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Genetic Counselors' Preparedness for Incidental Findings from Non-Invasive Prenatal Testing

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Abstract

The use of non-invasive prenatal testing (NIPT) for aneuploidy screening has increased dramatically in the last five years due to its high sensitivity and specificity. However, testing cell free fetal DNA (cffDNA) opens the door to maternal incidental findings. This study aims to assess genetic counselors' preparedness to respond to such incidental findings by surveying prenatal genetic counselors about their experiences with these cases. Surprisingly, 62% of the prenatal genetic counselors (89/143) in this study have encountered incidental findings in their practice, and many shared accounts of unique cases. In addition, participants were asked to respond to three hypothetical scenarios: an incidental finding of maternal mosaicism for Turner syndrome (45, XO) for which 83% of respondents felt "very prepared" to manage; an incidental finding of a maternal microdeletion, for which 72% of respondents felt "very prepared"; and an incidental finding of maternal malignancy, for which only 48% of respondents felt "very prepared" to handle. There was a statistically significant difference between the first two scenarios and the third, with participants feeling least prepared to manage an incidental finding of maternal malignancy. Participants were also surveyed about their interactions with testing labs, with 34% of respondents stating they had received results informally from the lab, and of those, 70% relayed those results to patients. Overall, genetic counselors felt prepared to counsel patients on incidental findings of maternal mosaicism and maternal microdeletions, yet unprepared to counsel patients on an incidental finding suggestive of maternal malignancy.

Keywords

Incidental findings; NIPT; NIPS; genetic counseling; maternal condition; maternal malignancy; discordant; cffDNA

Introduction

The most common cause of miscarriage and congenital birth defects is the presence of extra chromosomes in each cell of the individual (Carlson & Vora, 2017). Common chromosomal abnormalities include trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), and trisomy 13 (Patau syndrome) in which an extra chromosome 21, 18, or 13 is present in each cell, respectively. Sex chromosome aneuploidies, such as monosomy X (Turner syndrome) and Klinefelter syndrome (47, XXY), are also relatively common (Carlson & Vora, 2017). Down syndrome has a high prevalence (affecting 1 in 800 newborns) [Carlson & Vora, 2017]) and Patau and Edwards syndromes are associated with severe life-threatening birth defects, therefore is it

recommended that all patients be offered aneuploidy screening prenatally (Committee on Genetics, Society for Maternal-Fetal Medicine, 2017). Early diagnosis gives prospective parents the time and opportunity to make decisions about pregnancy termination or prepare for the birth of child with complex medical needs.

In general, both patients and physicians prefer non-invasive aneuploidy screening to avoid the risk of miscarriage associated with invasive diagnostic testing (Wilson et al., 2013). Traditionally, techniques such as the first trimester screen, quad screen, and ultrasound monitoring have been used to identify high-risk pregnancies. Invasive techniques such as chorionic villus sampling (CVS) and amniocentesis are diagnostic and may be offered to all pregnant women regardless of whether they are at low- or high-risk (Committee on Genetics, Society for Maternal-Fetal Medicine, 2017).

Recently, a new method of aneuploidy screening was developed called non-invasive prenatal testing (NIPT) using cell free fetal DNA (cffDNA). NIPT has become popular among patients and providers because it has higher sensitivity and specificity than other available screens. In addition, some versions of NIPT screen for sex chromosome abnormalities and common microdeletions, although these tests have lower degrees of sensitivity and specificity (Committee on Genetics, Society for Maternal-Fetal Medicine, 2017). The introduction of these more advanced tests has decreased the need for invasive procedures and increased the likelihood of incidental findings such as maternal malignancy or maternal conditions. These findings create difficult situations for both patients and healthcare providers, because there are no available guidelines on appropriate management.

Incidental findings due to discordant NIPT results

Though clearly a powerful screening tool, several unexpected challenges have followed NIPT's introduction to the clinical setting; particularly challenging are discordant results (a positive result on NIPT and a normal fetal karyotype). In a 2015 study by Illumina of 18,161 NIPT results, 32 were found to be discordant with respect to fetal sex reported by karyotype/ultrasound. Four of the 32 discordant results were due to unique circumstances: patient's history of kidney transplantation from a male donor giving rise to XY NIPT result when the fetus was in fact female; co-twin demise; and fetal ambiguous genitalia (Bianchi, Parsa, et al., 2015).

Another cause of discordant results is previously unidentified genetic variations in the mother. An incidental finding is defined as information produced by a test which may have clinical implications but is unrelated to the initial indication for testing (Smith et al., 2015). Incidental findings – including maternal mosaicism, maternal chromosomal abnormalities, and maternal malignancy – have been reported in patients who had NIPT and warrant new consideration of NIPT in clinical practice. Many questions remain about the best ways to conduct informed consent for NIPT, discuss the possibility of incidental findings, and interpret and report incidental findings when they occur.

Mosaicism

Mosaicism is a phenomenon in which an individual has two genetically different cell lines within their body. This is typically caused by mitotic nondisjunction occurring early in development. Mosaicism can occur in the woman carrying the pregnancy, in the fetus, or in the placenta. Since a common method of NIPT (MPSS-based) does not discriminate between maternal and fetal DNA, maternal mosaicism is a major contributor to discordant test results, and ultimately incidental maternal findings. Another source of discrepancy comes in the form of confined

placental mosaicism (CPM) in which the fetus and the placenta have differing cell lines despite having the same embryonic origin. CPM occurs in 1-2% of viable pregnancies, but it can cause false positive NIPT results. CPM would not be considered an incidental finding, because it is related to the indication for testing. Maternal mosaicism, however, would be an incidental finding.

In a 2014 study, researchers looked at sex chromosome aneuploidies (SCA) identified via NIPT (Wang et al., 2014). Out of 187 abnormal results, sixteen (8.5%) were due to altered or mosaic karyotype of the mother (Wang et al., 2014). This study demonstrated that maternal mosaicism can cause discordant NIPT results, potentially leading to patients discovering they are mosaic for Turner syndrome. The incidence of mosaic Turner syndrome increases in frequency as a woman ages (Machiella et al., 2016); however, age-related mosaicism is generally asymptomatic (Russell et al., 2007).

The incidental finding of maternal mosaicism becomes challenging when the patient is not aware of their mosaic status. Although generally benign, maternal mosaicism may affect future family planning or lead to the discovery of previously undiagnosed conditions. Clinicians must decide whether to include the possibility of uncovering such results in their pre-test counseling discussions regarding NIPT.

Maternal Conditions

Newer versions of NIPT offer patients the opportunity to screen for common microdeletion syndromes, such as Prader-Willi/Angelman syndrome, Cri-du-chat syndrome, and 22q11.2 deletion syndrome. There is limited data regarding the sensitivity and specificity of these tests, but they have already been taken up by many providers due to the severity of the conditions and the non-invasiveness of the screening methodology. The addition of microdeletion screening to NIPT introduces the chance of incidentally finding a maternal condition. The most common such

incidental finding reported in the literature is maternal 22q11.2 deletion syndrome. McDonald-McGinn et al (2001) estimated that 10% of cases of 22q11.2 deletion syndrome were inherited. For this reason, parental testing is recommended for all patients diagnosed with this syndrome (McDonald-McGinn & Zackai, 2008).

A study published in 2016 found that of 97 pregnancies reported as high-risk for 22q11.2 deletion syndrome via NIPT, two were suspected to be of maternal origin: one was confirmed by diagnostic testing and the other was lost to follow-up, though the latter patient had previously lost a pregnancy affected with 22q11.2 deletion syndrome (Gross et al., 2016). The authors did not elaborate on how these findings were received by the patients.

The implications of an incidental finding of a maternal condition could be much more significant than those of maternal mosaicism, creating challenges for conducting informed consent and reporting of NIPT results. It is unclear whether knowledge of this possibility is essential to informed consent, or whether genetic counselors should discuss the possibility only following a positive result. Others may argue that NIPT is not validated to diagnose maternal conditions, and therefore it should not be discussed at all. The most recent guidelines from the American College of Medical Genetics offer no clear instructions regarding incidental findings, other than recommending that providers discuss the possibility with patients (Gregg et al., 2016).

Maternal Malignancy

Cancer is a disease caused by the accumulation of mutations, which may progress to abnormalities in chromosome number. DNA from cancer cells can be shed into the bloodstream, and there, much like cffDNA, can be identified by NIPT. The chromosomal abnormalities emitted by tumor cells are often of such aberrant formation that they could not be produced by a viable fetus. When such findings arise in the setting of cffDNA screening during pregnancy, this can

lead to challenging situations regarding interpretation of results, communication of the results to patients, and medical management.

Identifying maternal malignancy via NIPT has been documented in the literature. In a 2015 study, researchers looked at 125,426 samples from women who underwent NIPT for aneuploidy screening of chromosomes 13,18, 21, X, and Y. Of those, 3,757 had positive results and underwent invasive testing. Of the 3,757 positive results, ten women whose NIPT results were discordant with the invasive testing were later diagnosed with cancer after further medical examination (Bianchi et al., 2015). Another study published in 2015 reported that, in 4,000 pregnant patients who underwent NIPT, three women were found to have “aberrant genome representation profiles” consistent with cancer. These women were subsequently referred for whole-body MRI, which revealed tumors in all three women (Amant et al., 2015). Both studies demonstrated that NIPT could detect malignancy in women during pregnancy, leading to very real and unexpected outcomes for these patients. However, neither study offered insight into how providers discussed these results with the patients.

Earlier this year, a study was published which surveyed over 300 genetic counselors about their experiences with NIPT and views on reporting results which could indicate maternal malignancy. The results indicated that 95% of respondents were aware that NIPT results could indicate maternal malignancy. There was less agreement about how to counsel and follow patients with these suspicious results: 77% reported they would disclose such results to patients if they were not documented clearly in the report from the lab, yet nearly all genetic counselors surveyed stated that they would disclose the finding if it were clearly documented on the test report. More than half of respondents reported that they would not feel comfortable counseling this type of session (Giles et al., 2017). When asked how they would follow a patient with this result,

participants gave a variety of responses, including referring to oncology, referring to OB/MFM, or primary care physician; repeat NIPT; and invasive testing. Most (91%) stated they would need more data and guidelines. This study also surveyed respondents on the content of their pre-test counseling sessions for NIPT, with only one third mentioning the possibility of rare, unexpected results (Giles et al., 2017). This survey indicated that genetic counselors were willing to disclose incidental findings to patients but were eager for more guidance and data to inform their approach. Although this study was informative and novel, it focused on maternal malignancy and did not collect opinions regarding other incidental findings such as maternal conditions or maternal mosaicism (Giles et al., 2017).

The above research illustrates the complicated situations which can follow discordant NIPT results and highlights the need for more guidance on management of incidental findings in the clinic. The opinions and experiences of genetic counselors who have dealt with incidental findings from NIPT will be an essential contribution to such guidelines. The purpose of this study is to understand how genetic counselors are currently handling incidental findings from NIPT, and how prepared the genetic counseling field is to handle them in the future.

Methods

An online survey was designed to collect genetic counselors' experiences and opinions of handling incidental findings from NIPT. An email invitation to participate in the study included a link to the survey and was sent to the National Society of Genetic Counselors' listserv. All genetic counselors who had counseled in a prenatal setting at any point in their career were eligible to participate. All data was collected anonymously. This survey gathered participants' demographic information, experiences in counseling in the prenatal setting, and their responses to three

hypothetical scenarios of incidental findings. The survey included a combination of close-ended and open-ended questions.

The scenarios targeted three circumstances of incidental findings from NIPT: maternal mosaicism, maternal microdeletion, and maternal malignancy. In the first scenario, the possibility of NIPT revealing maternal mosaicism for 45,XO (Turner syndrome) was introduced. This scenario was considered low stakes because maternal mosaicism for 45,XO is relatively common in older women who can spontaneously shed an X chromosome from some cells with no health implications. The second scenario described a false positive NIPT result for 22q11.2 deletion syndrome. This scenario increases the stakes because a diagnosis of 22q11.2 in the patient would change reproductive risks for future pregnancies and likely introduce new medical management/surveillance of the mother for cardiac defects and other abnormalities associated with this condition. The third scenario was designed to examine genetic counselors' responses to NIPT results showing possible maternal malignancy. In this case, the results of the NIPT indicated a high risk for monosomy 13 and trisomy 18. Compared to the first two, this scenario was crafted to have more serious medical implications for the woman and fewer established guidelines for management.

Each scenario was followed by a series of questions regarding results disclosure and follow-up, including questions such as: "How prepared do you feel to counsel this patient?", "Would you contact the performing lab to inquire about these results?", "When would you discuss the possibility that NIPT could reveal incidental findings with the patient?", "What further genetic testing would you recommend?", "Would you discuss these results with the lab?", "What is your experience with a scenario like this?", and "Would you discuss with the patient the future medical impact of these results?" These questions were not meant to test participants' knowledge, but

rather to assess how consistent responses were across the study sample. A Chi Square test was used to assess relationships between responses to questions.

Results

The survey yielded 183 respondents, of which 93.99% (172/183) were Caucasian, 0.55% (1/182) Black, 1.64% (3/183) Hispanic, 3.28% (6/183) Asian, and 0.55% (1/183) who identified as Other; 95.05% (174/183) identified as female. Further demographic information can be found in Table I and Table II.

The most common reason for referral noted by respondents was advanced maternal age. As shown in Figure 1, respondents ordered NIPT from a wide variety of companies. During pretest counseling, 42% of respondents routinely discussed the possibility of incidental findings, while 28% did not and 29% sometimes discussed the possibility. Figure 2 shows the specific types of incidental findings that genetic counselors mentioned during informed consent. For those who did not discuss incidental findings during pretest counseling, Figure 3 shows the various reasons they selected, the most common of which was that an incidental finding is a rare occurrence.

In response to the question, “Do you regard the lab performing NIPT as a useful resource when clarifying discordant NIPT results which suggest an incidental finding?”, 67% answered yes, 3% answered no, and 30% answered somewhat. In addition, 11 people elaborated in the comments section that their answer would depend on which lab they were using.

As shown in Figure 4, 33% (46/143) of respondents had encountered maternal mosaicism, 39% (56/143) had encountered a maternal condition, and 21% (30/143) had encountered maternal malignancy; 38% (54/143) had not encountered any incidental findings in their practice.

Regarding informal reporting, 34% of respondents stated they had received results informally from the lab, and of those, 70% had relayed those results to patients. Genetic counselors had mixed responses to informal reporting by the lab, with 30% of respondents remarking about requesting a formal report from the lab. One response in this category was as follows: *“I have argued to them that they should not report anything to me verbally that they are not willing to put in writing. This places me at a liability.”* Many were worried about the ethical and legal implications of such informal reporting; 19% said that this put them in an uncomfortable position. One person said they would *“collect as much information as possible and share information with the patient. It would feel immoral to withhold that information from the patient.”* In contrast, 18% said they would thank the lab for giving them the information. Another stated, *“I would be receptive to their insight and would reach out to colleagues and any relevant journal articles to further assess.”*

Scenario 1: Maternal mosaicism

In response to the scenario on maternal mosaicism, 83% (124/150) felt very prepared to counsel this patient, 16% (24/150) felt somewhat prepared, and only 1% (2/150) felt not at all prepared. A slight majority (58%, 87/150) stated they would contact the performing lab to inquire about the results, while 42% (63/150) would not. Two thirds (66%, 99/150) would recommend a maternal karyotype, while 27% (41/150) would not recommend any further testing.

In the open-ended questions, several genetic counselors described their experiences with this finding. One said:

“My two patients that ended up having X mosaicism had low level (~4-5%) XO mosaicism in blood that was likely due to maternal age-related X dropout, and they were appreciative knowing the potential ways this could affect screening in future pregnancies.”

However, not all genetic counselors felt comfortable with this scenario. Another respondent said:

“I wish you had an “I don't know” option, these scenarios are not easy to deal with and I honestly don't think I would have even thought of the possibility of maternal mosaicism.”

Another genetic counselor explained her approach as follows:

“I would offer a maternal karyotype but only if the mother is interested in learning more about her own health; she may have or may not have reasons to investigate or want NOT to know.”

One genetic counselor gave her opinion on her experience with patients' reactions to maternal mosaicism:

“Most women are not that concerned if they are asymptomatic. In some cases, the mosaic NIPS result validates concerns the patient has always had but patients do not seem negatively concerned when counseled appropriately.”

Scenario 2: Maternal condition

In the second scenario where NIPT leads to a suspicion of 22q11.2 deletion syndrome in the mother, 72% (104/145) felt very prepared to counsel this patient, 26% (37/145) felt somewhat prepared, and 1.38% (2/145) felt not at all prepared. When asked about disclosure to the patient, 12% (17/145) said that they would not discuss the possibility that NIPT could reveal a maternal condition. The majority (74%, 108/145) would contact the performing lab to inquire about the NIPT results, and most would recommend further testing in the form of a microarray or FISH (see Figure 5). There were a variety of answers to the question of further management recommendations for the potential maternal 22q11.2 deletion syndrome as seen in Figure 6, though 52% stated that they would make a referral to Genetics. Approximately a third (31%) chose the

“Other” category to stipulate that they would not make any recommendations until the maternal condition was confirmed.

Several respondents described experiences similar to the scenario presented. One in-depth experience was particularly noteworthy:

“[The] patient was referred to our fetal care center for suspected 22q deletion in her fetus. NIPT...had been previously drawn by her referring OB d/t suspected fetal TOF and came back high risk for 22q deletion. Pt came to our fetal center and had a normal fetal echo. Family was relieved thinking that since the heart was normal, the 22q was probably a false positive. Apparently no one had looked at the report from her referring MD's office closely because the result said fetus was expected to be at 50% risk for 22q d/t suspected maternal deletion. When I met with the patient, she was clearly dysmorphic and reported a history of learning disabilities. At that point I had to go back and discuss the technology behind [NIPT], what her results actually suggested, and explain that I felt it was likely she had 22q deletion syndrome herself. Patient took it pretty well, agreed to maternal FISH which confirmed deletion in her. We recommended that pt have echo and some thyroid tests which were all normal. I also made sure to educate the referring MD office about how to deal with those types of results in the future. She declined amnio but agreed to 22q FISH on cord blood which confirmed deletion in her baby.”

Some genetic counselors viewed this incidental finding as a benefit to patients. For example one respondent said,

“Patients seem to appreciate this information and it often validates concerns the family has already had. Plus, they appreciate that this gives them more accurate recurrence risk information, etc.”

Another's comment about the occurrence of 22q11.2 deletion syndrome highlighted that incidentally finding a maternal condition may not be as rare as genetic counselors may believe them to be:

“Happens more frequently at my clinic because we have a fetal center and get a lot of babies with congenital heart defects where mom refuses amniocentesis for prenatal diagnosis. I can think of 5 off the top of my head where we were very suspicious that mom had 22q and some we then were able to confirm.”

Several more genetic counselors commented on the positive predictive value: *“If the fetal testing was negative, I would not offer further work-up. The PPV for 22q11.2 via NIPT is only 20%”,* meaning that the counselor would understandably assume that the NIPT produced a false positive result. Another commented, *“Without being prompted to suspect mom and in the context of a completely normal medical history for her, I wouldn't jump straight to thinking about testing mom given the low PPV for microdeletions on NIPT”*. For these same reasons, a genetic counselor mentioned being hesitant to order this testing in the first place: *“I don't often order 22q because it is unknown how often maternal conditions are picked up, as well as the PPV altogether.”*

Scenario 3: Maternal malignancy

In response to the maternal malignancy scenario, there was a steep drop in response rate, with only 52 genetic counselors completing the questions for this scenario. Of those who did, 48% (25/52) felt very prepared to counsel the patient and 52% (27/52) felt somewhat prepared. The vast majority (92%) indicated they would contact the performing lab. Figure 7 shows great variability in when genetic counselors would first discuss the possibility that NIPT could reveal maternal malignancy.

Several participants gave examples of cases similar to this scenario. One genetic counselor said,

“Received phone call from lab indicating that results were not consistent with indication for testing and would be technically reported as ‘non-reportable’. GC from lab offered to send poster regarding maternal malignancies identified through cfDNA. Patient had family history of breast cancer and BRCA mutation, although patient had not undergone testing herself. Informed MFM and patient's primary OB of results of testing and conversation with lab GC prior to contacting the patient. Upon contacting patient told her that results could indicate something benign, but that similar results had also been identified in individuals with cancer. Patient stated she had been noticing an increased in breast lumps and had been putting off seeing her breast surgeon (whom she was already established with given family history), but that this testing was incentive to get in with breast surgeon ASAP. Within a couple of weeks she was diagnosed with breast cancer and found to be BRCA1 positive. She underwent neoadjuvant chemotherapy and then surgery and additional treatments after delivery.”

A less dramatic account of this type of incidental finding was, *“maternal fibroids but not malignancy - referred her for whole body MRI.”* Another genetic counselor said, *“This has come up many different times (too many to give specifics on each). Possible malignancy gets direct referral to cancer clinic for evaluation.”*

One of the respondents reflected on their role as a genetic counselor, saying

“I mention the possibility of a whole-body MRI but I don't know that it is within my scope to ‘recommend’ it. Then again, I suppose I don't know whose scope it's within if not mine.”

Statistical Analysis

There were several factors associated with increased perception of preparedness to handle incidental findings from NIPT. Seeing a large number of patients per week was one factor associated with increased preparedness; all (100%, 11) of the genetic counselors who saw 21 or more patients in a week felt very prepared for scenario 1, while 30% (15) of those who saw 11 or fewer patients felt only somewhat prepared ($p < 0.05$). Discussing incidental findings during pretest counseling was also associated with higher levels of preparedness; including the possibility of maternal mosaicism in pretest counseling meant higher levels of perceived preparedness in response to Scenario 1 ($p < 0.05$). This association was also significant for those responding to Scenario 3 ($p < 0.05$). In addition, referring to the rarity of incidental findings as a reason for not discussing incidental findings with patients was related to lower perceived preparedness for Scenario 3 ($p < 0.05$).

In comparing preparedness for the three scenarios, 82.4% (98) were very prepared for Scenario 1 and Scenario 2, yet only 56.6% (25) felt very prepared for Scenario 1 and Scenario 3, a difference that was significant ($p < 0.001$). Throughout the statistical analysis, there was a different pattern of associations for Scenario 3 (maternal malignancy) as compared to Scenarios 1 and 2. The variable of years as a genetic counselor was not associated with feeling prepared for Scenarios 1 or 2; however, it was related to Scenario 3. Only 23.8% (5) of those in practice for 5 years or less felt very prepared for Scenario 3, while 60.0% (6) of those in practice for 6 to 10 years and 66.7% (14) of those in practice 11 or more years felt very prepared for this case ($p < 0.05$).

Feeling prepared for Scenario 1 and Scenario 2 was not related to discussing incidental findings during pre-test counseling. However, preparedness for Scenario 3 was related to having

discussed incidental findings during the pre-test counseling and having counseled a patient with this finding ($p < 0.05$). Three quarters (75.0%, 9/12) of those who had encountered maternal malignancy felt very prepared while only 40.0% (16) of those who had not encountered this condition felt very prepared to counsel this patient.

Discussion

Scenario 1: Maternal mosaicism

Overall, genetic counselors felt prepared to handle cases of incidental findings related to maternal mosaicism of 45,XO (Turner Syndrome). This result was expected because of the low-stakes nature of this incidental finding. The surprising result related to this scenario was the frequency with which this incidental finding had been encountered in a sample size of 186 respondents. Several participants mentioned that age-related loss of an X chromosome is very common, making them less suspicious that the patient's mosaicism would have medical implications. Others commented that it could have been a twin pregnancy, and early demise of a 45,X fetus could explain the discordant testing results. While these explanations cannot be ruled out, the focus of this study was to examine responses to incidental findings.

Scenario 2: Maternal condition

In Scenario 2, 9% of respondents answered that they would only recommend further genetic testing if there were clinical suspicion of maternal 22q11.2 deletion syndrome. 22q11.2 deletion syndrome is highly variable, and the possibility that a patient may be affected with this condition cannot be ruled out based solely on genetic counselors' observations. 22q11.2 is a medically actionable

condition in which patients would benefit in knowing their diagnosis. Missing opportunities to make a genetic diagnosis can have serious implications for both the patient and their pregnancies

Like Scenario 1, it was surprising to hear about direct experiences with incidental findings of maternal cases of microdeletions and duplications of 22q. When this survey was released, it was thought that the anticipated small sample size would yield few to no genetic counselors with experiences similar to this scenario. The open-ended responses to this scenario proved otherwise. In addition, many counselors relied on the low positive predictive value of the test for this type of finding as the explanation for the result. However, if the cause of a false positive is never investigated, it is possible that genetic counselors are missing adult women with this condition.

Scenario 3: Maternal malignancy

This scenario had a steep drop in survey participation when compared to Scenario 1 and 2; about two thirds of the people who responded to Scenarios 1 and 2 did not complete Scenario 3. One possible explanation is that participants found this scenario more challenging than the first two, and were not interested in spending the necessary time to consider the case. The genetic counselors who felt the least prepared to handle this situation were likely the ones who did not complete the survey. If this explanation is true, the results for Scenario 3 would overrepresent preparedness of the field.

Limitations of the study

There were several limitations to this study, the first being sample size. This was especially impactful for the third scenario, which only elicited 52 responses. This may have been due to the length of the survey (this was the final question set), or the challenging subject matter. Regardless,

there was a precipitous drop-off in participation compared to the 150 and 145 people who responded to the first and second scenario, respectively.

In addition, announcing that the topic of study was incidental findings may have predisposed participants to be extra sensitive to incidental findings in the hypothetical scenarios and to entice those with particular interest or competence in navigating incidental findings to participate. It is possible that many participants would have dismissed the scenarios as false positives, but because these cases were presented in the context of incidental findings research, they viewed them in that light. The suggestion bias may mean that these results do not truly represent how genetic counselors would respond to these scenarios in an actual clinical setting.

Another limitation to this study is the diversity of clinic structures present in this sample. Although it is useful to represent the field of prenatal genetics broadly, institutional restrictions may have influenced participants' answers. For example, genetic counselors in this study used a wide variety of genetic testing companies. Different labs have different policies; some laboratories are more liberal in communicating suspicions of incidental findings, whereas others are more conservative. While the choice of which lab to use may be dictated by external forces, it still shapes a genetic counselor's past experience and current preparedness for incidental findings.

Research Recommendations

The majority of the genetic counselors in this study have encountered an incidental finding via NIPT, which suggests the prevalence is much higher than previously reported. As the use of NIPT increases and more conditions are added to the screening platforms, challenges of incidental findings will only increase in number, scope, and complexity. Research is needed to generate guidelines for practice in light of the possibility of discordant results and incidental findings. This may come in the form of counseling the patient about the possibility of discordant results during

the informed consent process, or having standardized protocols for results disclosure and follow-up testing. More research needs to be done to determine the best method for following up on discordant NIPT results suggestive of incidental findings. A survey of patient experiences would be particularly useful, as would statistics showing the percentage of discordant results which are due to incidental findings of maternal origin.

Conclusion

As with all new technologies, implementation of NIPT has been accompanied by unexpected challenges. This study describes genetic counselors' experiences with and responses to incidental findings from NIPT, including maternal mosaicism, maternal 22q11.2 deletion syndrome, and maternal malignancy. The results highlight steps which could be taken to ensure genetic counselors are prepared to handle these difficult situations. Genetic counselors benefit from having experience counseling a patient about incidental findings first-hand, reviewing the literature, and performing pre-testing counseling about specific types of incidental findings. In addition, genetic counselors who cited rarity as their reason for not discussing incidental findings during pretest counseling felt less prepared. Increasing awareness of this possibility may change this perception of rarity and make genetic counselors more prepared for these scenarios.

The biggest barrier to pretest counseling about incidental findings is the perception that incidental findings are too rare to be a major concern and therefore do not warrant additional time spent discussing the possibility during the informed consent process. Time with patients is already limited and counselors try to keep sessions focused on the most relevant topics. However, this study suggests that it may be important for both the patient and the genetic counselor to discuss specific incidental findings that may occur during NIPT testings. Patients may benefit from

knowing that unexpected information about their health may be discovered through prenatal screening. Genetic counselors may benefit by increasing their feeling of preparedness to manage incidental findings should they occur.

While this study did not specifically set out to collate first-hand experiences with incidental findings, it did find that genetic counselors have seen each one of these scenarios play out in their clinics. The positive predictive value of NIPT results helps determine the real risk of the pregnancy being affected, but fails to explain why a false positive result was positive in the first place. This study gives some insights to why that may be and how genetic counselors are responding to these types of results.

Genetic counseling as a profession has not arrived at a consensus on how to handle incidental findings from NIPT, and in general, genetic counselors do not feel adequately prepared to respond to them. As shown by the responses to the three hypothetical scenarios, feelings of preparedness decreased as the stakes of the findings increased; genetic counselors felt the least prepared to respond to maternal malignancy, the most significant finding with respect to the mother's health.

Conflicts of Interest

Janel Case and Paige Hazelton declare that they have no conflicts of interest.

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All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Table I

		%	n
<i>Ethnicity</i>	White	94	172
	Black	0.5	1
	Hispanic	1.6	3
	Asian	3.3	6
	Other	0.6	1
<i>Location</i>	Region I	10.4	19
	Region II	21.9	40
	Region III	9.8	18
	Region IV	30.6	56
	Region V	9.8	18
	Region VI	16.9	31
	Other	0.6	1
<i>Age (in years)</i>	18 to 24	5.5	10
	25 to 34	58.5	107
	35 to 44	20.2	37
	45 to 54	9.8	18
	55 to 64	4.9	9
	65 to 74	1.1	2
<i>Gender</i>	Female	95.1	174
	Male	4.9	9
<i>Years in Practice</i>	New graduate	20.2	37
	1-5	31.7	58
	6-10	18.0	33
	11-15	7.7	14
	16+	22.4	41

Table II

	%	n
<i>Years in a Prenatal Setting</i>		
New grad	19.6	31
1-5	41.1	65
6-10	13.9	22
11-15	5.7	9
16 or more	19.6	31
<i>Approximately how many prenatal patients do/did you see in a week?</i>		
11 or fewer	33.5	53
12-14	29.8	47
15-17	20.9	33
18-20	8.9	14
21 or more	7.0	11
<i>Among your patients, what is the most common reason for referral?</i>		
Advanced maternal age	70.3	111
Ultrasound findings	15.8	25
Family history	0.6	1
Other (please specify)	13.3	21
<i>What is the criteria for ordering NIPT at your institution?</i>		
Offered to all	43.7	69
Must have an indication/high risk	32.8	51
High risk or by request	14.6	23
Other	9.5	15
<i>Approximately how many times per week do you report results of NIPT?</i>		
0	8.9	14
1-5	43.0	68
6-9	24.1	38
10-15	16.5	26
16 or more	7.6	12

Figure 1

Which test is routinely ordered at your institution? (Check all that apply)

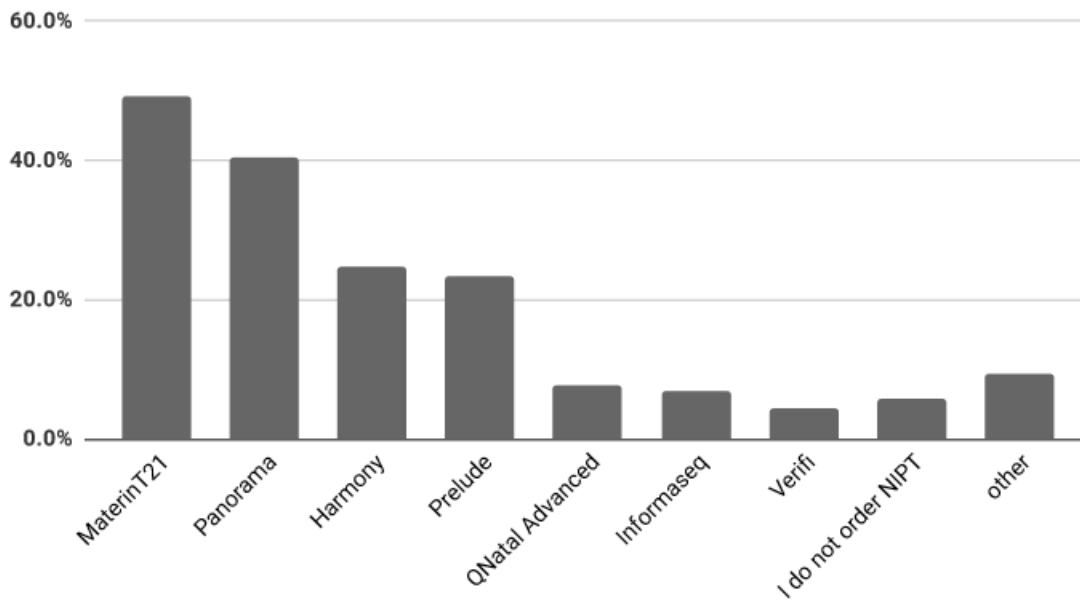


Figure 2

Which possibilities do you discuss in pretest counseling? (Check all that apply.)

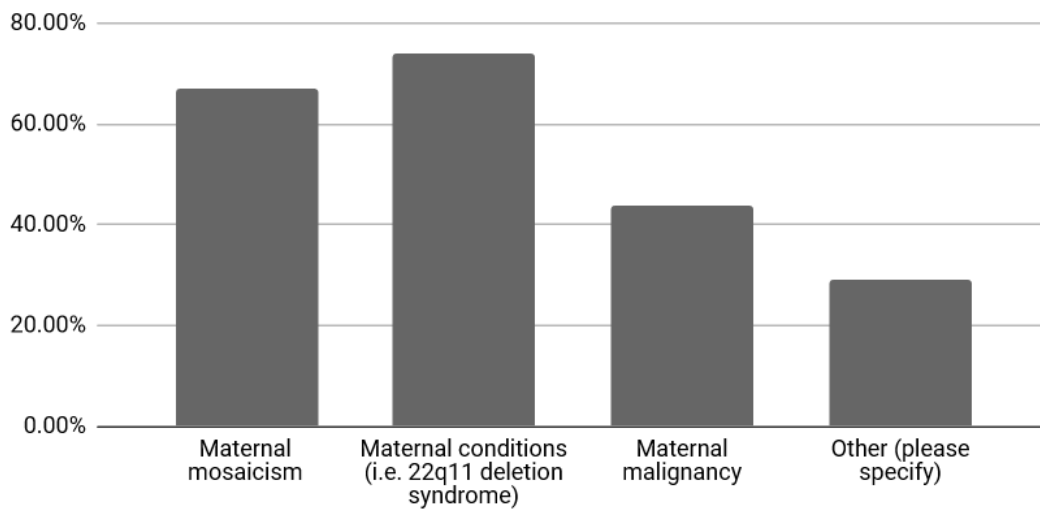


Figure 3

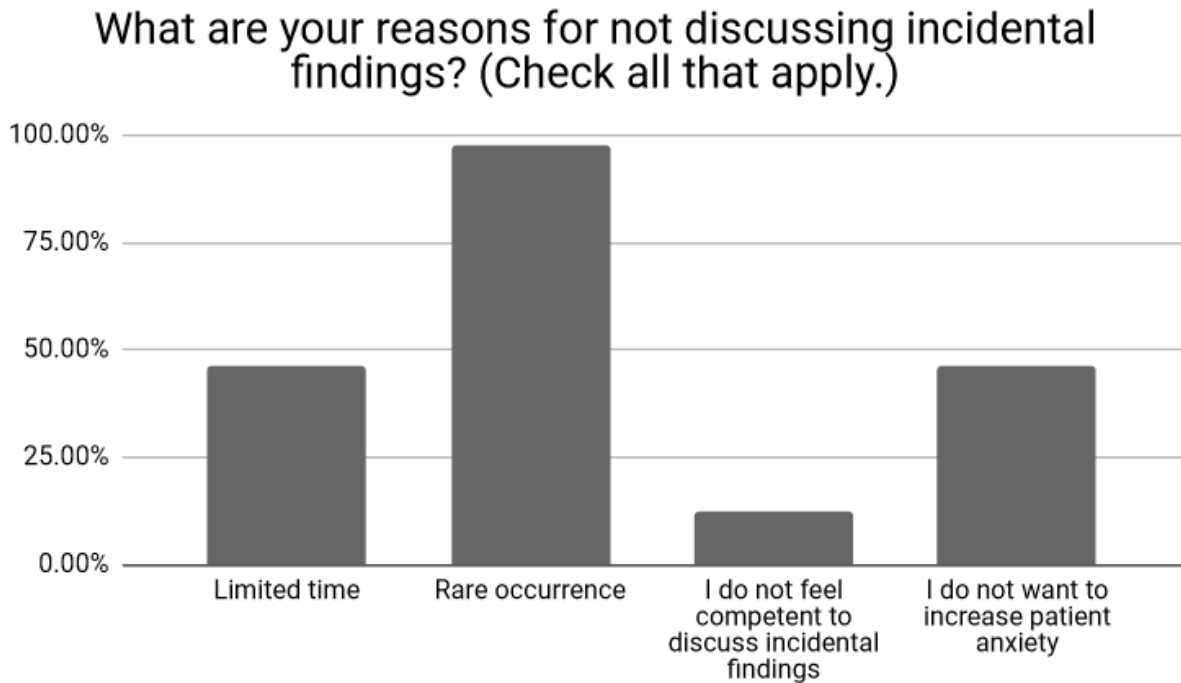


Figure 4

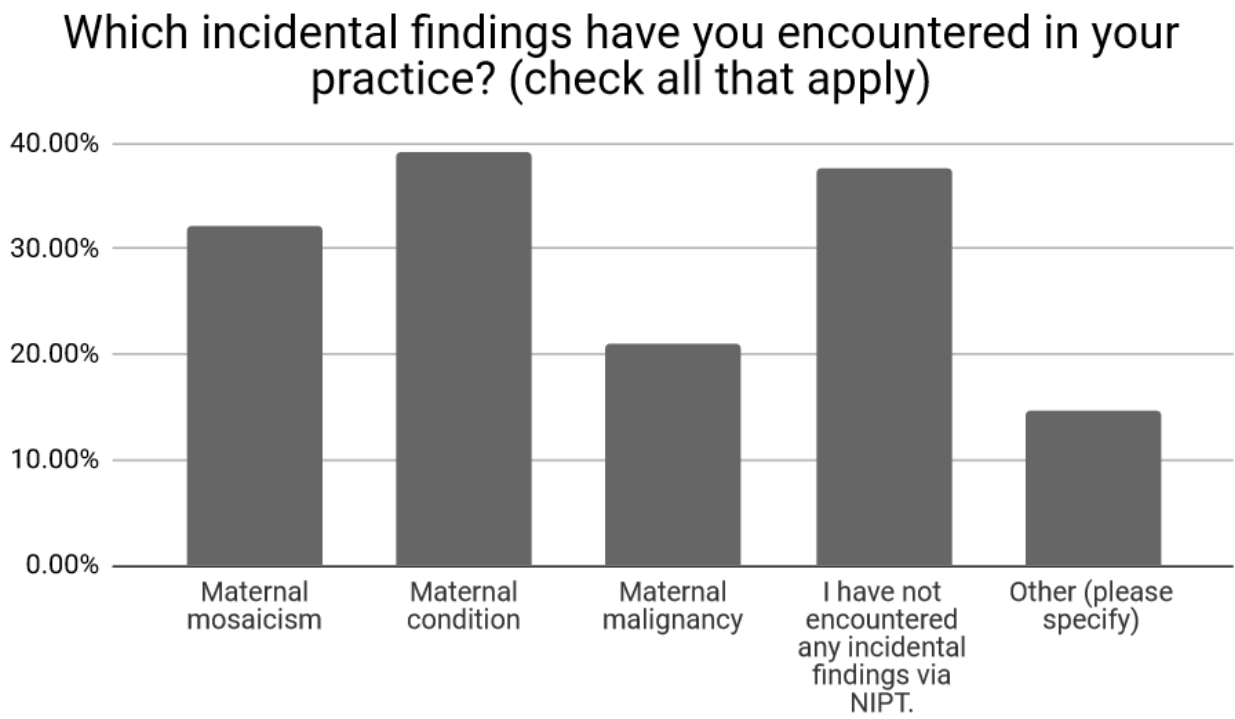


Figure 5

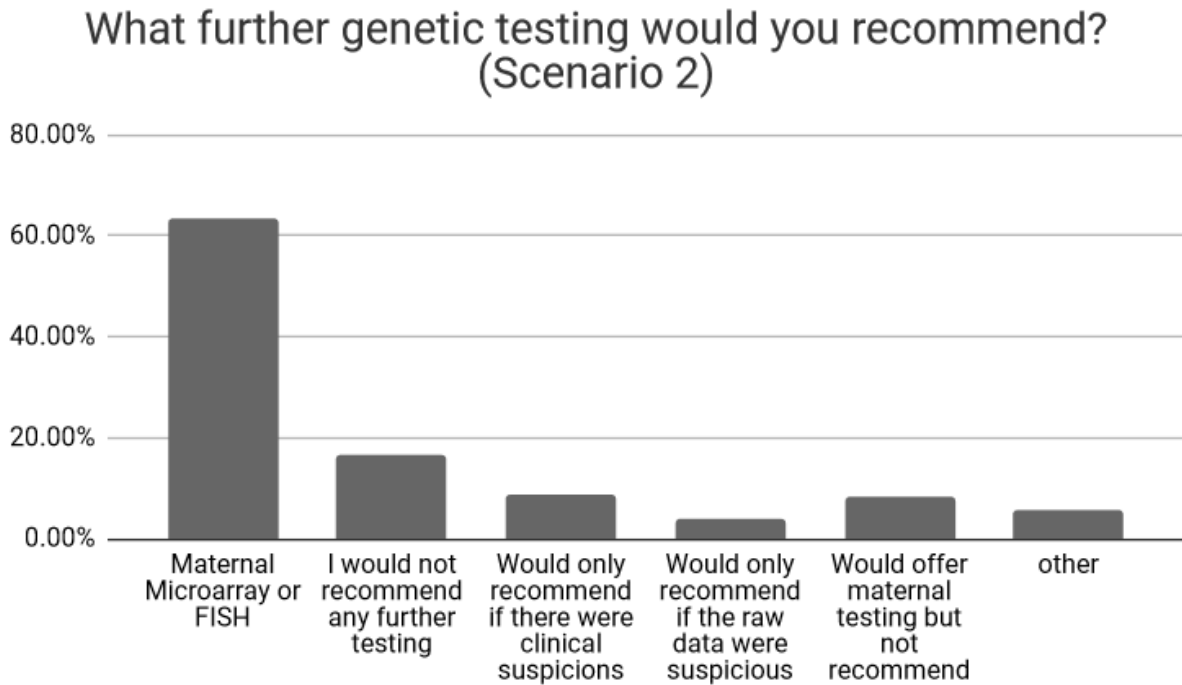


Figure 6 - Scenario 2

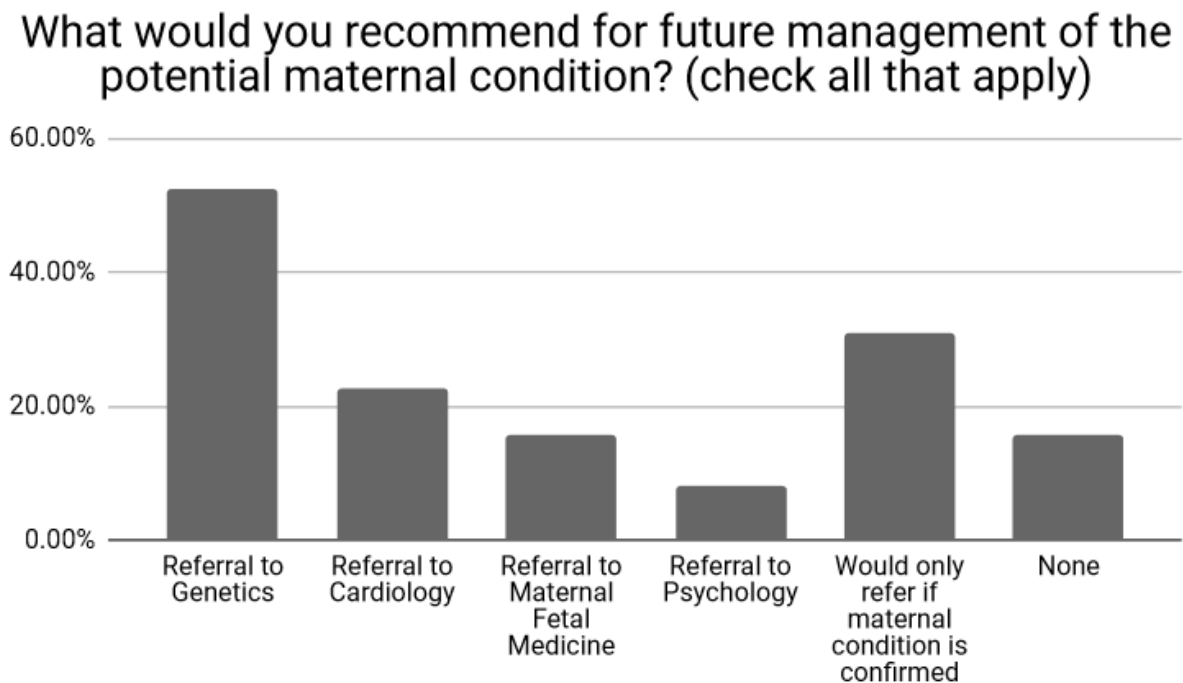
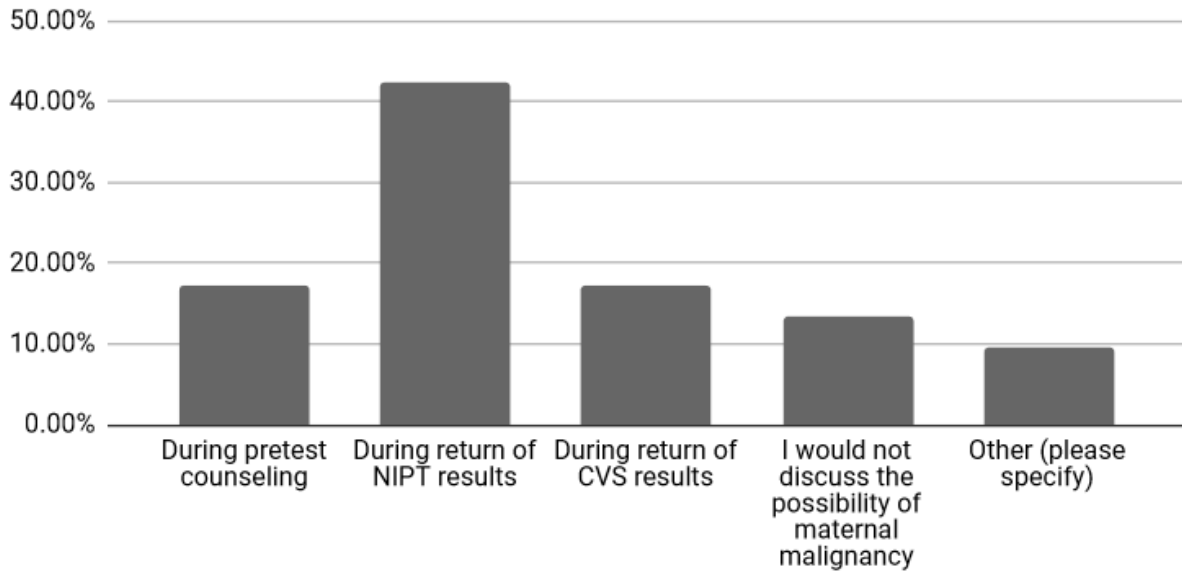


Figure 7

When would you discuss the possibility NIPT could reveal maternal malignancy?



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Appendix

Scenario 1: Maternal mosaicism

A 37yo pregnant woman is referred for genetic counseling due to advanced maternal age. After counseling, she decides to undergo NIPT; the results are reported as high risk for Turner Syndrome (45,X) and you counsel the patient on the characteristics of Turner syndrome and confirmation by diagnostic testing. The patient decides to pursue an amniocentesis for confirmation; the results of the fetal karyotype are normal female (46,XX).

In this scenario the possibility of NIPT revealing maternal mosaicism for XO (Turner's syndrome) was introduced. As mentioned in Wang et al. 2014, there is a small but significant portion of discordant sex chromosome aneuploidy results through NIPT that can be attributed to maternal origins. This scenario is low stakes because maternal mosaicism for XO is relatively common in older women who lose an X chromosome with age with no health implications. There is a small risk for future pregnancies to be affected if the mosaicism is in the germline cells.

Scenario 2: Maternal condition

A 25yo pregnant woman is referred for routine prenatal genetic counseling at 11 weeks and decides to undergo NIPT. Her results are reported as high risk for 22q11.2 deletion syndrome. You call her with the results and ask her to return for a follow-up appointment. The patient opts for a microarray via CVS to confirm the result. The microarray returns normal for all conditions.

This scenario was chosen because of the nature of 22q11.2 deletion syndrome, in that its phenotype can widely range within the same family, and although it is mostly found de novo, it can be passed through families. It is conceivable that a mother may get to child raising years and not know that she has this syndrome due to a milder phenotype. This scenario increases the stakes because a diagnosis of 22q11.2 would change reproductive options, specifically future pregnancies would be at a 50% risk for this condition and because of its range of presentation would be at risk of being more serious than the mother's phenotype. There would also likely be new medical

management/surveillance of the mother for cardiac defects and other abnormalities associated with this condition. Psychosocial considerations would also be in play.

Scenario 3: Maternal malignancy

A 40yo pregnant woman at 11 weeks gestation is referred for genetic counseling due to advanced maternal age. Nervous about being “too old”, the patient opts for NIPT. The NIPT reports a high risk for monosomy 13 and trisomy 18. You call the patient and ask her to return for a follow-up appointment. A recent ultrasound revealed no fetal anomalies. The patient undergoes a CVS which reports a normal karyotype.

This scenario was designed to examine genetic counselors’ responses to NIPT revealing possible maternal malignancy. Compared to the first two, this situation has more serious medical implications, and fewer established guidelines for management. For example, in the second scenario, if the genetic counselor suspected that the patient had 22q11.2 deletion syndrome, there is a clear way to confirm that suspicion (maternal FISH or microarray). Conversely, there is no clear way to determine whether the patient truly does have cancer; there is no obvious follow up which would rule out all possible malignancies. Because of the high stakes and the lack of confirmatory testing, scenario 3 was hypothesized to be the one for which genetic counselors are the least prepared.