

Obstetrician and Gynecologist Utilization of the Noninvasive Prenatal Testing Expanded Option

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Abstract

Objective 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. In October 2013, the option to screen for additional trisomies and select microdeletion syndromes became clinically available. The complex testing methods, oftentimes unclear clinical utility of results, and lack of professional guidelines renders it challenging for clinicians to keep abreast of evolving prenatal screening options. We undertook a survey to assess physicians' awareness of, utilization of, and attitudes toward the expanded NIPT option.

Study Design Obstetricians attending hospital service meetings in the Houston Texas Medical Center completed an anonymous survey regarding the utilization patterns of expanded NIPT.

Results Overall, 85 obstetricians were surveyed. While all respondents indicated awareness of NIPT in its traditional form, 75% (64/85) were aware of the expanded testing option, and 14% (12/85) reported having ordered the expanded NIPT option. A total of 91% (77/85) expressed that practitioners need more information regarding the screening.

Conclusion Based on these findings and the fluid landscape of prenatal screening, education, and reeducation of health care professionals is imperative to ensure responsible patient counseling, informed consent, and appropriate posttest management.

Keywords

- ▶ noninvasive prenatal testing
- ▶ microdeletion
- ▶ prenatal screen

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Background

Since it first became clinically available in October 2011, noninvasive prenatal testing (NIPT) has been well studied. It has been shown to have high detection rates as well as significantly lower false-positive rates, and higher positive predictive values for detection of trisomy 21 and trisomy 18 when compared with alternative screening options.^{1–7} NIPT has been widely accepted by professional societies as a clinically valid prenatal screen when utilized with good clinical judgment and proper informed consent.^{8–11}

In October 2013, the option 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) became available. As of June 2015, there have been no large, prospective studies that address the ability of this technology to detect these additional trisomies and microdeletion syndromes in maternal serum. Several proof of concept studies have demonstrated the technology's ability to detect subchromosomal abnormalities, yet the most comprehensive study to date estimates positive predictive values for the examined microdeletion syndromes ranging from 3.8 to 17.0%.^{12–19} 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 remain uncertain. This gap between available information and informed interpretation presents physicians and other health care providers with the difficult decision of whether to offer this testing to patients and how to clinically utilize results with little published guidance from professional societies.^{20,21} 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 objective of this study was to characterize current practices among obstetricians regarding the expanded NIPT option to determine whether any education is needed or desired by those implementing this new testing opportunity in their practices.

Methods

Eligibility included physicians whose obstetrical departments were affiliated with the genetic counseling program at the University of Texas Graduate School of Biomedical Science at Houston. Physicians who attended Houston area obstetrical departmental meetings were surveyed from September 2014 to February 2015. To be included in this study, respondents must have indicated their primary practice setting was as a specialist in obstetrics and gynecology. All participants were completely trained and beyond their residency. Information was collected by an anonymous survey, which contained three sections: demographic information, assessment of awareness of the expanded NIPT option, and description of obstetrician's attitudes toward the expanded NIPT option. The survey was distributed at 12 clinic sites located at 4 institutions (Memorial Hermann, 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 (Microsoft Corp., Redmond, WA). A comparison between groups was performed using contingency tests (Chi-square analysis or Fisher exact test) or Kruskal–Wallis tests where appropriate. Statistical significance was assumed if $p < 0.05$.

Results

A total of 118 surveys were distributed, of which 78% (92/118) were returned. Seven individuals did not meet the inclusion criteria of practicing primarily in Obstetrics and Gynecology and were excluded from all analyses. Therefore, the final sample size for analysis was 85. The survey queries were selective in terms of which respondents were eligible to answer each question, which resulted in varying numbers of total responses. See ►Table 1 for complete demographic data. The majority 80% (68/85) reported practicing in a private setting. The median time participants reported practicing in the indicated setting was 12 years (range, 0.13–40 years).

NIPT and Expanded NIPT Knowledge and Awareness

A summary of participants' clinical utilization of NIPT is included in ►Table 2. All participants indicated that they were aware of NIPT, with 75% (64/85) reporting that they were aware of the expanded testing option of NIPT. The majority of those who have ordered NIPT reported that

Table 1 Demographics of eligible respondents ($n = 85$)

Demographics	<i>n</i> (%)
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)

Table 2 Obstetrician responses to questions about clinical utilization of NIPT

Responses	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 learn about expanded testing? Check all that apply. (n = 64)	
Medical literature	31 (48)
Professional society/conference	15 (23)
Colleague	10 (16)
Marketing from laboratories that offer it	30 (47)
Educational lecture	12 (19)
Other	2 (3)
If you order NIPT, what laboratory 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 (AMA, 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)

Abbreviations: AMA, advanced maternal age; CVS, chorionic villus sampling; MFM, maternal–fetal medicine; NIPT, noninvasive prenatal testing.

they were aware of the expanded testing option of NIPT (80%, 55/69). This is compared with those who did not report having ordered NIPT, of whom only 64% (7/11) indicated that they were aware of the expanded testing option ($p = 0.05$). The majority of participants (82%, 69/85) indicated having ordered NIPT and an additional 5% (4/85) responded that they always refer to a maternal–fetal medicine subspecialist (MFM) or genetic counselor for NIPT. The median number of NIPT orders per month was 4 (range, 1–30). Just under half of the participants (49%, 35/71) reported never seeing a positive result. Among the remaining participants, about half (51%, 19/37) had seen only one

positive result with nearly all (97%, 36/37) having seen not more than five positive results. Overall, obstetricians report making appropriate recommendations following a positive NIPT result by offering diagnostic testing (32%, 22/69) and/or referrals to subspecialists (71%, 49/69).

A total of 12 individuals (17%, 12/69) reported that they order the expanded testing option when ordering NIPT. Only one participant reported having seen a positive expanded NIPT result. ▶ **Table 3** contains a summary of the clinical utilization of expanded NIPT. When asked what factors are used when determining when to offer expanded NIPT, the most common response was insurance coverage/consideration of whether

Table 3 Obstetrician responses to questions about clinical utilization of expanded NIPT

Responses	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)	
Before 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)

Abbreviations: CVS, chorionic villus sampling; MFM, maternal–fetal medicine; NIPT, noninvasive prenatal testing.

the patient can afford it (58%, 7/12). Respondents who order expanded NIPT tended to refer to a subspecialist, such as an MFM or genetic counselor, only after receiving a positive result (83%, 10/12) rather than before ordering (17%, 2/12). Finally, half (50%, 6/12) of the respondents who do order expanded NIPT report that they tell patients that the testing is 99 to 100% accurate. No respondents selected accuracies lower than 90% or indicated that they do not tell patients this information. Participants were also asked about their perceptions of expanded NIPT (► **Table 4**). Although, no professional guidelines concerning the expanded NIPT option had yet been published, 31% (20/64) indicated that they were aware of professional guidelines for the expanded NIPT option. Over two-thirds (68%, 58/85) of respondents indicated that they were unsure whether their laboratory of choice offers expanded NIPT in an opt-in or opt-out format. Finally, 41% (35/85) reported that they either currently order expanded NIPT or plan to incorporate expanded NIPT into their practices in the future.

Attitudes toward Expanded NIPT

Participants were asked to share their attitudes toward expanded 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 screening 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. Of those who did not report ordering expanded NIPT, only 34% (25/73) indicated that they felt at least somewhat comfortable explaining the testing to patients, whereas the majority (83%, 10/12) of those who reported ordering expanded NIPT indicated that they felt at least somewhat comfortable explaining it to patients ($p = 0.012$). In addition, 14% (10/73) of those who reported that they do not order the expanded testing option identified it as a diagnostic test, compared with 33% (4/12) of those who reported that they have ordered expanded NIPT ($p < 0.01$).

Table 4 Obstetrician responses to questions about perceptions of expanded NIPT

Responses	n (%)
Are you aware of professional guidelines concerning the expanded NIPT option? (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)

Abbreviation: NIPT, noninvasive prenatal testing.

Table 5 Obstetrician responses to questions about comfort with expanded NIPT (n = 85)

Responses	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)

Abbreviation: NIPT, noninvasive prenatal testing.

Participants were asked to react to a series of statements regarding attitudes toward expanded NIPT by indicating whether they agree, disagree, or were unsure (→ **Table 6**). Despite comfort level and utilization, a majority of participants (91%, 77/85) 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. To further characterize the attitudes of obstetricians who were previously aware of the expanded testing option of NIPT, the responses were compared with 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, almost one-fifth (19%, 12/64) agreed with the statement 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 a little added benefit ($p < 0.05$). In addition, out of the respondents who were aware of expanded NIPT, about half (49%, 31/64) disagreed with a statement that the testing will replace invasive testing, whereas 18% (2/11) of those who were not aware of expanded NIPT disagreed with this statement ($p < 0.01$). Finally, 40% (25/64) of those who were aware of expanded NIPT agreed that it will become standard of care, whereas over half (56%, 5/11) of those who were not previously aware of expanded NIPT agreed with this statement ($p < 0.05$).

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% (13/35) agree that expanded NIPT will replace invasive procedures. This is compared with just under one-quarter (22%, 7/31) of those who reported being either somewhat uncomfortable or very uncomfortable with explaining the testing to patients who agreed with the statement that expanded NIPT will replace invasive testing ($p = 0.03$). Similarly, 41% (14/34) of those who are either somewhat comfortable or very comfortable explaining expanded NIPT to patients agreed with the statement that clinical utility and validity have been established for NIPT expanded testing. In contrast, only 7% (2/30) of those who are somewhat uncomfortable or very uncomfortable explaining expanded NIPT agree that clinical utility and validity have been established for expanded NIPT ($p = 0.03$).

The source from which obstetricians learn about the expanded testing option of NIPT is associated with 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 with those whose sole source of information was marketing from laboratories performing the testing. Of those who selected a single source of information about expanded NIPT, the majority 71% (10/14) of those who had obtained

Table 6 Obstetrician attitudes toward expanded NIPT (*n* = 85)

	Agree (%)	Unsure (%)	Disagree (%)	No response (%)
The expanded NIPT 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 expanded NIPT option will affect my practice	29 (34)	28 (33)	25 (29)	3 (4)
The expanded NIPT 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 expanded NIPT	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)

Abbreviation: NIPT, noninvasive prenatal testing.

information from only laboratory marketing were unsure of whether they would incorporate it into their practice in the future. In comparison, only 19% (5/26) of those who learned from only academic sources were unsure ($p < 0.01$).

Discussion

This study demonstrated that the majority of obstetricians surveyed were aware of the expanded NIPT option, yet few have actually utilized it in clinical practice. Not all physicians are comfortable talking with patients about the test and many overestimate its diagnostic ability. Physicians surveyed expressed a strong desire for more information regarding expanded NIPT.

This study revealed that one prominent source of information about expanded NIPT for physicians is marketing from laboratories that perform the test. While education from manufacturers, can benefit ordering physicians, and encourage them to learn more about prenatal testing options, currently available marketing materials from companies may not provide a full picture of the implications of this screening. For example, marketing 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 in 2,000, the positive predictive value is less than 5%.²² Although many obstetricians are receiving information about expanded NIPT from laboratories, participants in this study who had learned about expanded NIPT from academic sources were significantly more likely to plan to consider incorporating expanded NIPT into their practices in the future. 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 guidelines published by professional societies.

Although few professional guidelines specific to expanded NIPT have been published, guidelines for other types of screening can provide direction when new testing becomes available. A joint statement by the American College of Medical Genetics, the American College of Obstetricians and Gynecologists, the National Society of Genetic Counselors, the Perinatal Quality Foundation, and the Society for Maternal Fetal Medicine (SMFM) on expanded carrier screening cautions that if residual risk information has not been determined, laboratory reports should clearly communicate the limitations of interpretation of screening.²³ This guideline calls upon laboratories and health care professionals to communicate the results of carrier screening for patients in a realistic manner. It is reasonable to think that discussion surrounding expanded NIPT should follow suit with the same urgency. Furthermore, the observed overestimation of expanded NIPT's accuracy and diagnostic ability parallels a finding from Benn et al, which reported that nearly half of obstetricians view traditional NIPT as a full substitute for invasive testing.²⁴ However, the majority of physicians in this study reported making proper recommendations following a positive result, including offering invasive, diagnostic testing, and/or a referral to a specialist such as an MFM or a genetic counselor.

Limitations to this study include that participants may not have interpreted all questions as intended. This study population was limited by size, geography, and practice setting; therefore, it may be difficult to generalize these findings to obstetricians 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. This may suggest that these results underestimate the need and desire for physician education regarding expanded NIPT.

It is preferable that patients receive accurate and appropriate information before testing for purposes of both informed consent and prevention of psychological harm. Knowledgeable pretest counseling is particularly pertinent to expanded NIPT due to the complex nature of the technology and the often unfamiliar information it can produce, a concept which supports the SMFM recommendation for pretest counseling by a health professional, such as a genetic counselor, and the International Society for Prenatal Diagnosis recommendation for inclusion of clinical significance information in expanded NIPT reports.^{20,21} 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 health care professionals who provide information about expanded NIPT to patients is crucial. Practitioners must consider whether the ability to prenatally screen for subchromosomal abnormalities is sufficient basis for performing the testing.

In addition, this study reveals that while less than half of obstetricians report being at least somewhat comfortable explaining expanded NIPT to patients, they are aware of the gaps in their knowledge about this prenatal screening and unequivocally desire more information about it. As the participants were accessed through obstetrical departmental meetings, educational presentations by knowledgeable colleagues at these meetings may be a good starting point. Obstetricians 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. Health care professionals have a responsibility to educate themselves and others regarding the expanded NIPT option and other prenatal screens to ensure that patients receive optimal care.

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