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NIPT Results Indicative of Maternal Neoplasms: Genetic Counselors' Preferences and Attitudes

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GENETIC COUNSELORS' PREFERENCES AND ATTITUDES

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A

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Performing non-invasive prenatal testing (NIPT) on a pregnant woman with a chromosomally abnormal neoplasm may incidentally lead to the diagnosis of cancer due to the coexistence of circulating tumor and placental DNA. Published information regarding NIPT's accuracy for neoplasm screening is limited, and guidance for patient management is currently lacking. This challenges clinicians' ability to counsel patients regarding the implications of these results, which often is the responsibility of a genetic counselor. Over three hundred board-eligible/certified genetic counselors were surveyed regarding their awareness, preferences, and attitudes towards NIPT's ability to indicate maternal neoplasms. Despite 95% of this cohort being aware of this possibility and 77% reporting that they would disclose these results if indicated, only 29% routinely communicate this possibility to their patients in a pre-test setting. Management recommendations that were made by counselors were highly variable, and over half stated that they would feel uncomfortable or very uncomfortable counseling a patient with these results. While less than half of counselors believed that the current benefits of NIPT's neoplasm screening ability outweigh its potential harms, 80% recognized it would be beneficial in the future. A vast majority of counselors in this cohort felt institutional or national guidelines were needed regarding the management of patients with NIPT results indicating maternal neoplasms.

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INTRODUCTION

Cell-free DNA (cfDNA) was first identified in 1947 as fragments of nucleic acids circulating in the blood of healthy individuals [1]. Since this initial discovery, circulating cfDNA has been found to originate from two additional sources: tumor cells of cancer patients [2], and placental cells of pregnant women [3]. These landmark discoveries have become the basis of various diagnostic and screening technologies for both the fields of oncology and obstetrics.

Cell-free DNA is found in the plasma of cancer patients in higher quantities compared to individuals without cancer, the concentration of which has been shown to inversely correlate with prognosis and decrease in response to successful treatment [2]. These cfDNA fragments are believed to originate from the cancer cells of a tumor and represent the genetic makeup of the malignancy, which often has genetic mutations or aberrant chromosome complements [4, 5]. Circulating tumor DNA (ctDNA) has been the object of interest for cancer research and clinical test developers, as it has been proposed that specific ctDNA biomarkers may be identified for tumors that cannot be directly or routinely biopsied. Analysis of ctDNA, also referred to as a "liquid biopsy," may be used to eliminate the need for invasive, painful, and costly procedures, and can be used to gauge tumor evolution and the development of resistance to therapy over time [4]. A 2014 study by Bettegowda et al. [6] found detectable levels of ctDNA in patients with metastatic and localized cancers of all stages, as well as in cases where cancer had not yet been detected with standard imaging, indicating a possible mechanism of early cancer detection. In their blinded study, Bettegowda et al. attempted to establish the sensitivity and specificity of the "liquid biopsy" by analyzing *KRAS* mutations in primary tumors of 206 metastatic colorectal cancer patients compared against *KRAS* mutations identified in the patient's plasma, which yielded a sensitivity of 87.2% and a specificity of

99.2%. While clinical laboratories have already begun to offer “liquid biopsies” as a screening method to patients at risk for cancer [7], the sensitivity and specificity of ctDNA for early cancer detection remains largely undefined. Even if this noninvasive method is proven to be accurate, it does not yet directly indicate from where in the body the ctDNA is originating. Additionally, a biopsy of the primary tumor is still needed in order to determine if it is malignant or benign in nature, and to assess its degree of potential metastasis [6].

Similarly, aneuploidy screening through Noninvasive Prenatal Testing (NIPT) analyzes circulating cfDNA from placental cells that are found at an average concentration of approximately 10% in maternal serum during pregnancy [8]. NIPT avoids the risk of miscarriage associated with prenatal diagnostic procedures and is a highly sensitive screen for specific chromosome conditions [9]. A meta-analysis by Gil et al. [10] examined 37 relevant studies to assess the performance of NIPT in screening for aneuploidies. The study reported the sensitivity to be greater than 99% for trisomy 21, 96% for trisomy 18, and 91% for trisomy 13 with false positive rates of < 0.1%, 0.13%, and 0.13%, respectively. Known explanations for false positive results, or results discordant between NIPT and fetal karyotype, include statistical error, vanishing twin/co-twin demise, placental, fetal, and/or maternal mosaicism, undiagnosed maternal aneuploidy, copy number variants (CNVs), and abnormal chromosome compliment relating to maternal neoplasms [9, 11].

Malignant tumors are found in about 1 in 1000 pregnant women, and benign neoplasms of many types, such as uterine leiomyomas, are also observed [12]. The most common cancers diagnosed during pregnancy are associated with those found in women of reproductive age—breast and cervical cancer, leukemia, and lymphoma make up over 75% of reported cases [12]. The massively parallel shotgun sequencing (MPSS) technology utilized by some NIPT companies is able to assess genomic gains and losses across several chromosomes but cannot

make the distinction between cell-free fragments originating from different tissue sources. Therefore, since many malignancies are chromosomally unstable [5], the coexistence of circulating tumor cfDNA and placental cfDNA may incidentally lead to abnormal NIPT results that raise a suspicion for cancer in pregnant women who have NIPT performed for aneuploidy screening, as the results generated in these scenarios (monosomies or multiple aneuploidies) are often not compatible with life or reflect fetal findings [13-15].

Published information regarding NIPT's neoplasm screening ability, intentional or incidental, is limited. Osborne et al. published the first case of maternal cancer that was diagnosed following discordant NIPT results in 2013. The patient's NIPT results were positive for both trisomy 13 and monosomy 18, and were confirmed on repeat NIPT samples at various points throughout the pregnancy. However, fetal anatomy, karyotype, and placental biopsy were normal. Following delivery, the patient experienced significant pelvic pain and was diagnosed with high-grade neuroendocrine sarcoma, with 80% of the examined cells demonstrating the previously observed aneuploidies [16]. Subsequently, two NIPT laboratories presented abstracts that reported cases of maternal cancers incidentally indicated by NIPT at the 2015 ACMG Annual Clinical Genetics Meeting [17, 18]. One report described two cases of multiple genomic gains or losses, one of which led to a diagnosis of invasive grade 2 breast cancer. A malignancy was not found in the other patient [17]. The second abstract reported seven confirmed, separate cases of maternal malignancy out of 37 NIPT results that detected multiple aneuploidies [18]. Bianchi et al. (2015) published a retrospective study of pregnant women who had an abnormal NIPT result involving chromosomes 21, 18, 13, X, and Y, and were subsequently diagnosed with cancer. This study included the previously described cases. This report found that out of 125,426 NIPT tests, 3,757 were abnormal for one or more aneuploidies. Out of this group, 10 women were reported to have been diagnosed with cancer

following their prenatal testing. Seven of these 10 cases screened positive for multiple aneuploidies. Diagnoses included lymphoma, leukemia, colorectal, anal, and neuroendocrine cancers. Upon further inspection of these cases, chromosomal aberrations were found spanning the entire genome. Even though follow-up for both normal and abnormal results was significantly limited, the risk for cancer when multiple aneuploidies were detected and fetal karyotype was normal was estimated to be 20 – 44% [19]. Later, Snyder et al. (2016) sought to determine the etiology of monosomy or multiple aneuploidies by conducting a retrospective analysis of patient follow-up and concluded that there are multiple causes for these results, either maternal, fetal, and placental in nature [20]. Uterine leiomyomas (fibroids) with an abnormal chromosome compliment have also been reported and can confound NIPT results [21, 22]. Given that 40-60% of women are reported to have uterine fibroids by age 35 [23], this is yet another factor to consider in the face of abnormal NIPT results.

Ethical concerns as well as associated practical and legal considerations raised by incidental findings are not unique to NIPT. However, with respect to NIPT results indicative of maternal neoplasms, it is not clear what, if any, follow-up clinical evaluation is appropriate and little direction is available to help guide management and counseling. Yet, as of March 2016, laboratories performing NIPT via MPSS are either reporting results concerning for maternal neoplasm verbally to the ordering provider without documentation of these results on their reports, or are reporting results as multiple fetal aneuploidies that cannot feasibly reflect fetal findings. Recommendations have been proposed that pre-test NIPT counseling should include a statement about the possibility of incidental findings, whether they be maternal or fetal in nature [24], yet recommendations regarding post-test counseling and work-up in cases indicative of maternal malignancy are lacking and many clinicians, including genetic

counselors, may not be adequately equipped to counsel patients about these implications in the post-test setting.

While results indicative of maternal malignancies are still rarely encountered, the number of women being tested via NIPT has increased with the expansion of its use from "high-risk populations" – women at an increased risk for a fetus with aneuploidy – to the general population, meaning the number of incidental findings is likely to increase as more women undergo NIPT.

Prenatal or laboratory genetic counselors are often the ones involved in communicating NIPT results to patients or providers, particularly when they are abnormal. However, genetic counselors of all specialties may have a role in the management of NIPT results indicative of maternal neoplasms. Prenatal genetic counselors are often responsible for NIPT pre-test counseling, or are consulted to counsel patients post-test when abnormal NIPT results arise. Pediatric genetic counselors may aid in facilitating confirmatory testing of the baby at birth, and cancer genetic counselors may be sent referrals when ordering physicians are told by lab directors or lab genetic counselors that results may have a malignant etiology. Genetic counselors are known to specialize in communicating this information to patients and making appropriate recommendations for care. This study thus aims to assess genetic counselors' awareness of NIPT's ability to detect maternal neoplasms, how this may or may not affect pre-test NIPT counseling, how counselors prefer for non-validated incidental findings of maternal neoplasms to be reported and managed, and their attitudes regarding NIPT's neoplasm screening ability.

METHODS

Participants for this study were recruited via the National Society of Genetic Counselors (NSGC) and included English-speaking board-eligible or board-certified genetic counselors of all specialties. Members who agreed to participate were asked to complete an anonymous online survey after providing informed consent. The survey was split into two arms based on the participant's specialty of practice. Genetic counselors who indicated that they practiced in the prenatal setting, either exclusively or in combination with other specialties, completed the Prenatal Arm. Genetic counselors who indicated that they practiced in any other combination of specialties that did not include prenatal genetic counseling completed the Non-Prenatal Arm. The Prenatal Arm consisted of six sections with multiple choice questions and the opportunity to provide additional comments. The Non-Prenatal Arm was identical to the Prenatal Arm with the exception of the sections aimed at analyzing prenatal genetic counselors' pre-test counseling strategies for NIPT (see appendix for survey questions). The survey was uniquely developed for the purpose of this study, and thus did not utilize any formal validated measures. Participants were incentivized to complete the study with the opportunity to win one of two available gift cards by providing email addresses that were not linked to their survey. Responses were collected for a one-month period between September and October of 2015. Study data were collected and managed using REDCap electronic data capture tools hosted at The University of Texas Health Science Center at Houston [25]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. STATA statistical software was used to analyze data. The study was approved by the institutional review board at the University of Texas Health Science Center (HSC-MS-15-0442).

Statistical Analysis

Statistically significant relationships were determined after analyzing comparison groups either with Pearson χ^2 or Fisher's exact test. Comparison groups primarily focused on those practicing within particular specialties, and those who have had personal experience counseling about NIPT's ability to indicate maternal neoplasms. A *p*-value of < 0.05 was considered significant.

RESULTS

Demographics

A total of 367 participants responded to the survey, representing a response rate of approximately 13% of the NSGC membership at the time the survey was distributed. Twenty four participants were excluded from the study due to incomplete survey responses, leaving a final sample size of 343, for which 168 (49%) completed the Prenatal Arm, and 175 (51%) completed the Non-Prenatal Arm. The specialties of the 175 participants in the Non-Prenatal Arm included cancer, lab/industry, pediatrics/medical genetics, and a range of sub-specialties such as neurology, cardiology, pharmacogenetics, and psychiatric genetics.

The majority of participants indicated that they had 5 years or less of total experience practicing as a genetic counselor (59.8%, 205/343), as well as within their current specialty (69.4%, 238/343). The most common place of practice was a university medical center (42.3%, 145/343) or private hospital/medical facility (24.8%, 85/343). Genetic counselors were ascertained from across the country, with a majority of participants practicing in the Midwest (27.4%, 94/343). Eighty-seven percent of genetic counselors (298/343) reported that they were currently seeing patients, and 60% (206/343) indicated that they were currently discussing NIPT with either patients or providers. In order to assess for external validity, demographic

information of the dataset was compared against the 2014 National Society of Genetic Counselors Professional Status Survey (PSS); the sample population was found to be appropriately representative. Additionally, there were no statistically significant differences for any factors between the Prenatal and Other Arms ($p > 0.05$). A complete list of participant characteristics are described in Table 1.

Table 1 Participant demographics (n = 343)

Variable	n	%
Total Years Experience		
0 – 5 years	205	59.8
6 – 10 years	58	16.9
11 – 15 years	36	10.5
16 – 20 years	18	5.3
> 20 years	26	7.6
Total Years Experience in specialty		
0 – 5 years	238	69.4
6 – 10 years	45	13.1
11 – 15 years	30	8.8
16 – 20 years	12	3.5
> 20 years	18	5.3
Institution Type		
University medical center	145	42.3
Private hospital/medical facility	85	24.8
Public hospital/medical facility	59	17.2
Physician's private practice	25	7.3
Commercial laboratory	34	9.9
Other	14	4.1
Two or more institution types	19	5.5
Region		
Northeast	50	14.6
Mid-Atlantic	42	12.2
Southeast	43	12.5
Southwest	53	15.5
Midwest	94	27.4
West	30	8.8
Northwest	16	4.7
Other	15	4.4
Currently seeing patients		
Yes	298	86.9
No	45	13.1
Currently counseling about NIPT		
Yes	206	60.1
No	137	39.9

Awareness

As seen in Table 2, a majority of genetic counselors surveyed (95%, 326/343) reported they were previously aware of NIPT's ability to indicate maternal neoplasms, with most having first learned of it through a professional conference, peer-reviewed journal, or discussion forum. Thirty (20 Prenatal Arm, 10 Non-Prenatal Arm) reported that they first learned about this possibility by encountering this case in their own personal experience.

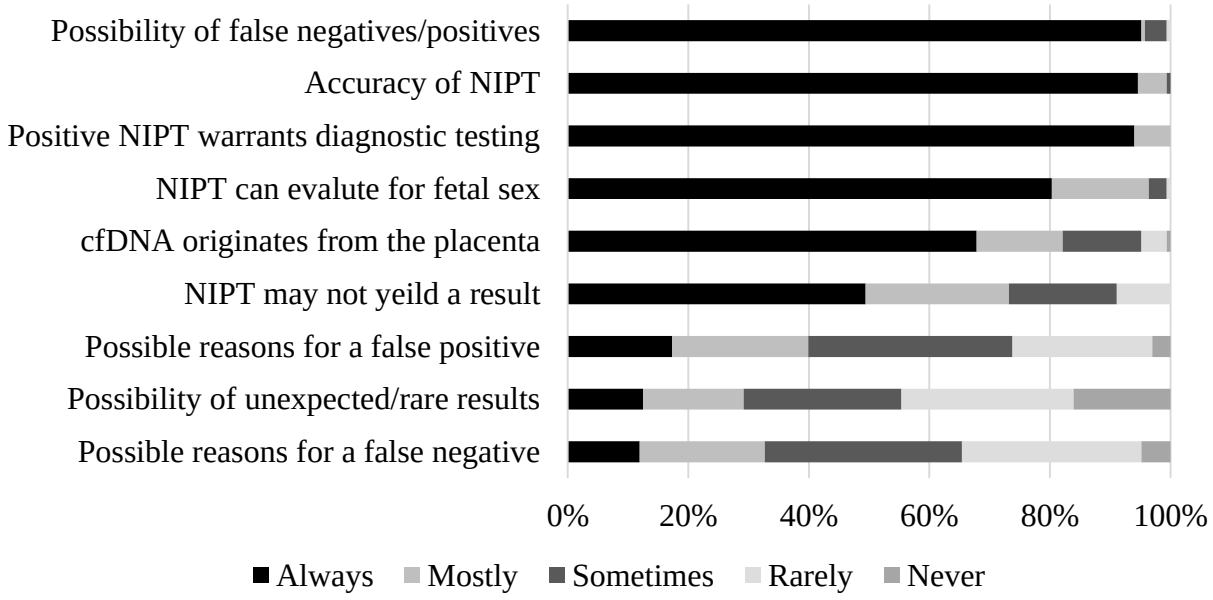
Table 2 Awareness of NIPT's ability to indicate maternal neoplasms, n (%)

Source	Prenatal n = 168	Non-Prenatal n = 175	Total n = 343
Professional conference, journal, discussion forum	96 (57.1)	104 (59.4)	200 (58.3)
Colleague	31 (18.5)	35 (20.0)	66 (19.2)
Personal experience	20 (11.9)	10 (5.7)	30 (8.7)
Popular media	8 (4.8)	3 (1.7)	11 (3.2)
I was not previously aware	7 (4.2)	10 (5.7)	17 (5.0)
Other	5 (3.0)	7 (4.0)	12 (3.5)
I do not recall	1 (0.6)	6 (3.4)	7 (2.0)

Pre-test counseling for NIPT

Genetic counselors who completed the Prenatal Arm ranked how frequently various pre-test counseling points were included when discussing NIPT for a routine indication such as for advanced maternal age by using a Likert scale ranging from "always" to "never." Figure 1 demonstrates the frequencies for each pre-test counseling point. Of note, counseling that NIPT

Figure 1 Frequencies of pre-test counseling discussion points for NIPT



results may indicate unexpected or rare conditions in the pregnancy or mother was "always" discussed only 12.5% of the time, with 44.6% "rarely" or "never" mentioning this possibility. Prenatal counselors who had personally experienced a case in which NIPT results indicated maternal neoplasms were more likely to include this statement in their pre-test counseling (p =

0.028). There were no other statistical correlations found between inclusion of this statement and other measured variables.

A majority (67.7%, 109/161) of counselors who completed the Prenatal Arm reported that their pre-test counseling had not changed since becoming aware of the possibility that NIPT could indicate maternal neoplasms, as illustrated in Table 3.

Table 3 Perceived changes in pre-test counseling for NIPT

Perceived change	n*	%
Yes, it has greatly changed	6	3.7
Yes, it has slightly changed	46	28.6
No, it has not changed	109	67.7

*Six participants who were not previously aware were not instructed to answer this question (n = 161)

Counselors were more likely to report that their pre-test counseling had changed if they had encountered this type of case in their own clinical experience ($p < 0.001$), or if they had more years of experience overall ($p = 0.003$). However, general awareness of NIPT's neoplasm screening ability did not play a role in change of pre-test counseling ($p = 0.154$). Out of the 20 Prenatal Arm counselors who reported having personal experience, 11 further elaborated on how their pre-test counseling has changed since this experience. Four stated that they will explicitly discuss cancer as a possibility in every pre-test counseling session for NIPT, while 3 stated that they now vaguely allude to the possibility of detecting "maternal health factors." Three participants in this subgroup said they treat it on a case-by-case basis, and one reported they no longer use an NIPT platform where this is a possibility. For the remaining 148 Prenatal Arm counselors who did not have personal experience with this indication, 71 (48.0%) participants chose to describe their changes, or lack of changes, to pre-test counseling, as illustrated in Table 4.

Table 4 Free responses: perceived changes in pre-test counseling (n = 71)

Yes, it has changed (n = 31)
Inclusion of vague statement (n = 17, 54.8%) *"I counsel that other chromosome changes may be identified that need further clarification, but I do not specifically counsel that changes may reflect a neoplasm/cancer."* Always discuss (n = 5, 16.1%) *"I always, always, always incorporate this into my consent process now. I think it's extremely important that this testing can reveal more about Mom than we were expecting, and I think it's essential that the patient understands this."* Case by case basis (n = 4, 12.9%) *"If the patient has a personal history/high risk of cancer or a strong family history of cancer, I discuss the possibility that NIPT can occasionally detect cancers. The information has not been incorporated into typical counseling sessions because of the rarity of this type of result and the lack of data available on likelihoods, outcomes, etc."* Added to consent form (n = 3, 9.7%) *"We have added a short part to our verbal consent that states that some results may tell us information about the patient's health and could require follow-up testing."* Other (n = 2, 6.5%)
No, it has not changed (n = 40)
Don't discuss (n = 26, 65.0%) *"Still a lot of unknowns at this point. As a practice, we have decided not to change things yet."* *"With many types of prenatal genetic screening (ultrasound, traditional maternal serum screening, etc.) there is a possibility of incidentally obtaining information that suggests increased risk of a maternal or fetal health condition unrelated to the primary purpose of the screen. In my opinion, pre-test counseling would serve no useful purpose and could lead patients to mistakenly believe that one of the roles of NIPT is cancer screening."* Previously aware (n = 4, 10.0%) *"I only started counseling patients after I learned of this."* Use different lab (n =3, 7.5%) *"I do not counsel about uncovering possible maternal cancers because I am told by the lab whose test we use that their technology isn't going to pick that up."* Other (n = 7, 17.5%)

Reporting preferences

Participants who completed the Prenatal Arm were asked to state whether or not they would disclose NIPT results indicative of a maternal neoplasm to a patient or provider if results were not explicitly documented on the report – as was the current practice at the time of this survey – versus if they were clearly documented on the report. Of those who completed the Prenatal Arm, 76.8% (129/168) indicated that they would disclose this information to a patient even if it was not documented on the report. Twenty-one percent (36/168) indicated they were unsure if they would disclose, and 1.8% (3/168) reported they would not disclose this information in any capacity. One-hundred twenty six (75.0%) participants chose to provide reasons for why they would disclose this to a patient or not. Commonly observed response themes and accompanying examples are illustrated in Table 5. Conversely, almost all participants stated that they would disclose this to a patient if it were clearly documented on the test report (99.4%); one individual indicated that he or she was "unsure."

Table 5 Free responses: choice to disclose if results were not documented (n = 126)

Yes, I would disclose (n = 116)
Ethical principles (n = 55, 47.4%) *"I likely would. I think it's important to note that we don't know how good the test is at identifying neoplasms/cancer, and that it might not be the reason we're seeing what we're seeing, but the patient has the right to know and investigate further."* *"I feel it would be unethical not to inform them to give them the chance to be checked for malignancy."* Significant health implications (n = 35, 30.2%) *"This has vital implications for the patient's health and an appropriate work-up should be performed."* *"I would rather subject the patient to possibly unnecessary worry and cancer screenings than have her pass away from a potentially treatable cancer (or have a more complex treatment course) if it had been found early because I mentioned it."* Consult with provider first (n = 10, 8.6%) *"It would be discussed with the MFM first and we would decide how to best handle the situation together."* Other (n = 16, 13.8%) *"I would likely think that yes, I would; but I imagine that as an office, we would need to make ourselves aware of the medical/legal aspects of informing a patient of an essentially undocumented result. I can't imagine NOT saying something, but I don't exactly know what I would say or what recommendations I would make."* *"Case-by-case basis. I would want to talk with the lab first. I would also want to consider what could have made the data look that way – ie does the patient have fibroids that could cause concern for cancer on NIPT?"*
No, I would not disclose (n = 10)
No data/not validated/no guidelines (n = 6, 60.0%) *"I would have to discuss with my MFM team and our director first. Since there is no guideline, it's like we are looking in the dark without a flashlight. Plus, insurance won't cover the expensive MRI, CT, etc. based on an abnormal [NIPT] result because there is so little data. I don't' want my patient to get stuck with a huge bill only to find nothing and keep her up at night for the rest of her life."* *"No. The testing has not been validated to test for maternal neoplasm and the data is sparse. There are no recommendations for following a patient in this scenario."* Other (n = 4, 40.0%) *"Unless I have a report in writing from the performing lab, I have no basis to disclose an incidental finding to the patient."* *"If I disclosed this information, then I am assuming personal liability for whether this information is correct or not."*

Participants of both arms were asked if they believe the potential benefits of NIPT's neoplasm screening ability outweigh its potential risks both currently and in the future. They were also asked if NIPT companies should report non-validated findings, such as for neoplasms/cancer. Responses are recorded and discussed in the *Attitudes* section below. Counselors in the Prenatal Arm were more likely to disclose this information in the absence of documentation if they believed that both currently, and in the future, the benefits of NIPT's ability to indicate maternal neoplasms outweigh the potential harms ($p < 0.001$ and $p = 0.027$, respectively). Counselors who were more likely to withhold this information believed that NIPT companies should not report non-validated findings ($p < 0.001$). There were no significant differences in choice to disclose between those who had personal experience counseling this type of case versus those who did not ($p = 0.489$).

All participants (Prenatal and Non-Prenatal Arms) were asked for their opinion regarding the reporting of incidental findings of maternal neoplasms. A significant majority (69.1%) believed that findings should be discussed by a lab director as well as documented on the report. A smaller number (12.5%) believed that findings should continue to be discussed by a lab director, but not documented on the report. Three percent of participants felt that findings should not be reported in any capacity, whereas 12.8% were unsure. For those who elaborated on their answers (n = 193), commonly observed response themes and accompanying examples are listed in Table 6.

Table 6 Free responses: preferences for maternal neoplasm results reporting (n = 113)

Documentation

"Potentially clinically relevant findings shouldn't be excluded from the report. Relying only on direct communication could result in miscommunication if multiple providers are involved (OB, MFM, primary care, etc.)."

"It is extremely frustrating for legal and ethical reasons for findings to be disclosed to a medical provider and yet not included on the report."

Justification for referrals

"Documentation of increased risk is important for insurance coverage regarding cancer screening."

"Labs should always be willing to document any reports they are providing. In addition, if insurance coverage of follow-up is ever an issue, documentation of an initial, initiating event would be pretty much essential."

Discussion

"I feel like it should not be included on the report because NIPT is not designed to pick it up, and we do not yet know what the performance is like for detection of maternal cancer (PPV, follow-up recommendations ,etc.). However, I do feel that the lab director should ALWAYS call the ordering provider when these results are found, since the follow-up should be on a case-by-case basis."

"It depends on how reliable the results are – I see no issues in discussion with a GC (aside from the usual concerns about how much patients remember what we tell them, etc.), but inclusion on a report can sometimes lead providers to think 'definitely' when the scenario is 'possible.'"

Incidental findings are common

"They are incidental findings, not exactly the same but similar to the ones we encounter with WES. These NIPT findings shouldn't be ignored any more than the WES incidental findings. However, the ability to screen for them should be validated first and guidelines need to be established so GCs know where to refer patients once these abnormal results are reported."

"It is a medically actionable finding. It was not a part of the initial consent but 1) it should be, and 2) if a lung tumor is picked up by a lung x-ray for pneumonia, it is still reported."

Opt in or out

"There should be an opt out option on the form for individuals to select whether or not they would like to receive any incidental findings."

Results should not be reported

"Technically we consent for NIPT as a test that gives information about the baby, not the mom."

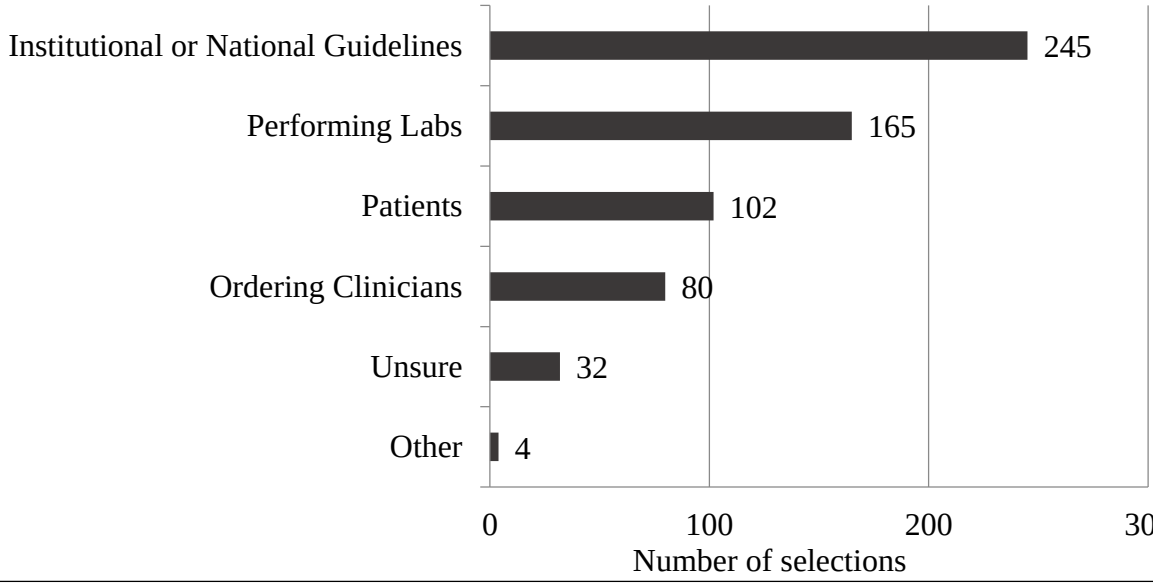
"NIPT has not been validated for this purpose and laboratories should not offer information that they cannot include on a report."

"I don't think we have enough data, at this time, to know what percentage of double aneuploidies or aberrant results actually end up being diagnosed as maternal cancer. I feel that if more data emerges and shows that the majority of the time it is maternal neoplasm, then we can put it on the report without causing undue fear and anxiety. If it is a minority of cases, I don't know if having that on a report would have some sort of potential insurance implications for that person as a 'risk for cancer' was diagnosed."

Individuals who reported personal experience with this type of case were more likely to feel that results should be discussed AND documented (p = 0.024). Additionally, those who believed that both the current and future benefits of NIPT's ability to indicate maternal neoplasms outweigh the harms were more likely to believe that findings should be discussed AND documented ($p < 0.001$ for both factors).

All participants were asked who they believe should decide as to whether NIPT incidental findings of maternal neoplasms/cancer are reported (select all that apply). Responses are summarized in Figure 2. This was not influenced by the counselors' area of practice, as those who reported practicing in a lab or industry setting were not more likely to feel that performing labs should be involved in this decision (p = 0.450).

Figure 2 Who should decide if NIPT neoplasm results are reported? (n = 628)



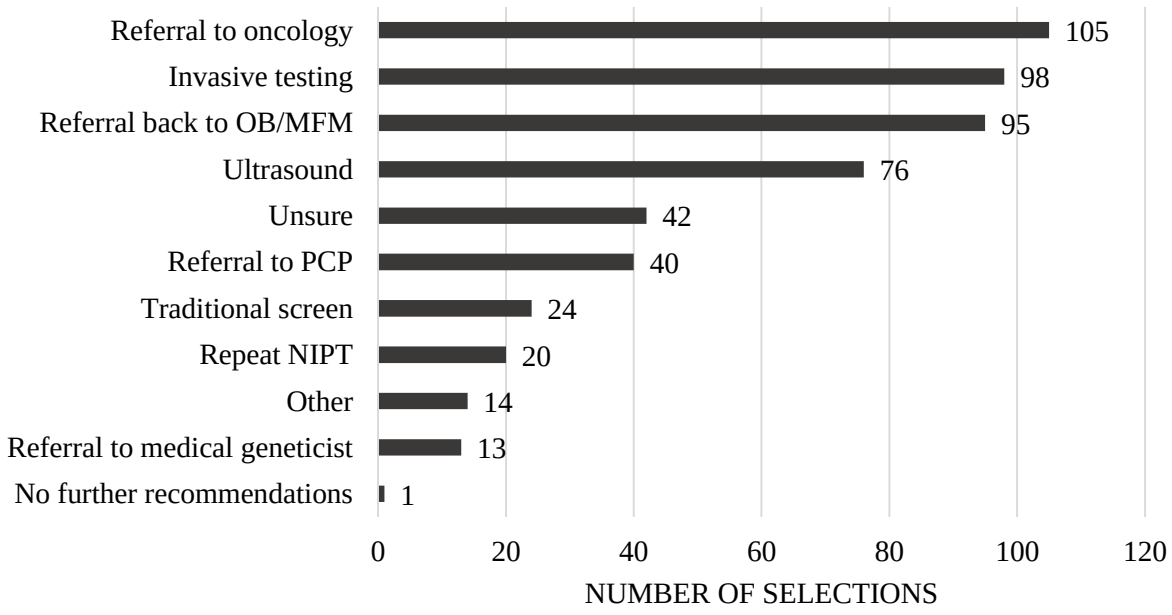
Counseling strategies

A majority of counselors who completed the Prenatal Arm (51.8%) reported that they would feel either uncomfortable or very uncomfortable counseling this type of indication.

Counselors were more likely to feel comfortable counseling these cases had they already encountered one in their personal experience ($p < 0.001$). Conversely, counselors were more likely to feel uncomfortable if they believed that the benefits of NIPT's ability to indicate maternal neoplasms do not currently outweigh the harms ($p < 0.001$), and that NIPT companies should not report non-validated findings ($p = 0.009$).

When asked what further recommendations, options, or referrals would be made when counseling a case for which NIPT results indicate a maternal neoplasm, counselors were asked to choose all that apply from several selections. Eighty-six percent of participants felt that more than one recommendation or referral was appropriate, with an average of 3 selections per participant. Twenty-five percent of participants indicated they were unsure about what recommendations or referrals they would make in this setting. The number of selections is depicted in Figure 3. Of note, "other" recommendations included offering whole-body MRIs or referrals to cancer genetic counselors.

Figure 3 Recommendations/referrals (n = 528)



The subgroup who reported personal experience with this indication recommended equally diverse follow-ups, with a nine of the available eleven options being selected at least once (n = 79). Counselors in this subgroup were more likely to suggest a referral to oncology (p = 0.004), recommend performing a traditional screen (p = 0.044), or an invasive test (p = 0.001). However, counselors with personal experience were less likely to select "unsure" as an option (p = 0.025). There were no significant differences for the other selections.

Counselors were asked to select from any of the available options summarized in Figure 4 that they felt would better help prepare them for counseling a patient with this indication. A majority (91.2%, 315/343) felt that more than one resource was needed, with an average of 3 selections per participant.

Figure 4 Resources needed by counselors (n = 1,133)

Attitudes

As previously stated, participants of both arms were asked if they believed that the potential benefits of NIPT's ability to screen for neoplasms/cancer outweigh its potential

harms, both currently and in the future. Additionally, counselors were asked their opinion as to whether NIPT companies should report non-validated findings, such as for neoplasms or cancer. Findings are summarized in Figure 5a and Figure 5b, respectively.

Figure 5a: Attitudes regarding NIPT's ability to indicate maternal neoplasms (n = 343)

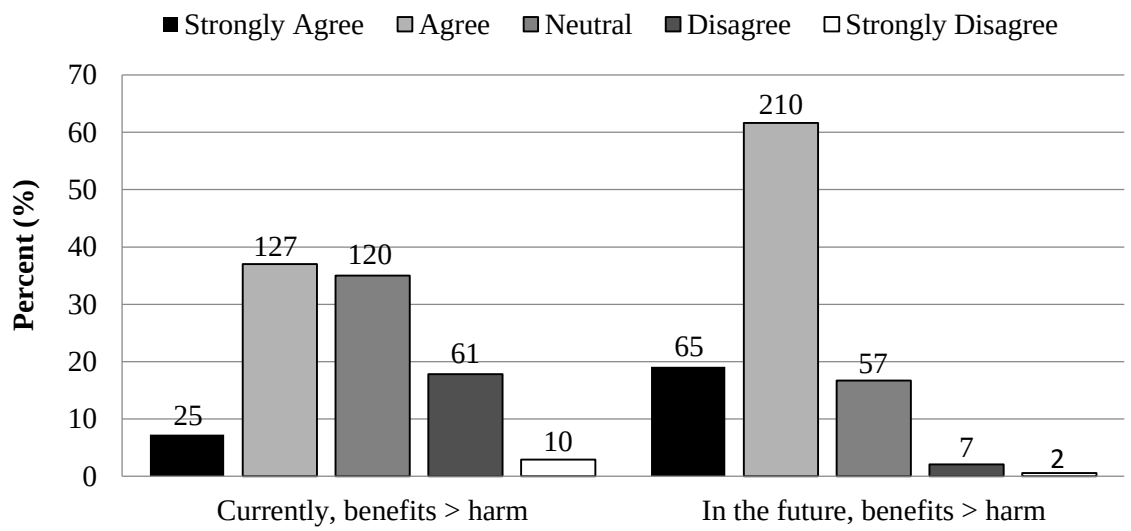
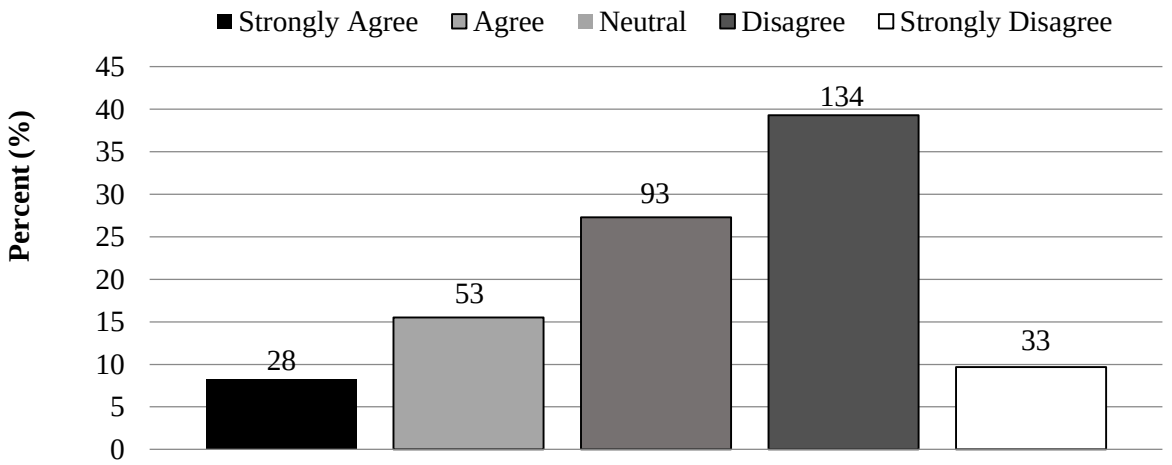


Figure 5b: Attitudes regarding NIPT's ability to indicate maternal neoplasms (n = 343)



A majority of counselors from both arms either agreed or strongly agreed that the benefits of NIPT's ability to indicate maternal neoplasms currently outweigh its harms. Counselors who reported personal experience with an NIPT neoplasm case were more likely to agree that benefits outweigh the harms both currently and in the future (p = 0.026 and p = 0.043, respectively). There was a significant positive shift of responses on the Likert scale when asked about the potential future benefits; counselors were more likely to express agreement in this scenario than in the former ($p < 0.001$).

About half of all counselors felt that despite these feelings not being validated, NIPT labs should still report these to providers. Lab and pediatric genetic counselors were less likely to agree (p = 0.083 and 0.575, respectively), whereas counselors who practiced in prenatal and cancer settings were more likely to agree with this statement (p = 0.001 and 0.004, respectively).

DISCUSSION

Three hundred forty-three genetic counselors were surveyed on their awareness, preferences, and attitudes regarding the ability of NIPT to indicate maternal neoplasms. Despite the rarity of this indication, our study shows that the majority (95%) of genetic counselors were aware NIPT results may indicate maternal neoplasms at the time they were surveyed. This awareness is most likely attributed to the fact that data regarding NIPT's ability to detect maternal malignancy was presented at a national genetics conference (ACMG) [14, 15], as well as published by Bianchi et al. [19] shortly prior to the survey distribution. This is corroborated by the fact that the majority of participants (58.3%, 200/343) stated that they learned of NIPT's ability to indicate maternal neoplasms through a professional conference, peer-reviewed journal, or discussion forum. However, when asked about "maternal neoplasms," a specific

delineation was not made in this survey between malignant/cancerous neoplasms and benign neoplasms such as fibroids. The world "fibroid" was only mentioned by two participants in the study, while different variations of "not necessarily cancer" were mentioned 13 times. However, phrases such as "significant health complications," "life-saving," or "cancer" were mentioned 60 times. Therefore, a conclusion cannot be made as to whether respondents were aware that NIPT can raise concern for BOTH benign and malignant neoplasms, as opposed to just malignancy.

Although awareness of NIPT's ability to indicate maternal cancers was high among all counselors, and recommendations have been proposed to include the discussion of the possibility of "maternal or fetal incidental findings" in pre-test counseling [24], only 29% of prenatal counselors who discuss NIPT report routinely including this statement in their pre-test counseling, with 44.6% reporting they "rarely" or "never" discuss it. Simply becoming aware of NIPT's neoplasm screening ability did not seem to introduce a significant change to counselors' pre-test counseling for NIPT ($p = 0.154$). Rather, a change to pre-test counseling was observed when counselors instead had encountered this indication first-hand ($p < 0.001$). This suggests that these experiences have greatly influenced the way in which these counselors have chosen to approach pre-test counseling for NIPT.

However, those who have made changes to their pre-test counseling cite inconsistent methods for communicating this possibility to patients. Most counselors (47.6%, 20/42) said they now include a vague statement about the possibility of uncovering "unexpected results," but some (21.4%, 9/42) will always explicitly mention that neoplasms or cancer can confound results. Others (7/42, 16.7%) treat the discussion of this on a case-by-case basis, including this only for patients who have a personal history of caner, are "information-seeking," or "highly anxious." Those who have decided not to discuss this possibility in the pre-test setting cite

barriers such as a lack of validated data or guidelines for patient management. Only 10% (4/41) of respondents who elaborated on their choice to not change their pre-test counseling stated that they do not order NIPT through a lab that performs testing via MPSS. This data shows that despite large awareness amongst counselors, the discussion of the possibility of "maternal or fetal incidental findings" in pre-test counseling is not routinely being done even when testing is being ordered through labs that can indicate this finding, bringing into question if true informed consent is being obtained at the time of pre-test counseling.

While the possibility of unexpected or rare results is not always addressed in pre-test counseling, 76.8% of the prenatal counselors surveyed reported that they would disclose results suspicious for maternal neoplasms to a patient, even if not clearly documented on the test report. This is despite the fact that approximately half of counselors reported they would feel "uncomfortable" or "very uncomfortable" counseling this type of indication. Counselors who support disclosure of results largely cited an ethical obligation to disclose results that may have significant health implications for their patient. Therefore, it appears that many counselors are comfortable stepping outside of their comfort zone if they perceive a benefit to their patient.

Additionally, 69.1% of counselors across specialties felt that NIPT results indicative of maternal neoplasms should be both documented on the test report and discussed by the lab director in order to better understand the implications of the results and to justify further workup. Many individuals alluded to how this situation is not much different than incidental findings being uncovered with other genetic tests. As one participant stated, "They are incidental findings, not exactly the same but similar to the ones we encounter with [Whole Exome Sequencing]. These NIPT findings shouldn't be ignored any more than the WES incidental findings."

Conversely, counselors who did not support disclosure of these results, and who did not believe these results should be reported or documented, consistently cited the overall lack of data and guidelines as barriers. One participant summarized it as "looking in the dark without a flashlight." Given the paucity of available information about the sensitivity, specificity, or positive predictive value of NIPT's ability to screen for maternal neoplasms, it is not unreasonable for counselors to have these reservations. Furthermore, unlike medically actionable incidental findings uncovered from other medical tests, the need for medical action following abnormal NIPT results indicating maternal neoplasm has not yet been clearly defined. It is also uncertain what, if any, appropriate clinical evaluation or follow-up might be in these situations. This was further evidenced by the wide variation in recommendations or referrals that were suggested by the surveyed group when counseling a case for which NIPT results indicate maternal neoplasm. A majority (86%) would recommend more than one referral, and the most common selection made was for a referral to oncology. However, as Bettegowda [6] and Bianchi [19] found, it is possible that the neoplasm generating cfDNA is not yet to a stage where it would be detected by standard imaging. On average, detection of malignancy occurred approximately 5 months (range: 3 weeks – 39 weeks) after having an abnormal NIPT result in Bianchi's cohort [19]. Additionally, the neoplasm may not even be malignant and require cancer treatment, as is the case for uterine fibroids. Some counselors in this cohort as well as in prior literature [26] suggested that whole-body MRI's be offered to these patients. But without documentation of NIPT results justifying this workup, it is unlikely that insurance companies will cover these tests, some of which are contraindicated during pregnancy. This is without considering the fact that, as of April 2016, whole-body MRIs do not yet exist as a CPT code and are not recognized as a billable test by insurance companies [27]. And since not all malignancies are immediately detected following NIPT results, the timing and

duration of performing this workup is unclear. These frustrations were frequently cited by counselors in this cohort.

Despite all of these limitations, 44% (152/343) of all counselors surveyed believed that the benefits of NIPT's ability to indicate maternal neoplasms outweigh its potential harms. This held particularly true for counselors who had personal experience with this indication (p = 0.026). Additionally, counselors who practiced in prenatal or cancer settings were more likely to agree that NIPT laboratories should report non-validated data such as neoplasms/cancer (p = 0.001 and p = 0.004, respectively). This implies that those counselors who encountered this indication first-hand may be more likely to appreciate its utility or have directly observed its value, despite its clear limitations. It also implies that prenatal and cancer counselors appreciate knowing more information from the laboratories even when limited.

As the number of high-risk and low-risk women undergoing NIPT expands, it is not unreasonable to predict that results indicating maternal neoplasms may become more common. Expanded non-invasive methods evaluating genome-wide copy number variants may also capture more women with neoplasms of altered chromosomes not routinely analyzed with traditional NIPT (21, 18, 13, X, and Y). While it can be assumed that the majority of the burden of pre-test and particularly post-test counseling will fall on prenatal counselors, further workup may call upon involvement and collaboration between counselors from multiple specialties.

Ultimately, NIPT was not designed to detect maternal neoplasms, or maternal genetic aberrations in general. However, this is a real possibility of the testing and a majority (80.2%) of counselors believe that the benefits will outweigh the harms in the future. Currently however, the inconsistencies observed in pre-test counseling, recommendations for patient management, and reporting preferences demonstrate a need for national or institutional

guidelines to establish a standard by which counselors can base their counseling. Ninety-one percent of counselors in this cohort across all specialties ultimately affirmed that guidelines were necessary to better prepare for these cases both pre- and post- test, and to make appropriate recommendations. Additional counselors make a call for more literature and case reports, as well as discussion and presentations through various platforms, including national conferences.

Limitations

This study could possibly reflect a skewed population, biased by ascertainment, in which counselors who were not familiar with this topic may have been dissuaded to participate in the survey. Additionally, as previously discussed, this survey was distributed shortly following the annual ACMG conference in 2015, in which this topic was discussed. Those who attended this conference could have thus been more aware and educated about this possibility, and more inclined to participate.

Additional limitations included a study design that was not based upon validated measures. The subgroup that represented counselors with personal experience with a case in which maternal neoplasms were indicated with NIPT was derived from a question aimed to assess awareness. This group represented those who selected "I have encountered a case like this in my personal experience" when asked, "How did you first learn of this possibility?" This may have inadvertently excluded those who have encountered such a case, but had learned about this possibility prior to that event. Therefore, this sample (n = 30) may not encompass everyone who experienced a case like this first-hand. Further limitations to study design included the exclusion of an explicit definition of "neoplasm," as previously discussed.

Future Directions

As evidenced by genetic counselors' desire for more information, the next most appropriate step would be to publish more data regarding NIPT's neoplasm screening ability. Due to the rarity of these events, collaboration amongst researchers, clinicians, and laboratories is needed.

As these results have equal implications for OB/GYNs who might encounter them in clinical practice either with or without access to a genetic counselor, future research might explore similar factors regarding the awareness, preferences, and attitudes of OB/GYNs. Governing bodies that produce guidelines such as the American College of Obstetrics and Gynecology and the National Society of Genetic Counselors may be prompted to create recommendations for patient counseling and management.

Additionally, exploring patient preferences may provide an interesting view of how to move forward with developing or later, adapting guidelines. This could include an examination of the psychosocial effects of receiving incidental findings with such a range of implications, from a fibroid to a cancer that cannot be detected with imaging.

CONCLUSION

While NIPT results suggestive of maternal neoplasms are thought to be rare, they present a challenge for clinicians since little direction is currently available to help guide patient counseling and management. These results have the potential to indicate significant health implications for the patient, and the majority of counselors in this study felt the information was beneficial. However, a majority do not feel properly equipped to counsel this indication due to a lack of data. This study demonstrates a need for collaboration amongst

clinicians, researchers, and laboratories to publish data, and prompts institutional or national governing bodies to create guidelines from which clinicians can base their practice.

APPENDIX

Survey Questions

1. How many total years of experience do you have as a genetic counselor?
    a. 0 – 5 years
    b. 6 – 10 years
    c. 11 – 15 years
    d. 16 – 20 years
    e. > 20 years
2. How many total years of experience do you have in your current specialty?
    a. 0 – 5 years
    b. 6 – 10 years
    c. 11 – 15 years
    d. 16 – 20 years
    e. > 20 years
3. In what type of institution do you currently work? [select all that apply]
    a. University medical center
    b. Private hospital/medical facility
    c. Public hospital/medical facility
    d. Physician's private practice
    e. Commercial laboratory
    f. Other: _____
4. In what region do you currently work?
    a. Northeast: CT, MA, ME, NH, NY, RI, VT
    b. Mid-Atlantic: DE, MD, NJ, PA, VA, WV
    c. Southeast: AK, AL, FL, GA, LA, MS, NC, SC, TN
    d. Southwest: AZ, CO, NM, OK, TX, UT
    e. Midwest: IA, IL, IN, KA, KY, MI, MN, MO, NE, ND, OH, SD, WI
    f. West: AK, CA, HI, NV
    g. Northwest: ID, MT, OR, WA, WY
    h. Other: _____
5. Do you currently see patients:
    a. Yes
    b. No
6. Do you currently counsel patients about non-invasive prenatal testing OR discuss non-invasive prenatal testing with medical providers?
    a. Yes
    b. No
7. What is your current genetic counseling specialty? [select all that apply]
    a. Prenatal
    b. Cancer
    c. Laboratory/Industry
    d. Pediatrics/Medical Genetics
    e. Other: _____

PRENATAL ARM

8. For the below section, assume you are counseling a patient for a routine indication for non-invasive prenatal testing (NIPT), such as advanced maternal age (AMA), positive quad screen, etc. Please select the frequency for which you discuss the following during PRE-TEST COUNSELING for NIPT:

	Always	Most of the time	Sometimes	Rarely	Never
NIPT can evaluate for fetal sex					
Accuracy of NIPT					
NIPT may not yield a result					
Cell-free DNA originates from the placenta					
Either false negatives or false positives may occur					
Confirmation of a positive NIPT result warrants further diagnostic testing, such as CVS or amniocentesis					
Possible reasons for a false positive result					
Possible reasons for a false negative result					
Results may indicate unexpected or rare conditions in pregnancy or mother					

9. Are you aware that NIPT results have prompted concern for and/or have led to the diagnosis of maternal neoplasms/cancers in pregnant women? If so, how did you first learn that NIPT could indicate maternal neoplasms?
    a. I was not previously aware that NIPT could indicate maternal neoplasms/cancer
    b. I have encountered a case like this in my own clinical experience
    c. From a colleague
    d. A professional conference, peer-reviewed journal, or discussion forum
    e. Popular media, such as an online news article
    f. I do not recall
    g. Other: _____

10. Since becoming aware of NIPT's ability to indicate maternal neoplasms/cancer, has your NIPT PRE-TEST counseling changed?
    a. Yes, it has greatly changed
    b. Yes, it has slightly changed
    c. No, it has not changed

11. Please feel free to elaborate. [free response]

Pregnant patients with abnormal NIPT results indicative of maternal neoplasms/cancers with chromosomal abnormalities originating from the tumor have been reported. As of June 2015, concerns for neoplasms/cancer are not documented on the NIPT report, but are verbally discussed by laboratory directors, or are reported as multiple aneuploidies in some cases.

12. If an NIPT laboratory informed you of a concerning NIPT result indicative of a possible maternal neoplasm/cancer, but this information was NOT included on the NIPT report, would you disclose this information to your patient?
    a. Yes
    b. No
    c. Unsure

13. Why or why not? [free response]

14. If an NIPT laboratory informed you of a concerning NIPT result indicative of a possible maternal neoplasm/cancer, but this information WAS included on the NIPT report, would you disclose this information to your patient?
    a. Yes
    b. No
    c. Unsure

15. Why or why not? [free response]

16. What further recommendations, options, or referrals would you make, if any? [select all that apply]
    a. No further recommendations
    b. Referral to oncology
    c. Referral back to OB/GYN or MFM
    d. Referral to PCP
    e. Referral to medical geneticist
    f. Repeat NIPT
    g. Perform traditional screening test (FTS, quad)
    h. Invasive testing (CVS, amniocentesis)
    i. Ultrasound
    j. Unsure
    k. Other: _____

17. How comfortable would you feel counseling a patient about NIPT results indicating maternal neoplasms/cancer?
    a. Very comfortable
    b. Comfortable
    c. Neutral
    d. Uncomfortable
    e. Very uncomfortable

18. How would you prefer for incidental findings of possible maternal neoplasms/cancer to be reported?
    a. Findings should NOT be reported
    b. Findings should be discussed by a lab director or lab genetic counselor AND included on the report
    c. Findings should be discussed by a lab director or lab genetic counselor but NOT included on the report
    d. I do not have a preference
    e. Unsure
    f. Other: _____

19. Why or why not? [free response]

20. Who should be making the decision as to whether NIPT incidental findings of possible maternal neoplasms/cancer are reported? [select all that apply]
    a. Performing labs
    b. Ordering clinicians
    c. Patients
    d. Institutional or national guidelines
    e. Unsure
    f. Other: _____

21. What information do you feel would help better prepare you for these cases?
    a. Institutional or national guidelines for reporting, management, and consent
    b. Peer-reviewed publications or published case reports
    c. More presentations or discussions regarding these cases at national conferences such as NSGC, ACMG, ACOG, etc.
    d. Laboratory-provided data on sensitivity and specificity for neoplasm screening
    e. Unsure
    f. Other: _____

Please indicate your level of agreement with the following statements:

22. At this time, I believe the potential benefits of NIPT's ability to screen for neoplasms/cancer outweigh the potential for harm
    a. Strongly Agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly Disagree
23. In the future, I believe the potential benefits of NIPT's ability to screen for neoplasms/cancer outweigh the potential for harm
    a. Strongly Agree
    b. Agree
    c. Neutral

d. Disagree
e. Strongly Disagree

24. NIPT companies should not report non-validated findings, such as maternal neoplasms/cancer
    a. Strongly Agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly Disagree

NON-PRENATAL ARM

NIPT (noninvasive prenatal testing) is a blood test that analyzes cell-free fetal DNA in maternal circulation. The test is offered to women during pregnancy and is primarily used to screen for fetal aneuploidies such as trisomy 21, trisomy 18, and trisomy 13. Pregnant patients with abnormal NIPT results indicative of maternal neoplasms or cancers with chromosomal abnormalities originating from the tumor have been reported. As of June 2015, concerns for neoplasms/cancers are not documented on NIPT reports, but are verbally reported by laboratory directors, or are reported as multiple aneuploidies in some cases.

8. Were you previously aware that NIPT results have prompted concern for and/or have led to the diagnosis of maternal neoplasms/cancers in pregnant women? If so, how did you first learn that NIPT could indicate maternal neoplasms?
    a. I was not previously aware that NIPT could indicate maternal neoplasms/cancer
    b. I have encountered a case like this in my own clinical experience
    c. From a colleague
    d. A professional conference, peer-reviewed journal, or discussion forum
    e. Popular media, such as an online news article
    f. I do not recall
    g. Other: _____

9. How would you prefer for incidental findings of possible maternal neoplasms/cancer to be reported?
    a. Findings should NOT be reported
    b. Findings should be discussed by a lab director or lab genetic counselor AND included on the report
    c. Findings should be discussed by a lab director or lab genetic counselor but NOT included on the report
    d. I do not have a preference
    e. Unsure
    f. Other: _____

10. Why or why not? [free response]

11. Who should be making the decision as to whether NIPT incidental findings of possible maternal neoplasms/cancer are reported? [select all that apply]
    a. Performing labs
    b. Ordering clinicians
    c. Patients
    d. Institutional or national guidelines
    e. Unsure
    f. Other: _____

12. What information do you feel would help better prepare you for these cases?
    a. Institutional or national guidelines for reporting, management, and consent
    b. Peer-reviewed publications or published case reports
    c. More presentations or discussions regarding these cases at national conferences such as NSGC, ACMG, ACOG, etc.
    d. Laboratory-provided data on sensitivity and specificity for neoplasm screening
    e. Unsure
    f. Other: _____

Please indicate your level of agreement with the following statements:

13. At this time, I believe the potential benefits of NIPT's ability to screen for neoplasms/cancer outweigh the potential for harm
    a. Strongly Agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly Disagree

14. In the future, I believe the potential benefits of NIPT's ability to screen for neoplasms/cancer outweigh the potential for harm
    a. Strongly Agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly Disagree

15. NIPT companies should not report non-validated findings, such as maternal neoplasms/cancer
    a. Strongly Agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly Disagree

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