

Women's Experiences of Publicly-Funded Non-Invasive Prenatal Testing in Ontario, Canada: Considerations for health technology policy-making

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Abstract

Non-Invasive Prenatal Testing (NIPT) via fetal DNA in maternal blood has been publicly funded in Ontario, Canada for high risk women since 2014. We solicited women's experiences and values related to this new health technology to describe how this test is currently being used in Ontario and to provide information about patient priorities to inform future policy decisions about the use of NIPT. Guided by constructivist grounded theory methodology, we interviewed

38 women who had diverse personal experiences with NIPT. Participants' accounts of their values for decision-making about NIPT heavily relied on three mutually modulating factors: timing, accuracy, and risk. The values expressed by women conflict with the way that publicly funded NIPT has typically been implemented in Ontario. We offer recommendations for how NIPT might be integrated into prenatal care pathways in a way more consistent with women's values.

Keywords

Prenatal testing, prenatal screening, non-invasive prenatal testing, patient values, health technology, health policy, Ontario, Canada, qualitative research

Introduction:

In this study, we investigated women's experiences with a new prenatal testing technology, non-invasive prenatal testing (NIPT) in Ontario, Canada. NIPT is also known as Non-Invasive

Prenatal Screening (NIPS) (Gregg, Best, Monaghan, Bajaj, & Skotko, 2013) and has been available in Ontario since 2011. The Ontario Ministry of Health and Long Term Care (MOHLTC) began reimbursing providers for this test on an individual basis in early 2014 (Gamma Dynacare, 2014). Tests are funded for women at high risk of fetal aneuploidy, and applications for reimbursement must be made by a health care provider, typically a physician. By soliciting women's experiences, opinions, and values of this technology, this paper provides information on patient priorities that may be important for future policy-making about this technology, in Ontario and other jurisdictions.

The term "non-invasive prenatal testing" (NIPT) refers to a new type of prenatal screening test that is currently used to detect chromosomal conditions through the analysis of cell-free fetal DNA found in a sample of maternal blood (Chitty, Hill, White, Wright, & Morris, 2012; Hill, Barrett, White, & Chitty, 2012; Wright, Wei, Higgins, & Sagoo, 2012). NIPT is considered non-invasive because it involves a single blood sample from the mother; this terminology is consistent with other types of prenatal screening that only require a blood sample, rather than a sample of amniotic fluid or placental tissue. NIPT has been simultaneously developed by a number of different private companies, who each use different techniques to analyze fetal genetic material (Vanstone, Yacoub, Winsor, Giacomini & Nisker 2015). NIPT is unique from current prenatal screening tests because it is able to detect these conditions as early as 9 weeks gestation, with higher accuracy than existing screening tests and without the risk of miscarriage associated with existing diagnostic tests (Vanstone, King, de Vrijer & Nisker, 2014; Wright & Burton, 2009; Wright et al., 2012). NIPT screens for several chromosomal conditions (i.e trisomy 13, 18, 21) as well as sex chromosome abnormalities. More conventional prenatal

screening tests screen for the same trisomy conditions as well as open neural tube defects and indications of placental dysfunction, but generally provide results later in pregnancy with lower detection rates and higher false positive rates. Screening results from NIPT and conventional prenatal screening tests should be confirmed with invasive diagnostic tests such as amniocentesis (American College of Obstetricians and Gynecologists, 2012; Benn et al., 2013; Devers et al., 2013; Langlois & Brock, 2013). Table 1 summarizes Ontario's current prenatal screening and diagnostic tests, in terms of their purpose, invasiveness of procedure, application at different stages of gestation, and commonly cited accuracy statistics.

NIPT became commercially available in Canada in 2011. In late February 2014, Ontario's publicly-funded Health Insurance Plan (OHIP) began funding NIPT for high risk women on a patient-by-patient basis (Gamma Dynacare, 2014). OHIP circulated referral forms detailing the risk criteria necessary for reimbursement to specialist genetics and obstetrics clinics and to clinicians providing obstetrical care. NIPT technology has not been addressed by either Ontario's health technology assessment committee nor has the reimbursement policy been subject to broad consultation. At the time of writing (February 2015), OHIP has made no public announcement regarding its policy to fund NIPT for high-risk women in Ontario.

In Canada, medically necessary health care and physician services are publicly funded through a system of health insurance programs administered by each province or territory. Ontario, the province where this research was conducted, is a large province in central Canada which expends 11.3% of its GDP on healthcare (Canadian Institute for Health Information, 2014). Physician services in Ontario are reimbursed through a number of different means; most

physicians work on a fee-for-service model. There is no specific fee for offering NIPT and physicians do not receive extra compensation if patients accept this or any other prenatal screening test; physician time spent discussing NIPT would be reimbursed as a prenatal visit or consultation. Diagnostic tests, such as amniocentesis, are billed by physicians as a separate procedure (Ministry of Health and Long Term Care, 2015).

There are well-established guidelines for prenatal screening in Ontario, which have evolved since the provincial introduction of a prenatal screening program in the mid 1990s (Carroll & Reid, 1997). In Ontario, all pregnant women should be offered the option of participating in publicly-funded prenatal screening for open neural tube defects, chromosomal conditions such as trisomies 13,18 and 21, and placental disease (Chitayat, Langlois, & Wilson, 2011). The most common first-tier screen offered in Ontario is Integrated Prenatal Screening (see Table 1), which involves an ultrasound and blood work at the end of the first trimester, paired with additional blood work in the middle of the second trimester. Results from this screen are typically received between 16-20 weeks gestation, although results from the first trimester portion may be returned earlier (Okun et al., 2006). If the results indicate a higher risk of having an affected pregnancy, the woman can choose to proceed with further diagnostic testing (i.e. amniocentesis), which will provide QFPCR results in 1-7 days, with microarray results typically available in 2-4 weeks. If the amniocentesis confirms a chromosomal condition or ultrasound confirms the presence of an open neural tube defect, the woman has options to terminate or continue her pregnancy. For some neural tube defects, in-utero surgery is a therapeutic option. The initial offer of screening should be made by the woman's primary prenatal care provider. If the results of that screen or other pre-existing conditions indicate she has a higher risk of having

an affected pregnancy, she may be referred to a specialist or specialist team (e.g. maternal fetal medicine specialist and/or medical geneticist, potentially with a genetic counselor).

There are many potential options for the integration of NIPT into conventional prenatal screening and testing pathways. The issue of how and when NIPT can most optimally be used is complicated by the still-developing state of evidence about this technology, the multiple points at which it could be integrated into the care pathway, and the lack of evidence around women's values and preferences concerning the role of this technology.

The developing evidence on NIPT is complicated by the fact that this technology is actually multiple similar technologies provided by several private industry sources, who use different proprietary algorithms to analyze different types of genetic material (Gregg et al., 2013; Langlois & Brock, 2013; Vanstone et al., 2015). Given the variation between different brand names of NIPT (e.g. genetic material analyzed, proprietary algorithms, available evidence on sensitivity and specificity), any meta-analyses of this data should be interpreted very cautiously, or each version of NIPT may be considered individually (Langlois & Brock, 2013; Vanstone et al., 2015). Much of the existing evidence about the detection rate, sensitivity, and specificity of NIPT is from studies conducted by industry-funded researchers in high risk populations. Some recent evidence contradicts the high detection rates cited by previous studies (Wang et al., 2014). Evidence of efficacy in average-risk populations is still developing (American College of Obstetricians and Gynecologists, 2012; Benn et al., 2013; Langlois & Brock, 2013).

NIPT could be integrated into prenatal care pathways at multiple points. Current professional society guidelines from Canada and other countries recommend that NIPT be considered as a complement rather than a substitute for existing first-tier screening tests, due to the lack of evidence of efficacy in the general population of pregnant women, and the fact that NIPT does not include detection of several conditions (e.g. neural tube defects) included in existing first tier screening tests (American College of Obstetricians and Gynecologists, 2012; Benn et al., 2013; Devers et al., 2012; Langlois & Brock, 2013). These guidelines describe NIPT as a second-tier screen, providing the opportunity to identify false positive results from first tier screening tests, allowing some women to forego invasive diagnostic testing (Norton, Rose, & Benn, 2013; Wilson, Langlois, & Johnson, 2007). Public funding in Ontario is consistent with these guidelines, offering NIPT only to women considered at high risk of fetal aneuploidy. Women who are not at high risk of fetal aneuploidy may access NIPT by paying out of pocket, approximately \$800-1000 CAD. Risk of fetal aneuploidy is determined by a number of factors, including results of first tier prenatal screening tests, soft markers visible on ultrasound, maternal age, or previous trisomy pregnancy.

A third challenge to the optimal integration of NIPT in Ontario is the lack of incorporation of social values and patient perspectives. The term "values" has many different meanings to those engaged in health policy and clinical practice (Giacomini, Hurley, Gold, Smith & Abelson, 2004). Here we use the term in its general sense to refer to women's preferences and beliefs -- specifically, about the desirability (or undesirability) of NIPT's features, objectives, effects, risks, and alternatives. We have elicited values about NIPT by asking women how they chose to engage with this technology, and for their preferences,

opinions, and beliefs about optimal uses of prenatal screening and diagnosis. While NIPT is very new, it has diffused quickly and many women have used NIPT at different points in their pregnancy, for different purposes. Understanding women's values and experiences with NIPT is crucial to the development of socially responsive and ethical policies about this technology. These perspectives may assist in designing an implementation program that best serves patients. A responsive implementation program may mean designing thresholds of risk which are meaningful to women, introducing informed choice materials about NIPT and comparable tests which are responsive to the questions women have and the information they desire, and designing continuing education materials for health care providers which enable them to best facilitate informed choice decisions about this new technology.

A patient-responsive implementation program may help to alleviate many concerns attendant to our current prenatal testing system, including anxiety about testing-related miscarriage, receiving results at a relatively late gestational age, difficulty understanding risk statistics, and the possibility of false positive and false negative results (Bekker et al., 1999; Constantine, Allyse, Wall, De Vries, & Rockwood, 2013; Ferm Widlund, Gunnarsson, Nordin, & Hansson, 2009; Gekas, Gondry, Mazur, Cesbron, & Thepot, 1999; Jaques, Sheffield, & Halliday, 2005; Kohut, Dewey, & Love, 2002; Lafarge, Mitchell, & Fox, 2013). However, the integration of NIPT could also exacerbate several longstanding concerns related to prenatal testing in general, including cursory counseling sessions that may result in uninformed choices about testing, subtle institutional pressures to choose testing, and the continued decrease of visibility and support for people with disabilities (Anderson, 1999; Boardman, 2014; Deans & Newson, 2011; McKechnie, Pridham, & Tluczek, 2014; Schwennesen, Svendsen, & Koch, 2011;

Silcock, Liao, Hill, & Chitty, 2014; van den Heuvel et al., 2010). Similar to other prenatal tests for disability, NIPT is a "morally challenging"(Hofmann, 2008) technology with potential impacts beyond the users who come into direct contact with this technology. Policy around NIPT should consider the social and ethical implications of this technology alongside questions of efficacy and cost (Hofmann, 2008).

This qualitative grounded theory study examines how Ontario women have experienced the process of publicly-funded NIPT in 2014, with the aim of identifying women's values about this process to inform future formal policy-making about this new health technology. We contrast the experience of publicly-funded NIPT in Ontario with privately-paid for NIPT experienced by Canadian women in Ontario. In this examination, we consider NIPT from a policy perspective, soliciting values and experiences from early users with the intent to inform future policy decisions about the funding, prioritization, and scope of this technology. We have limited our consideration of NIPT to applications of the test currently available.

Methods:

We used constructivist grounded theory methodology for this study, as it allows exploration of a topic about which little is known (Charmaz, 2006). Iteration between data collection and analysis and the progressive theoretical refinement of the research focus allowed us to analyze generally how women engage with the process of publicly-funded NIPT and then pursue more refined questions that focus on women's values, experiences, and opinions for the broader implementation of this technology in Ontario's health system.

Because publicly-funded NIPT in Ontario requires the submission of an application for funding by a health care provider detailing why a particular woman is high-risk, most applications for publicly-funded NIPT are made from tertiary care centers that provide specialist care to women with high risk pregnancies. Accordingly, we started recruitment at a high-risk prenatal diagnostics unit located at a tertiary health care center in Ontario. Physicians and genetic counselors assisted in recruitment by passing women who had been offered NIPT a "consent to contact" form for the research. Our research assistants later contacted consenting women to provide more information about the study and schedule an interview with interested individuals.

We started with a convenience sample of any woman offered NIPT who would have qualified for public funding. Practically, this meant that we asked the staff at the high-risk prenatal diagnostics unit to give our consent to contact form to any woman offered NIPT in their clinic. After completing our initial rounds of analysis we sampled theoretically based on issues of interest from our emerging analysis. Theoretical sampling had two aims: to recruit a more diverse sample of experiences with publicly funded NIPT and to recruit women who paid out of pocket for NIPT. To accomplish the first aim, we asked the prenatal diagnostics unit to recruit particular types of women (e.g. women who declined NIPT, women who were referred for reasons other than a positive result from Integrated Prenatal Screening). We started to recruit women who had paid out of pocket for NIPT in order to contrast their values and desires for this technology with our main study group. To recruit these women, we used several approaches: online advertisements on pregnancy-related websites and classified ad sites; snowball sampling with existing participants and personal networks; and posters in the privately run labs which collect blood samples for NIPT. Data collection proceeded until we reached theoretical

saturation, as determined by adding three more interviews and through discussion with the research team (Charmaz, 2006).

Data collection consisted of individual interviews conducted with 38 women who had personal experience with NIPT. All data was collected between April-November 2014. Data was collected through individual interviews conducted in person or by telephone, as preferred by the participant. Interviews were conducted by MV, KY and DH. The average interview took 50 minutes. Most interviews lasted between 45-60 minutes; the shortest interview lasted 12 minutes and the longest interview lasted 75 minutes. Interviews were audio-recorded and transcribed verbatim. Participants received a \$20 honorarium for their time; 4 participants declined the honorarium.

We explained our study to participants as aiming to gather women's values, experiences, and opinions on NIPT in the hopes of informing future potential policy about this new health technology. The interviewers asked women to recount their experience with NIPT and other related prenatal testing technologies. We asked each woman about her experiences and opinions with each stage of engagement of the technology, including who was involved in the decision-making process (e.g. health care professionals, partner). We also asked more general questions about values and opinions of NIPT and prenatal testing technologies in general. For ethical reasons, we did not directly ask women to disclose their test results or what they planned to do with those results and our informed consent and recruitment materials clearly stated that participants did not need to provide this information to be eligible for the study. All but one woman chose to disclose this information in conversation about their experiences.

We analyzed our data using grounded theory techniques of staged coding, starting with a line-by-line code and progressing through focused and theoretical coding (Charmaz, 2006). We employed the technique of constant comparative analysis to compare our data across themes, participants, categories of experience, and outcomes (Corbin & Strauss, 2008). Three researchers [MV, KY, DH] independently coded the data, compared coding to discuss discrepancies, and arrived at a consensus. At multiple stages, the analysts brought emerging themes for discussion to the entire research team. Emerging findings and themes were member-checked by introducing these concepts in future interviews (Charmaz, 2006; Flick, 2008). Triangulation was performed across participants and across analysts to ensure credibility of findings (Flick, 2004). NVivo® 10 software was used for data management.

The research team used several reflexive techniques to examine their own positions in relation to the research. First, extensive reflective memos were kept by researchers involved in interviewing and coding [MV, KY, DH]; consistent with constructivist grounded theory methodology, these memos were reviewed and discussed amongst the team as part of the process of analysis (Charmaz, 2006). Reflexive conversations about each researcher's relationship to the data formed part of our analytic discussions and guided future research decisions. For instance, during the research, [MV] became pregnant with her first child. In order to ensure that her own views on prenatal screening and testing were not unduly influencing her analytical stance, several techniques were used. MV kept a reflective journal of her own experiences with prenatal screening. KY acted as a "critical friend", conducting a formal interview with MV about her own experiences with prenatal screening, and considering those responses and MV's reflective journal in relation to their emerging analysis as a way of questioning assumptions and ensuring

analysis stayed grounded in the data and was not unduly influenced by MV's personal perspective (Grace, 1998).

This study received research ethics approval from the Hamilton Integrated Research Ethics Board. A formal letter of information and consent was provided to all participants before the interview. The interviewer secured informed consent by discussing this document and offering the opportunity to ask questions at the time of the interview.

Results

We summarize the demographic profile of the participants in Table 2. Compared to the average Canadian pregnant woman, our participants were older, more educated, more likely to receive care from a family physician, and more likely to live in an urban area (Public Health Agency of Canada, 2009; Statistics Canada, 2012). Our participants had a diverse array of experiences with NIPT, summarized in Table 3. Our sample of 38 women included women who considered NIPT at various stages of pregnancy, from pre-conception to mid second trimester. The sample includes women who accessed publicly funded NIPT, those who paid privately for NIPT, and those who declined. Many of the women received genetic counseling about NIPT, but regardless of whether or not she had received genetic counseling, each woman was aware of and considered multiple forms of prenatal screening or testing, and explanations of NIPT reflect these understandings (see Table 1 for a summary of other prenatal tests available in Ontario). In general, participants demonstrated a strong understanding of NIPT and alternative screening and diagnostic tests, potentially reflecting the number of participants who accessed genetic counselling, and the high education level of our sample.

Our results describe the way that each woman decided on a course of action based on her values, personal circumstances, and the availability and palatability of the options available to her. Three criteria figured prominently across these accounts: *timing*, *accuracy*, and *risk*. Throughout all accounts, women described clear preferences for accurate results, very early in pregnancy, obtained with no risk to the mother or fetus. Prenatal testing technology cannot yet meet all of these criteria, meaning that when choosing a prenatal test, women must decide which features to prioritize and which to compromise. Priorities and compromises changed depending on personal circumstances, with each factor modulating the woman's assessment of the other factors and influencing her decision-making process. We explicitly asked women who else was involved in their decision-making process. While many mentioned the test to their partners, friends, or mothers, the vast majority of women talked about the decision-making process in individual terms, indicating that they were the main decision-maker.

Participant quotes are contextualized with coded information about how that woman encountered NIPT. This code includes the notation "A" for accepted NIPT or "D" for declined. Multiple A's or D's signify multiple offers of NIPT, in the same or different pregnancies. The number following A or D signifies the trimester in which NIPT was offered. "PC" means NIPT was offered pre-conception. "\$" signifies that this woman was eligible for public funding. For example, a quote might be identified as "A2\$", which would mean that this woman was offered NIPT in her second trimester, accepted, and was eligible for public funding. "A1 A2\$" refers to a woman who paid out of pocket for NIPT in her first trimester and then repeated the test in her second trimester, with public funding.

1. *The Timing-Accuracy-Risk triad of decision-making*

1a) *Timing.*

Discussions of timing were framed in terms of gestational age. Gestational age, measured in weeks, refers to how far along the pregnancy is. A typical pregnancy lasts 40 weeks from the date of the woman's last menstrual period. NIPT can be performed as early as 9 or 10 weeks gestation, with results available about 2 weeks after blood is drawn. Women expressed a strong preference for accessing NIPT as early as possible, so that if needed, decisions about confirmatory testing and termination could be made sooner:

"If the test was available to me and I was aware of it at the 10 week mark or soon after, I think that would be a very different situation, because you would be taking whatever other steps were required sooner" (A2\$)

The timing of NIPT was affected by waits for appointments at specialized clinics, waits for funding approval from the provincial health insurance plan (1-5 business days), and then the wait for results (6-21 days). These processes could mean up to four weeks between when a woman heard about NIPT and when her results were available. T The wait for results was typically described as very stressful, as the "deadline" for confirmatory testing and termination loomed:

"It took almost three weeks. ... I was concerned because I knew the amnio had to happen at a certain time and that if we had to make any decisions regarding the pregnancy that had to happen at a certain time." (A2\$)

There is also the possibility that the NIPT results may be inconclusive and require a re-draw of blood, which would then be shipped back to the lab for a second round of testing. Not all women

mentioned this, but for the five women who talked about this, the possibility of an inconclusive result was stressful:

“Chance of not getting a result from the NIPT ... to go through the test and to not actually have anything, you know time is ticking, so just making sure that we are going to get a reasonably good answer in a good amount of time was important” (A2\$)

All the women we spoke to understood that NIPT was fallible and that invasive testing was recommended for confirmation if positive results were received. For most of our participants, this meant accounting for potential additional time needed to have a confirmatory amniocentesis performed:

If an amnio is an inevitable thing anyway, is there a sense to doing this blood test in the middle? ... Is that actually just prolonging the timeline in the sense that you're waiting for the results from the [NIPT] test, then you're waiting for the results of the amnio and suddenly a couple of weeks have gone by, would that actually end up impacting your choice? (D1\$).

Discussions of timing were complex, with women describing the wide variety of factors that might affect the time they had to wait, and contextualizing this waiting time by discussing what it would mean to receive results at different gestational ages. These discussions were most common to women who were considering terminating an affected pregnancy. Women considering termination discussed perceptions of deadlines to make decisions about further testing or termination, describing the process of prenatal testing as a race against the clock: "you feel like it is ticking. It's like, everything is just building your anxiety" (A2\$). Participants made frequent references to time pressures: “I found out early enough that I'm able to have the two week wait [for NIPT results]. I'm still able to possibly have an amnio if I need it.” (A2\$) The idea of a deadline refers to the gestational age after which confirmatory invasive testing and

pregnancy termination are no longer available: "I was already at 19 weeks, so I wanted to do it all fast, because if you did want to abort or anything, god forbid, they say you should do it before 22 weeks, so it was kind of like I had maybe a week or two, not even" (A2\$). In Ontario, availability of termination varies by organization, health care provider, and condition detected. Women in our study described being informed of a deadline for termination around 22-24 weeks for a diagnosis of Trisomy 21 (Down Syndrome): "the deciding factor was timing within the 23 week allowable abortion" (A2\$).

References to a ticking clock or advancing deadline also refer to the changing lived experience of pregnancy and the impact that the experience of being pregnant has on many women's feelings about considering pregnancy termination:

"You feel the baby moving and the emotional impact of it, it's already a terrible decision to make and the longer you stay pregnant the worse it is. It's one thing if you're doing it at 15 weeks. It's a whole other thing and still I think, would probably carry a huge emotional burden as well. You feel the baby moving round and you're visibly pregnant, it's a whole different level of things." (D1 D2\$)

Due to the changing availability of testing and termination technologies and the evolving lived experience of pregnancy, the meaning of timing changed as gestational age advanced. As the pregnancy advanced, women's considerations around timing also influenced their assessments of accuracy and risk, as discussed in section 2, "How Timing, Accuracy and Risk Modulate Decision-Making".

1b) Accuracy.

Participants spoke about the accuracy of tests as a significant factor in their decision-making process. When they spoke about “accuracy”, the word was typically used in a general way that captured the concept of providing trustworthy and relevant information. A few participants who had higher levels of education talked about more specific features of accuracy, such as detection rates, false positive and negative results, sensitivity and specificity features of the test.

Eighteen women quoted specific “accuracy” rates for NIPT, ranging from 96% to 99.99%, generally close to the published detection rate of >98% (Table 1). Most women understood amniocentesis to be extremely accurate, with a slight variation between whether they considered amniocentesis to be 100% accurate, or less than 100% accurate but still more accurate than NIPT. Women differed, however, in their judgments of whether they considered the accuracy differences between NIPT and amniocentesis to be meaningful, with women who chose invasive testing (e.g. amniocentesis) over NIPT often emphasizing the difference between the accuracy of these two tests.

Amongst those who accepted NIPT, we heard pragmatic confidence in the accuracy of NIPT results. In some cases, women expressed a confidence in the accuracy of NIPT that erased the screening vs. diagnostic test distinction made by clinicians: "The results would be virtually the same as far as what we would know to be true about this pregnancy" (A2\$), "Although it's not diagnostic, it's very very close" (A2\$). Some women used other information about the test to justify their confidence in the accuracy of NIPT:

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"it provides very similar results to what an amnio is, which is the gold standard, so they won't call the NIPT a diagnostic test yet because they don't have the kind of data and foundation studies to support it, but the accuracy is 99.8% so ... they're able to give basically diagnostic grade information" (A1).

This was particularly noticeable in the way that women described a high confidence in negative NIPT results: "If it comes back negative, you're pretty much fine not to worry about it because they are very accurate tests" (A2).

Women who chose amniocentesis were more concerned about the difference in accuracy between NIPT and amnio. These women struggled with whether they could trust NIPT results, often deciding that they would require the accuracy of an invasive diagnostic test to feel confident in the results. In the most extreme example of this view, one woman (D1\$) chose to decline NIPT in favour of waiting for an amniocentesis because it was more accurate: "I want the most accurate test available. ... even a 1% [difference in accuracy] for me is too big a risk if there is another test that will tell me definitively" (D1\$). This lack of confidence in NIPT was very rare in our sample- most women who declined NIPT in favour of amnio discussed the way that their decision was also modulated by timing: they prioritized amnio because it would give more accurate results more quickly.

While the possibility of false positive results was widely discussed in relation to other screening tests (e.g. IPS and FTS), very few participants discussed the possibility that they may receive a false positive or false negative from NIPT: "I know that the likelihood of getting an anomaly in your results with this test [NIPT] is so, so slim. I felt really comfortable with the results" (APC).

Women's confidence in NIPT accuracy was linked, in many cases, to their understanding of how the test worked- that it analyzed specific pieces of DNA rather than analyzing biomarkers or having an individual look for features on an ultrasound:

“Certainly an ultrasound is only as good as the technician, so obviously an anatomy scan can go horribly wrong if someone misses something” (APC)

“Those tests [IPS and Quad Screen] are really not that accurate, they're just looking for protein markers and they also add in your age and all these things ... whereas NIPT was almost like an amnio in terms what they look for in your blood” (A2).

1c) Risk.

Women described many different types of risk in their assessments of prenatal testing technologies. By far the most common type of risk described was the risk of miscarriage associated with invasive tests like amniocentesis or CVS, but women also used the language of risk to talk about the risk of increasing anxiety, or the risk of stress and worry. We also heard talk of “risk” in relation to the risk of inconclusive results and the risk of inaccurate results, two themes that have been discussed in prior sections.

Many women who chose NIPT described fear of testing-associated miscarriage as their main decision-making factor. The thought of losing an unaffected pregnancy weighed heavily against the opportunity to access more accurate information more quickly.

"Why would I risk losing the pregnancy by potentially causing a spontaneous abortion [miscarriage] by the amniocentesis and then to find out everything was just fine, that would be horrible." (A2\$)

This woman's description of her choice captures the most prevalent sentiment: "we wanted more information but we didn't want to risk the baby" (A2). The wish for more information from a test that was not associated with miscarriage was particularly strong amongst women who were not considering termination. For these women, NIPT would not be followed with confirmatory invasive testing, so choosing to do NIPT first was not cast as a way of postponing or potentially avoiding test-associated risk of miscarriage, but as a way of obtaining information they otherwise wouldn't have had access to due to the undesirability of the risk of miscarriage associated with diagnostic testing: "[NIPT] is 100 times better because I wouldn't want to do anything, even if it's a very minute percent, I know it's nothing, less than 1% is nothing for a miscarriage, but it's still a risk." (A2\$)

Women quoted a variety of statistics when describing their perceptions of what level of miscarriage risk was associated with amniocentesis. The majority understood that amniocentesis carried a risk of miscarriage that was near 0.5%, which is quite close to published rates (Table 1). Sometimes, the risk statistics the women quoted for the risk of amniocentesis were not congruent with generally accepted risk statistics for amniocentesis. For example, two women described an understanding that amniocentesis carried "maybe a 5%" (A2\$) risk of miscarriage, which is dramatically different from published rates of 0.6-1% (Table 1). Others did not quote specific statistics, but described the risk of miscarriage with language like "much higher chance of miscarriage" (D1) or "incredibly invasive ... so much risk" (D1\$ A1). These perceptions of the

risk of miscarriage being unacceptably high were also present in women who quoted accurate risk statistics: "even though the risk is less than 1% it still seems very terrifying" (A2\$)

Some women described wanting to avoid the risk of stress and worry associated with the negative experience of the invasive testing procedure, which was seen as uncomfortable, scary, and stressful:

"the most wonderful feature [of NIPT] is that you don't have to have a massive needle stuck in your belly and then you don't have to worry about the cramping afterwards and then worrying about whether the baby's ok. It sounded wonderful" (A2\$)

2. *How Timing, Accuracy, and Risk Modulate Decision-Making*

Each woman assessed the three factors in a different way, prioritizing some elements and compromising others in order to decide on a way forward. In these discussions, we were able to interpret how each factor modified the others, and how the personal circumstances under which a woman encountered the test affected the way she made her decision about what to do next.

Timing modulated accuracy and risk by changing the comparator technologies NIPT was being weighed against. For instance, women encountering NIPT early in pregnancy often compared the accuracy and risk of the test to IPS or FTS. The accuracy of NIPT compared very favorably to the other screening tests, "it's just light years beyond the IPS" (A2 A1 A1), especially with regards to the false positive and negative rate of those screening tests: "That was the ultimate deciding factor for me was that I wasn't comfortable with that 10% false negative rate [of FTS]" (A1). When considering NIPT in the first trimester, risk of test-associated miscarriage was not an important factor, due to the lack of risk associated with the screening

tests. Women who were considering NIPT in the second trimester compared it to amnio, typically assessing the test-associated risk of miscarriage as a much more important factor: “if you have 0 risk vs. any risk at all, why would I risk losing the pregnancy by potentially causing a spontaneous abortion by the amniocentesis and then find out everything was just fine?” (A2\$).

The importance of accuracy was modulated by timing. For women who were considering termination and facing the potential gestational age deadline for that procedure, accuracy and timing were very important interlinked factors. The later a woman was in pregnancy, the more likely she was to prefer an accurate test that would deliver results quickly, not wanting to risk running out of time and not having the option of termination available. “Because we were already so far along in the pregnancy, I couldn't wait any longer, I couldn't wait the 10 days for a non-conclusive test” (D1\$ A1). The understanding that confirmatory testing would be needed in the event of a positive NIPT result made women think more carefully about the accuracy of NIPT. Women considering NIPT late in the second trimester were more likely to emphasize the meaningful difference between the accuracy of NIPT and amniocentesis: “if my time wasn't ticking, I probably would have got that test [NIPT]. But I was already 20 weeks into my pregnancy, so I just wanted to know for sure.” (D2\$) Timing also modulated women's assessment of risk, with the risk of test-associated miscarriage less important to women who were later in pregnancy: “I'm sure that if it had been earlier in the pregnancy, and there would not have been that rush, this [NIPT] is definitely something I would have considered because it's risk-free” (D2\$)

Perceptions of the risk of miscarrying after amniocentesis were described by some women as changing with gestational age. For one woman, the perceived risk of testing-related miscarriage declined with advanced gestational age: "the chance of miscarrying with amnio that early in the pregnancy ... well, the percentage goes down significantly in 2 weeks so I was like, I can wait 2 weeks, do the DNA test [NIPT], if it still comes back with red flags, then we can do the amnio." (A2\$). For others, the perceived risk of testing-related miscarriage increased as gestational age advanced: "If there wasn't a risk factor there, I would have done it [amnio] for sure. I would like to know for sure. But just because we are so far along, the risk increases of bad things happening to your pregnancy, and so I had to make a decision on that." (A2\$)

For several women, their specific risk of having an affected pregnancy modulated the way they considered the test-associated risk of miscarriage. If the perceived risk of miscarrying was higher than the woman's personal risk of having an affected pregnancy, this was frequently cited as a justification for not choosing amniocentesis:

"It seemed very invasive and I forget if it was 1 in 300 or 1 in 350 but it worked out to be a higher risk of miscarriage from the amniocentesis than my child having one of the Down syndrome or trisomy 13 or 18. So I was like, why would I have that procedure if the risk is higher than actually having a child with one of those?" (A2\$)

Others mentioned that a very high risk of an affected pregnancy would make the test-associated risk of miscarriage more tolerable: "If they had told me I had a 1 in 3 risk of Trisomy 18, I probably would have jumped right to amnio" (A2\$).

Discussion

Interpretation of Results

From our participants' discussions of how they decided whether or not to pursue NIPT, we can understand their experiences and values about prenatal testing. These findings are consistent with quantitative studies that have found that women highly value the safety of NIPT, even over other factors they deem important such as the accuracy and timing of results (Hill, Fisher, Chitty, & Morris, 2012; Tischler, Hudgins, Blumenfeld, Greely, & Ormond, 2011); (Lewis, Hill, Silcock, Daley, & Chitty, 2014). Health care professionals and the general public may consider accuracy of NIPT to be more important than pregnant women do (Allyse, Sayres, Goodspeed, & Cho, 2014; Hill, Karunaratna, Lewis, Forya, & Chitty, 2013). The discrepancy found by previous studies between pregnant women's preferences and values for prenatal testing technologies and the preferences and values of clinicians and the general public highlights the unique way that pregnant women may be considering the compromises involved in choosing a prenatal test. Our study shows that women decide on a prenatal technology by choosing which aspects of the test to prioritize and which features they are willing to compromise based on their personal circumstances.

One potential compromise that women must consider is how much risk they are willing to assume, and what kind of risk. Our participants discussed their understandings of "risk" in many different ways. These discussions encompassed both clinical uses of the term, generally associated with numerical statistics that expressed the likelihood of association between two phenomena (e.g. undergoing an amniocentesis test and having a miscarriage) as well as more general meanings of the term, used by women to express the probability that an undesirable event would come to pass, such as test results proving incorrect, or anxiety and worry increasing with (or without) more information. Risk constructs are complex, socially constructed, and often

serve to identify what a particular socio-historical culture sees as negative or dangerous (Lupton, 1999; Lupton 2011). This constructed nature of risk has been well studied in many contexts, including prenatal screening (e.g. Heyman, Alaszewski & Brown, 2010; Hunt & deVoogd, 2003; Lippman, 1991; Lupton, 1999; Lupton 2011). In this study, we focus more narrowly on women's interpretations of numerical risk statistics and how these affect their decisions. Lay people (and many physicians) often lack the level of numeracy required to accurately interpret risk probabilities, and interpretations are further shaped by the personal significance of statistical information (e.g. Georgsson Ohman, Grunewald & Waldenstrom, 2009; Gigerenzer, et al, 2007; Gigerenzer & Gray 2011; Grimes & Snively, 1999; Keller & Siegrist, 2009; Miron-Shatz, Hanoch, Graef & Sagi, 2009). Our results suggest that women take very seriously the risk statistics they find, or are given. The decision of whether or not to pursue NIPT was described as balancing the personal risk statistic each woman is given (e.g. 1 in 100 risk of having an affected pregnancy) against the accuracy of each test (i.e. risk of receiving an incorrect result) and the risk of miscarriage after amniocentesis. Many participants referred to one or more of these risk statistics when explaining their decision-making process, sometimes drawing heavily on these statistics to justify their decision. Clearly, these risk statistics were very meaningful to our participants. However, the numbers several women quoted to us did not reflect clinically established figures. For instance, some women quoted the risk of miscarriage associated with amniocentesis as high as 5%, and others shared personal risk statistics that would not seem to qualify them for public funding. Beyond these relatively simple misunderstandings, many participants made qualitative statements which suggested that their interpretation of each statistic was very personal, and may not reflect the clinical community's understanding of that particular

risk. For example, many women who accepted NIPT did so because in their minds, the risk of miscarrying after amniocentesis was so high as to render that diagnostic test impossible to even consider. Others spoke at length about their personal risk of an affected pregnancy, offering a risk statistic that clinicians would likely consider very high, and describing it as not that worrisome. The offer of NIPT asks women to interpret and juxtapose several different types of risk: risk of carrying an affected fetus, risk of incorrect or inconclusive test results, risk of increased anxiety and stress if no further information was available about chromosomal status for the duration of their pregnancy. The different ways that women characterize and balance each of these types of risk highlights the personal nature of these decisions, and the difficulty with establishing universally meaningful risk thresholds for the purposes of making policy about NIPT. Policy makers will need to consider the variety of qualitative meanings women assign to risk and risk tradeoffs, in addition to the diversity in women's judgments of how "high" a given risk must be to justify testing and related services.

Data on clinical and demographic factors that are associated with NIPT uptake are still emerging; retrospective reviews of NIPT uptake have been conducted in Hong Kong and the United States (Chan et al., 2015; Chetty, Garabedian, & Norton, 2013; Larion et al., 2014; Taylor, Chock, & Hudgins, 2014; Vahanian et al., 2013). The studies led by Chetty (Chetty et al., 2013) and Chan (Chan et al., 2015) examined the uptake rates when NIPT was offered after an initial positive screening result for fetal aneuploidy, a comparable circumstance to that faced by many of our participants eligible for public funding. Both studies revealed that the availability of private-pay NIPT decreased the percentage of women declining all further testing and also decreased the percentage of women choosing invasive testing (Chan et al., 2015; Chetty et al.,

2013). Women in both jurisdictions were more likely to choose NIPT after a positive screen in the first trimester versus the second trimester (Chan et al., 2015; Chetty et al., 2013). Findings from Virginia, USA confirm this, showing that introducing NIPT decreased uptake of both CVS and amniocentesis, with a more significant decrease in amniocentesis rates, suggesting that women are more likely to choose NIPT when available in at an earlier gestational age (Larion et al., 2014). Hong Kong women who had an adjusted risk of Down Syndrome higher than 1:50 were more likely to choose amniocentesis or CVS than women with a lower level of adjusted risk (Chan et al., 2015). When NIPT was offered routinely to women at another California clinic, uptake was lower, but did increase amongst those who had higher levels of risk (Taylor et al., 2014). A third American clinic found that private insurance was the only factor associated with increased NIPT use (Vahanian et al., 2013). In general, these findings are congruent with the values expressed by our participants: women who were not considering invasive testing because of the associated risk of miscarriage felt more comfortable with NIPT, women identified the timing of results as a significant barrier to choosing NIPT late in the second trimester, and women considered their personal risk of having an affected pregnancy when deciding whether or not to accept invasive testing.

Policy Considerations

Women's priorities and values concerning the key features of prenatal testing technologies should be considered when making and implementing policy on NIPT coverage. These priorities and values are relevant to policy decisions about what prenatal tests to offer, to whom, and when. Currently, the values expressed by women in our study are incompatible with

the way that publicly funded NIPT has been implemented in Ontario. Specifically, the system is currently set up so that most women are offered NIPT after a high risk "screen positive" result from IPS. This results in most women being referred for additional testing well into the second trimester, requiring them to decide between the later and less accurate results of NIPT or the risk of miscarriage associated with amniocentesis. If NIPT was offered earlier in pregnancy, the comparator technologies (e.g. IPS, amniocentesis) would be different, and so would the exercise of prioritizing between accuracy, timing, and risk.

For the women in our study referred to NIPT earlier in pregnancy due to risk factors other than a positive screen (e.g. over 40 years at due date, previous trisomy pregnancy), the prioritization between accuracy, timing, and risk was different, and more satisfactory. For these women, the comparator technology was a first-tier prenatal screen such as IPS or FTS. When comparing NIPT to one of these tests, NIPT presented the opportunity to receive more accurate results earlier in pregnancy, creating a favorable situation and an easy decision to pursue NIPT over another screening test. Due to a grey area in funding, many women chose to pursue both NIPT and IPS, so they could receive the additional information about neural tube defects and placental dysfunction provided by IPS. This preference for earlier and more comprehensive information was also echoed by participants without known risk factors who chose to pay out of pocket in order to have earlier access to this technology. In their accounts, the improved accuracy and early results of NIPT were important enough to pay \$800-\$1000 to gain access to this technology. Professional guidelines are clear that NIPT has not yet established a sufficient evidence base regarding its accuracy in a low-risk population,(American College of Obstetricians and Gynecologists, 2012; Benn et al., 2013; Devers et al., 2012; Langlois & Brock, 2013)

although there are several trials currently ongoing with this population group (Centre Hospitalier Universitaire de Quebec, 2013). Many women expressed a wish to be offered NIPT early in pregnancy, regardless of risk status. However, evidence to justify the use of NIPT as a viable substitute for first tier prenatal screening in a general population is currently insufficient and equivocal (American College of Obstetricians and Gynecologists, 2012; Benn et al., 2013; Bianchi, Oepkes, & Ghidini, 2014; Bianchi & Wilkins-Haug, 2014; Gregg et al., 2013; Langlois & Brock, 2013).

One potentially justifiable way of offering NIPT earlier in pregnancy is to use an earlier determination of risk. Given the increased accuracy of NIPT, women and clinicians may find it acceptable to sacrifice the detection rate and false positive rate of first tier screening in order to offer earlier access to more accurate tests such as NIPT. Joann Johnson and colleagues have suggested that one way of doing this is to use First Trimester Screening (FTS) and widen the threshold of what counts as a "screen positive" (Johnson et al., 2013). This would result in an earlier detection of risk and earlier referral to NIPT. If referred after FTS, most women would gain access to NIPT between 12-14 weeks, giving more time to make decisions about pursuing further invasive testing. The higher false positive rate of FTS would mean that more women would receive an anxiety-provoking "screen-positive" result, but this result would be received earlier in pregnancy and the option of clarifying NIPT may assist in assuaging this anxiety. Our study and others indicate that earlier access is preferential to later access and NIPT is preferential to invasive diagnostic testing (Chan et al., 2015; Chetty et al., 2013; Larion et al., 2014). This potential use of NIPT would entail the disadvantage of assigning higher risk status to more women, which Heyman and colleagues have found may have negative psychosocial

consequences for some women, even after further tests suggest they are not at higher risk of chromosomal anomaly (Heyman et al., 2006).

Strengths and Limitations

This study is one of the first empirical qualitative examinations of the experiences and values of women who have had personal experiences with NIPT. To our knowledge, it is the first publication detailing women's personal experiences with publicly-funded NIPT. Ontario is one of the first jurisdictions to provide funding for this technology, and by speaking with some of the first women to experience NIPT under this new policy, we are able to provide guidance for other jurisdictions who are considering whether and how to fund NIPT.

This study describes the way that a particular group of women report their experience with NIPT. The women who participated in our sample were older and more educated than the average pregnant woman in our jurisdiction, and many had accessed genetic counseling, which may have resulted in their more thorough understanding of NIPT and the available testing options. The views expressed by the women in our study reflect experiences governed by a policy which is likely to shift and change as NIPT technology stabilizes and more evidence becomes available to inform policy decisions about the use of this technology. The comparator technologies and prenatal care pathway described by participants in our study are specific to the Ontario context; other jurisdictions may offer prenatal testing in a different way, resulting in a different set of decisions for women considering NIPT.

Implications for Future Research

Evidence on NIPT is still developing, including comparisons between the efficacy of different brands of NIPT, economic evaluations of NIPT, and effectiveness of NIPT in average risk populations. While this information will be important for jurisdictions considering whether and how to fund NIPT, those jurisdictions should also consider the social values of women who will be using this technology and the organizational implications of introducing this new technology. A holistic consideration of all of these factors will be needed for policy on the optimal implementation of NIPT within the prenatal care pathway. This holistic consideration should also examine the organizational, health human resources, and economic implications of different patterns of NIPT adoption.

Conclusion

This qualitative study solicited women's experiences with non-invasive prenatal testing during the first few months that publicly funded testing was available in Ontario. The values and opinions expressed about NIPT by women who have personal experience with this technology are inconsistent with the way it is has typically been implemented in Ontario so far. A revision of the current policy should consider this evidence that women value early access to accurate tests without associated risks of miscarriage when considering how and when NIPT should be implemented into the prenatal testing care pathway. These values can be used in future policy-making, to consider how NIPT may be integrated into the broader program of prenatal testing in Ontario in a way that is scientifically and economically sound, but also consistent with the values of patients.

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