since some questions which asked for the best response received multiple responses, some questions may not have been interpreted by participants as intended. In addition, some participants responded to questions in sections that they should not have completed due to selection. When possible, all potentially relevant responses were included in analysis and those obviously in discordance with the intent of the question were excluded. Another limitation to this study is the number of participants. Although the sample size did exceed the expected number, surveying a larger number of Ob/Gyns would provide further understanding of clinical utilization of the expanded NIPT option. Similarly, this study population was limited to Ob/Gyns who attended Obstetrical departmental meetings at large, urban hospitals and clinics in

Houston, Texas. The majority (80%) of this study population reported practicing primarily in a private setting. Therefore, it may be difficult to generalize these findings to Ob/Gyns from other geographical areas and diverse practice settings. Despite this limitation, the physicians included in this study who attend meetings and take the initiative to fill out a survey may be more likely to be familiar with the expanded testing option and more motivated to learn more about it. Therefore, this limitation may suggest that the results of this study underestimate the need and desire for physician education regarding expanded NIPT.

Future directions for study may include investigating the way that healthcare professionals present information regarding the expanded NIPT option to patients and whether the nuances of "accuracy" are discussed in detail, as the results of this study call into question the language used in a clinical setting. Characterizing how phsyicians discuss the reliability of a screen in a pre-test counseling setting would help to determine how information can be best communicated to healthcare professionals when providing education. Additionally, this study reveals that while less than half of Ob/Gyns report being at least somewhat comfortable explaining expanded NIPT to patients, they are aware of the gaps in their knowledge about this prenatal screen and unequivocally desire more information about it. Thus, future investigation should include assessment of how physicians desire to learn this information. Since the participants were accessed through Obstetrical departmental meetings, educational presentations by knowledgeable colleagues at these meetings may be a good starting point. What remains unknown is how best to access those providers not attending section meetings who are potentially being informed by laboratory representatives only. Ob/Gyns are ordering the expanded NIPT option and will presumably continue to do so, and the development of further professional guidelines for utilizing expanded NIPT is increasingly vital. Healthcare professionals have a responsibility to educate each other regarding the expanded NIPT option and other prenatal screens in order to ensure that patients receive optimal care.

APPENDIX

Appendix 1. Study Survey

Please answer the following questions based on your current practice.

PART I: Demographics

1. What is your gender?
   - ☐ Male
   - ☐ Female

2. What is your race?
   - ☐ White (non-Hispanic)
   - ☐ Hispanic or Latino
   - ☐ Black or African American
   - ☐ Asian or Pacific Islander
   - ☐ Other: _____

3. Which of the following best describes your area of practice? Please select one.
   - ☐ General Obstetrics and Gynecology
   - ☐ Gynecology only
   - ☐ Obstetrics only
   - ☐ Gynecologic Oncology
   - ☐ Maternal Fetal Medicine
   - ☐ Reproductive Endocrinology
   - ☐ Urogynecology
   - ☐ Other: _____

4. What is your primary practice setting? Please select one.
   - ☐ Private Practice
   - ☐ Academic/University Medical Center
   - ☐ Hospital-based
   - ☐ Other: _____

5. How long have you been practicing in this setting? _____ years

6. Before today, were you aware of Non-invasive Prenatal Testing (NIPT)?
   - ☐ Yes
   - ☐ No
   - ☐ I am unsure

7. Before today, were you aware of the expanded testing option of NIPT?
   - ☐ Yes
   - ☐ No
   - ☐ I am unsure

8. If yes, how did you initially learn about of the expanded testing option?
   - ☐ Medical literature
   - ☐ Professional society/conference
   - ☐ Colleague
   - ☐ Marketing from labs that offer it
   - ☐ Educational lecture
   - ☐ Other: _____

PART II: NIPT

Non-invasive prenatal testing (NIPT) is a screening option made clinically available in October 2011 that tests maternal serum for fetal aneuploidy. It can detect Down syndrome, trisomy 18, trisomy 13, and sex chromosome aneuploidy.

The expanded testing option of NIPT tests for the above aneuploidies and an additional set of microdeletion syndromes and in some cases additional trisomies. These conditions include 22q deletion syndrome (DiGeorge syndrome), 5p- syndrome (Cri-du-chat syndrome), Prader-Willi syndrome, Angelman syndrome,1p36 deletion syndrome, Trisomy 16, and Trisomy 22.

9. Have you ever ordered NIPT?
   - ☐ Yes – continue to question 10
   - ☐ No – skip to question 24
   - ☐ I always refer to an MFM/genetic counselor for NIPT – skip to question 12
   - ☐ I am unsure – skip to question 24

10. Approximately how many times do you order NIPT per month? _____ per month

11. If you order NIPT, what lab do you order from? Check all that apply.
   - ☐ Sequenom/MaterniT21 Plus
   - ☐ Natera/Panorama
   - ☐ Other: _____
   - ☐ It depends on _____
   - ☐ Verinata/Verifi/Illumina
   - ☐ Ariosa/Labcorp/Harmony
   - ☐ I am unsure

12. For which patients do you order/refer for NIPT? Check all that apply.
   - ☐ **All** patients at increased risk for fetal aneuploidy (maternal age, ultrasound finding, blood test, etc.)
   - ☐ **Only** patients at an increased risk for fetal aneuploidy who are unsure of or decline invasive testing
   - ☐ Patients who request it
   - ☐ All pregnant patients
   - ☐ I do not order/refer for NIPT
   - ☐ Other: _____

13. How many total positive NIPT results have you seen? _____ positive results

14. If a patient were to have a positive NIPT result, what would be your first recommendation? Please select the best answer.
   - ☐ I would offer CVS/amniocentesis
   - ☐ I would recommend a targeted ultrasound
   - ☐ I would refer the patient to a specialist, such as an MFM or genetic counselor
   - ☐ Other: _____
   - ☐ I am unsure

15. Are you aware of professional guidelines concerning the expanded testing option of NIPT?
   - ☐ Yes
   - ☐ No
   - ☐ I am unsure

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16. To your knowledge, does your laboratory of choice offer the expanded testing option in the opt-in or opt-out format?

☐ Opt-in ☐ Opt-out ☐ I am unsure

17. Do you order the expanded testing option when ordering NIPT?

☐ Yes – continue to question 18
☐ No – skip to question 24
☐ Depends on genetic counselor or MFM – skip to question 21
☐ I am unsure – skip to question 24

18. For which patients do you order the expanded testing option when ordering NIPT? Check all that apply.

☐ Family history of trisomy 16, trisomy 22, or a microdeletion syndrome
☐ Ultrasound indicative of trisomy 16, trisomy 22, or a microdeletion syndrome
☐ Those who request it
☐ Those who decline invasive prenatal diagnosis
☐ All pregnant patients who pursue NIPT
☐ Other: _____

19. For those patients for whom you do **not** order the expanded testing option of NIPT, what factors influence your decision not to order it? Check all that apply.

☐ Lack of interest from my patient
☐ My patient cannot afford it/it is not covered by their insurance
☐ I run out of time discussing options with my patient
☐ I feel it is not in my patient's best interest
☐ Not enough published data regarding accuracy
☐ My colleagues and/or institution do(es) not use it
☐ My professional society(ies) have not published guidelines
☐ No convenient access (ie local blood draw sites)
☐ I order this testing for all of my patients
☐ Other: _____

20. What do you tell your patients the accuracy is for the NIPT expanded testing option?

☐ 99-100% ☐ 90-98% ☐ 80-89%
☐ 70-79% ☐ <70% ☐ I am unsure
☐ I do not tell patients this information
☐ It depends on: _____

21. How many total positive NIPT expanded testing option results have you seen? _____ positive results

22. If a patient had a positive NIPT expanded testing result, what would be your first recommendation? Please select the best answer.

☐ I would offer CVS/amniocentesis
☐ I would perform a targeted ultrasound
☐ I would refer the patient to a specialist, such as an MFM or genetic counselor
☐ I am unsure

23. With regard to the NIPT expanded testing option, when do you refer patients to an MFM/genetic counselor?

- ☐ Prior to ordering the test
- ☐ Only when patients have a positive result
- ☐ I do not refer to genetic counselors for the NIPT expanded testing option
- ☐ I am unsure

24. Do you plan on incorporating the NIPT expanded testing option into your practice in the future?

- ☐ Yes
- ☐ I currently order NIPT expanded testing.
- ☐ I am unsure
- ☐ No (please comment): _____

PART III: Attitudes

25. How comfortable are you with explaining the expanded testing option of NIPT to your patients?

1	2	3	4	5
Very Uncomfortable	Somewhat Uncomfortable	Neutral	Somewhat Comfortable	Very Comfortable

26. Which do you consider the NIPT expanded testing option to be?

- ☐ A screen
- ☐ A diagnostic test
- ☐ Neither
- ☐ I am unsure

27. Check whether you agree or disagree with these statements:

	Agree	Disagree	Unsure
The NIPT expanded testing option provides little added benefit			
The conditions included in the expanded testing option were chosen arbitrarily			
The NIPT expanded testing option will affect my practice			
The NIPT expanded testing option will replace invasive procedures			
Practitioners need more information/education about the test/technology			
Clinical utility and validity have been established for NIPT expanded testing			
NIPT expanded testing is going to simplify prenatal diagnosis			
Prenatal diagnosis of microdeletion syndromes reduces lifetime medical costs			
The technology used in the NIPT expanded testing option is applicable to any microdeletions/duplications in the genome			
The NIPT expanded testing option will eventually be standard of care			

28. If you could add any genetic condition(s) caused by a microdeletion/duplication to the NIPT expanded testing option, what would you add? Please list as many as you would like to add.

_____

_____

Please provide any comments regarding this survey or the NIPT expanded testing option:

_____

_____

Thank you for your time! This completes your participation in this study. Please return this questionnaire to the blue folder. If you left the meeting without returning this questionnaire and would like your responses to be included in this study, please fax the questionnaire to: 713-512-7100.

BIBLIOGRAPHY

1. Chen S, Lau TK, Zhang C, Xu C, Xu Z, Hu P, Xu J, Huang H, Pan L, Jiang F, Chen F, Pan X, Xie W, Liu P, Li X, Zhang L, Li S, Li Y, Xu X, Wang W, Wang J, Jiang H, Zhang X. A method for noninvasive detection of fetal large deletions/duplications by low coverage massively parallel sequencing. Prenat Diagn. 2013 Jun;33(6):584–590.
2. Palomaki GE, Kloza EM, Lambert-Messerlian GM, Haddow JE, Neveux LM, Ehrich M, van den Boom D, Bombard AT, Deciu C, Grody WW, Nelson SF, Canick JA. DNA sequencing of maternal plasma to detect Down syndrome: an international clinical validation study. Genet Med. 2011 Nov;13(11):913–920.
3. Palomaki GE, Deciu C, Kloza EM, Lambert-Messerlian GM, Haddow JE, Neveux LM, Ehrich M, van den Boom D, Bombard AT, Grody WW, Nelson SF, Canick JA. DNA sequencing of maternal plasma reliably identifies trisomy 18 and trisomy 13 as well as Down syndrome: an international collaborative study. Genet Med. 2012 Mar;14(3):296–305.
4. Bianchi DW, Platt LD, Goldberg JD, Abuhamad AZ, Sehnert AJ, Rava RP. Genome-wide fetal aneuploidy detection by maternal plasma DNA sequencing. Am J Obstet Gynecol. 2012 May;119(5):890–901.
5. Norton ME, Brar H, Weiss J, Karimi A, Laurent LC, Caughery AB, Rodriguez MH, Williams J 3rd, Mitchell ME, Adair DC, Lee H, Jacobsson B, Tomlinson MW, Oepkes D, Hollemon D, Sparks AB, Oliphant A, Song K. Non-Invasive Chromosomal Evaluation (NICE) study: results of a multicenter prospective cohort study for detection of fetal trisomy 21 and trisomy 18. Am J Obstet Gynecol. 2012 Aug;207(2):137.e1–8.
6. Mazloom AR, Džakula Ž, Oeth P, Wang H, Jensen T, Tynan J, McCullough R, Saldivar JS, Ehrich M, van den Boom D, Bombard AT, Maeder M, McLennan G, Meschino W, Palomaki GE, Canick JA, Deciu C. Noninvasive prenatal detection of sex chromosomal aneuploidies

by sequencing circulating cell-free DNA from maternal plasma. Prenat Diagn. 2013 Jun;33(6):591-7.

7. Bianchi DW, Parker RL, Wentworth J, Madankumar R, Saffer C, Das A, Craig J, Chudova DI, Devers PL, Jones KW, Oliver K, Rava RP, Sehnert AJ. DNA sequencing versus standard prenatal aneuploidy screening. N Engl J Med. 2014 Feb 27;370(9):799-808.
8. American College of Obstetricians and Gynecologists. Practice Bulletin No. 545: noninvasive prenatal testing for fetal aneuploidy. Obstet Gynecol. 2012 Dec;120(6):1532-4.
9. Wilson KL, Czerwinski JL, Hoskovec JM, Noblin SJ, Sullivan CM, Harbison A, Campion MW, Devary K, Devers P, Singletary CN. NSGC Practice Guideline: Prenatal Screening and Diagnostic Testing Options for Chromosome Aneuploidy. J Genet Couns. 2013 Feb;22:4-15.
10. Benn P, Borell A, Chiu R, Cuckle H, Dugoff L, Faas B, Gross S, Johnson J, Maymon R, Norton M, Odibo A, Schielen P, Spencer K, Huang T, Wright D, Yaron Y. Position statement from the aneuploidy screening committee on behalf of the board of the international society for prenatal diagnosis. Prenat Diagn. 2013 Jul;33(7):622-9.
11. Bianchi DW, Wilkins-Haug L. Integration of noninvasive DNA testing for aneuploidy into prenatal care: what has happened since the rubber met the road? Clin Chem. 2014 Jan;60(1):78-87.
12. Jensen TJ, Dzakula Z, Deciu C, van den Boom D, Ehrich M. Detection of microdeletion 22q11.2 in a fetus by next-generation sequencing of maternal plasma. Clin Chem. 2012 Jul;58(7):1148–51.
13. Peters D, Chu T, Yatsenko, SA, Hendrix N, Hogge WA, Surti U, Bunce K, Dunkel M, Shaw P, Rajkovic A. Noninvasive Prenatal Diagnosis of a Fetal Microdeletion Syndrome. N Engl J Med. 2011 Nov 10;365(19):1847-8.
14. Srinivasan A, Bianchi DW, Hui H, Sehnert AJ, Rava RP. Noninvasive detection of fetal subchromosome abnormalities via deep sequencing of maternal plasma. Am J Hum Genet. 2013 Feb 7;92(2):167-76.

15. Yu S, Jiang P, Choy K, Chan K, Won H, Leung W, Lau E, Tang M, Leung T, Lo Y, Chiu RW. Noninvasive prenatal molecular karyotyping from maternal plasma. PLoS One. 2013 Apr 17;8(4):e60968.
16. Jia Y, Zhao H, Donghong S, Peng W, Xie L, Wang W, Jiang F, Zhang H, Wang X. Genetic effects of a 13q31.1 microdeletion detected by noninvasive prenatal testing (NIPT). Int J Clin Exp Pathol. 2014 Sep 15;7(10):7003-11.
17. Rampášek L, Arbabi A, Brudno M. Probabilitstic method for detecting copy number variation in a fetal genome using maternal plasma sequencing. Bioinformatics. 2014 Jun 15;30(12):i212-8.
18. Zhao C, Tynan J, Ehrich M, Hannum G, McCullough R, Saldivar JS, Oeth P, van den Boom D, Deciu C. Detection of fetal subchromosomal abnormalities by sequencing circulating cell-free DNA from maternal plasma. Clin Chem. 2015 Feb 20. pii:clinchem.2014.233312.
19. Wapner RJ, Babiarz JE, Levy B, Stosic M, Zimmerman B, Sigurjonsson S, Wayham N, Ryan A, Banjevic M, Lacroute P, Hu J, Hall MP, Demko Z, Siddiqui A, Rabinowitz M, Gross SJ, Hill M, Benn P. Expanding the scope of noninvasive prenatal testing: detection of fetal microdeletion syndromes. Am J Obstet Gynecol. 2015 Mar;212(3)332.e1-9.
20. SMFM.org. [Internet] Maternal serum cell-free DNA screening in low risk women. [cited 2015 March 24]. Available from: https://www.smfm.org/publications/157-smfm-statement-maternal-serum-cell-free-dna-screening-in-low-risk-women.
21. Fugh-Berman AJ, Scialli AR, Bell AM. Why lunch matters: assessing physicians' perceptions about industry relationships. J Contin Educ Health Prof. 2010 Summer;30(3)197-204.
22. Austad KE, Avorn J, Franklin JM, Campbell EG, Kesselheim AS. Association of marketing interactions with medical trainees' knowledge about evidence-based prescribing: results from a national survey. JAMA Intern Med. 2014 Aug;174(8):1283-90.

23. Panoramatest.com. [Internet]. Natera. [cited 2015 March 26]. Available from: http://www.panoramatest.com/healthcare-provider.
24. Sayres LC, Allyse M, Norton ME, Cho MK. Cell-free fetal DNA testing: a pilot study of obstetric healthcare provider attitudes toward clinical implementation. Prenat Diagn. 2011 Nov;31(11):1070-6.
25. Allyse M, Sayres LC, King JS, Norton ME, Cho MK. Cell-free fetal DNA testing for fetal aneuploidy and beyond: clinical integration challenges in the US context. Hum Reprod. 2012 Aug 3;27(11):3123–31.
26. Musci TJ, Fairbrother G, Batey A, Bruursema J, Struble C, Song K. Non-invasive prenatal testing with cell-free DNA: US physician attitudes toward implementation in clinical practice. Prenat Diagn. 2013 May;33(5):424-8.
27. Vora NL, O'Brien BM. Noninvasive prenatal testing for microdeletion syndromes and expanded trisomies: proceed with caution. Obstet Gynecol. 2014 May;123(5):1097-9.
28. Hall MP. Panorama non-invasive prenatal screening for microdeletion syndromes. Nat MD White Paper. 2014 April;V5:1-5.
29. Edwards JG, Feldman G, Goldberg J, Gregg AR, Norton ME, Rose NC, Schneider A, Stoll K, Wapner R, Watson MS. Expanded carrier screening in reproductive medicine – points to consider. Obstet Gynecol. 2015 March;125(3):653-62.
30. Benn P, Chapman AR, Erickson K, DeFrancesco MS, Wilkins-Haug L, Egan JFX, Schulkin J. Obstetricians and gynecologists' practice and opinions of expanded carrier testing and noninvasive prenatal testing. Prenat Diagn. 2014 Feb;34(2)145-52.

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