Non-Invasive Prenatal Testing: Ethics and Policy Considerations

Meredith Vanstone, PhD,1 Carol King, MD,2 Barbra de Vrijer, MD, FRCSC,2
Jeff Nisker, MD, PhD, FRCSC, FCAHS2,3
1Department of Clinical Epidemiology and Biostatistics, Centre for Health Economics and Policy Analysis, McMaster University, Hamilton ON
2Department of Obstetrics and Gynecology, Schulich School of Medicine and Dentistry, Western University, London ON
3Children’s Health Research Institute, London ON

Abstract
New technologies analyzing fetal DNA in maternal blood have led to the wide commercial availability of non-invasive prenatal testing (NIPT). We present here for clinicians the ethical and policy issues related to an emerging practice option. Although NIPT presents opportunities for pregnant women, particularly women who are at increased risk of having a baby with an abnormality or who are otherwise likely to access invasive prenatal testing, NIPT brings significant ethics and policy challenges. The ethical issues include multiple aspects of informed decision-making, such as access to counseling about the possible results of the test in advance of making a decision about participation in NIPT. Policy considerations include issues related to offering and promoting a privately available medical strategy in publicly funded institutions. Ethics and policy considerations merge in NIPT with regard to sex selection and support for persons living with disabilities.

INTRODUCTION
Recent advances in the detection and analysis of fetal DNA in maternal blood have led to the commercial availability of a new type of prenatal screening known as non-invasive prenatal testing.1,2 NIPT promises the detection of a number of genetic and chromosomal conditions in the first trimester of pregnancy, obviating the risk of miscarriage that accompanies invasive prenatal diagnostic procedures such as amniocentesis or chorionic villus sampling.1–3 While NIPT is not generally publicly funded in Canada, it is readily available to patients through a number of avenues, including placing information pamphlets and test kits in health care settings such as obstetrical units in hospitals and private clinics. NIPT has been shown to have a high negative predictive value, and it is plausible that Canadian jurisdictions may choose to provide public funding for NIPT in the future.4–6

NIPT has been recommended by the Society of Obstetricians and Gynaecologists of Canada7 and professional bodies in several other countries8–11 as a second level contingent screening test for women at risk for trisomy 13, 18, and 21, followed by amniocentesis to confirm positive tests. Scientists and professional bodies have clearly stated that while NIPT is significantly more accurate than existing screening methods, it is not sufficiently sensitive or specific to be considered a diagnostic test.12,13 NIPT
has also been proposed as a replacement for a first level screening test in both high and average risk populations and as a diagnostic test of single gene disorders. We provide here an overview of the science, health policy, and ethical implications that clinicians will want to understand regarding a new technology that they are increasingly being requested to engage with by patients and manufacturers.

**CLINICAL SCIENCE**

Non-invasive prenatal testing is a new type of prenatal screening test for genetic and chromosomal conditions. It is typically performed by measuring cell-free fetal DNA in maternal plasma, allowing the examination of fetal genetic material in a sample of maternal blood. Most of the current research and clinical application focuses on the use of NIPT for the detection of aneuploidy, in particular trisomies 13, 18, and 21, as NIPT offers a higher detection rate and lower false-positive rate than current screening modalities such as first trimester screening and integrated prenatal screening (Table). Clinical research has suggested a wide variety of other potential uses for NIPT, with varying degrees of evidence to support the clinical effectiveness of these uses. There are clinical trial results supporting the use of NIPT for the detection of fetal RhD status, selected gestational conditions (e.g., restricted growth), and fetal sex determination. Preliminary studies suggest that it has promise for detecting autosomal dominant paternally inherited disorders (e.g., Huntington disease), conditions arising from a de novo mutation (e.g., achondroplasia), and recessive conditions when parents carry different mutations (e.g., cystic fibrosis) but large clinical trials have yet to be conducted for these uses. Applications in earlier stages of development include testing for recessive conditions when parents carry the same mutation (e.g., β-thalassemia). Two teams have now sequenced an entire fetal genome, meaning that in the future any genetic condition might be identified by NIPT.

Since 2011, more than 10 independent large-scale clinical trials have been published assessing the use of NIPT to detect trisomies 13, 18, and 21, with many additional studies currently underway. Most trials used a population of women considered at high risk for trisomy; the results were consistent, with NIPT detection rates of more than 98% to 99%, and false-positive rates of less than 0.3%, for the detection of trisomy 21. The cfDNA detection rate for trisomy 18 is 97% to 100%, with a false-positive rate of 0.07% to 0.8%. These results suggest that NIPT is superior to existing prenatal screening modalities for trisomy testing in high risk populations (Table). Investigations are currently under way to assess the use of NIPT in average-risk populations. The largest study published thus far of average-risk women who underwent routine prenatal screening for aneuploidies reported a detection rate of 100% and a false-positive rate of 0.1% for NIPT. These authors concluded that NIPT is applicable to the general population, in which the prevalence of aneuploidy is much lower. Studies in smaller average-risk populations have reported very similar results.

Most commonly, NIPT measures cell-free fetal DNA in maternal blood. Cell-free nucleic acids, discovered in 1947, are present in maternal plasma. These molecules are being investigated for their potential to act as pregnancy-specific biomarkers for preeclampsia and fetal growth restriction. Another potential avenue for NIPT is the analysis of genes known to be expressed in the extravillous trophoblasts that have undergone programmed cell death. NIPT techniques other than cfDNA measurement are currently being studied, but are still under development and have not been tested in clinical populations. Developing techniques for NIPT include placental microRNA analysis. Placental microRNAs are small single-stranded noncoding RNA molecules present in the maternal plasma. These molecules are being investigated for their potential to act as pregnancy-specific biomarkers for preeclampsia and fetal growth restriction. Another potential avenue for NIPT is the analysis of genes known to be expressed in the extravillous trophoblasts that have undergone programmed cell death. Through the detection of cfDNA fragments of fetal Y-chromosomes in the blood of women carrying male fetuses. NIPT techniques other than cfDNA measurement are currently being studied, but are still under development and have not been tested in clinical populations. Developing techniques for NIPT include placental microRNA analysis. Placental microRNAs are small single-stranded noncoding RNA molecules present in the maternal plasma. These molecules are being investigated for their potential to act as pregnancy-specific biomarkers for preeclampsia and fetal growth restriction. Another potential avenue for NIPT is the analysis of genes known to be expressed in the extravillous trophoblasts that have undergone programmed cell death.

**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>cfDNA</td>
<td>cell-free fetal DNA</td>
</tr>
<tr>
<td>CVS</td>
<td>chorionic villus sampling</td>
</tr>
<tr>
<td>FTS</td>
<td>first trimester screen</td>
</tr>
<tr>
<td>IPS</td>
<td>integrated prenatal screen</td>
</tr>
<tr>
<td>NIPT</td>
<td>non-invasive prenatal testing</td>
</tr>
</tbody>
</table>

CfDNA is primarily derived from the placenta, the fetal hematopoietic system, and the fetus itself. The circulating cfDNA has a turnover half-life of 16.3 minutes (4 to 30 minutes), and is continuously released into the maternal circulation, providing a real-time snapshot of fetal DNA.
DNA regions.

specific DNA fragments, rather than the global analysis of
techniques that allow for more selective analysis of
make the test more efficient and less expensive through the
sequencing strategies continue to be developed, seeking to
adequate counts of the chromosome of interest. Newer
and so millions of fragments need to be sequenced to ensure
approach is not selective of the chromosome sequenced,
when a false-negative result is received.

unwanted or unanticipated births of children with aneuploidy
challenges of our current prenatal screening program,
to all women may alleviate some of the most common
Bianchi and colleagues suggest that offering NIPT screening
Clinical Utility of NIPT

production and clearance. Current NIPT strategies for
detection of fetal aneuploidy using cffDNA originated from the
development of massively parallel sequencing
techniques. By mapping and aligning short sequence tags of

cell-free DNA found in maternal plasma to a reference
human genome, these tags could be counted to determine
chromosome ploidy status. For instance, if there is an
increase in the relative number of tags on the affected
chromosome compared to the euploid chromosome,
this would be consistent with trisomy. However, this
approach is not selective of the chromosome sequenced,
and so millions of fragments need to be sequenced to ensure
adequate counts of the chromosome of interest. Newer
sequencing strategies continue to be developed, seeking to
make the test more efficient and less expensive through the
use of techniques that allow for more selective analysis of
specific DNA fragments, rather than the global analysis of
DNA regions. So far, newer sequencing strategies have not
compromised the robustness of the test.

Clinical Utility of NIPT

Bianchi and colleagues suggest that offering NIPT screening to
to all women may alleviate some of the most common
challenges of our current prenatal screening program,
including the fetal loss associated with invasive testing and
unwanted or unanticipated births of children with aneuploidy
when a false-negative result is received. Many women
may choose to use NIPT after receiving results from the
first trimester screen (where available), either because their
jurisdiction offers FTS instead of IPS, or because deciding to
proceed with NIPT after FTS allows a woman to access
an earlier result from the test, avoiding the need to complete
the second trimester portion of IPS. While FTS has a higher
false-positive rate than IPS, the addition of NIPT alleviates
this concern. Using NIPT after a positive result from FTS
allows a woman more time to make a decision about whether
or not to terminate her pregnancy, and allows access to an
earlier pregnancy termination, which may be less physically
risky and less emotionally traumatic.

NIPT does not have an upper limit for gestational age,
which means it can still be used by women who present
late for their first prenatal visit; such women otherwise
may be able to access only screening modalities with lower
sensitivity and specificity rates, such as the triple
or quadruple serum screens. Undergoing NIPT
is associated with significantly less fear of pain and
discomfort than amniocentesis or CVS. NIPT may be
more available, as blood can be drawn by a nurse, and CVS
or amniocentesis are challenging procedures that require
the skills of a specialist physician with specific training
and experience. NIPT may be appealing to women for
several reasons, including the lack of risk of miscarriage,
early availability of results, and high reliability of the results.
NIPT may be appealing to women who do not
wish to terminate their pregnancy in the event of a positive
trisomy result, but who wish to have more information so
they can begin to prepare for an affected child. NIPT may
also be appealing as a preliminary step in helping women to
decide whether or not they wish to pursue invasive testing,
since invasive testing is recommended to confirm positive
NIPT results.

NIPT also has many limitations. First, it is typically
available in Canada only privately or through a clinical
trial, which results in inequitable access. The issue
of access is discussed below, and may change in the
future. Other limitations of the test include test failures,
unclear results due to mosaicism, false-positive results
(0.1% to 0.2%), and the need for repeat testing by
amniocentesis. Test failures may be caused by a low
fetal fraction, unsuitable specimens, or failed quality
control. NIPT may not be as accurate in overweight or
obese patients because of a lower fetal fraction, even with
multiple repeats of the test. The “fetal fraction” is the
mean circulating amount of cffDNA in maternal serum;
typically, the fetal contribution to overall circulating free
DNA is about 10%. A fetal fraction of at least 4% is
required for adequate screening, as a low fetal fraction

<table>
<thead>
<tr>
<th>Screening option</th>
<th>Gestational age, weeks</th>
<th>Detection rate, %</th>
<th>False-positive rate, %</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trimester screening</td>
<td>11+0 to 13+6</td>
<td>87 to 90</td>
<td>5</td>
<td>NT, βhCG, PAPP-A, MA</td>
</tr>
<tr>
<td>Integrated prenatal screening</td>
<td>11+0 to 13+6 (part 1)</td>
<td>87 to 95</td>
<td>2 to 5</td>
<td>NT, PAPP-A, AFP, uE₂, βhCG, inhibin A, MA</td>
</tr>
<tr>
<td>Quad screening</td>
<td>15+0 to 19+6 (part 2)</td>
<td>81</td>
<td>5 to 7</td>
<td>AFP, uE₂, βhCG, inhibin A, MA</td>
</tr>
<tr>
<td>Non-invasive prenatal testing</td>
<td>10+0 to term</td>
<td>&gt; 98</td>
<td>&lt; 0.3</td>
<td>Cell-free fetal DNA in maternal plasma</td>
</tr>
</tbody>
</table>

could lead to false-negative results. For this reason, most NIPT test providers recommend testing after 10 weeks’ gestation; if the fetal fraction is too low at 10 weeks, the test can be repeated at a later gestational age. The fetal fraction has been found to be decreased in women with higher BMI and in women of Afro-Caribbean descent, leading to more frequently inconclusive results in these populations.\textsuperscript{45} Special counselling on this issue should be provided to overweight or obese women considering NIPT, because the time needed to use (and potentially repeat) NIPT may mean that other testing modalities can no longer be used if NIPT is ultimately unsuccessful. While NIPT has very similar sensitivity and specificity rates to CVS, it is less accurate than amniocentesis. There is preliminary evidence of efficacy of NIPT in multiple pregnancy, but at present it is recommended only for singleton pregnancy.\textsuperscript{77}

Currently, the results of NIPT take up to 10 days to receive, which may be longer than the wait time for results of integrated prenatal screening, amniocentesis, and CVS in many jurisdictions. When used after first trimester screening, NIPT results will still be available earlier than those of any other kind of screening, but if offered after a high-risk result from completed IPS, the seven- to 10-day wait for results may be unacceptable or undesirable for women. It is also important to consider the information that NIPT (unlike other screening modalities) does not provide, such as information about cardiac anomalies (increased nuchal translucency), placental insufficiency/preeclampsia risk, and neural tube defects (second trimester blood sample).\textsuperscript{69,78} For these reasons, NIPT may be most effectively integrated with existing screening programs, although that would increase the cost significantly. As with IPS, the purpose of offering NIPT is to provide women the opportunity to acquire information about their fetus, so that they can either prepare to raise an affected child or have the opportunity to terminate the pregnancy. It is important to counsel women explicitly about what options (e.g., preparation for the birth of an affected child, pregnancy termination) are available in the event of a confirmed trisomy.\textsuperscript{79,80}

**Public Opinion of NIPT**

Several projects have solicited patient and public views of NIPT.\textsuperscript{51-80} Surveys have shown that most women would be interested in obtaining NIPT (72%), although a significant minority (28%) were ambivalent or uninterested.\textsuperscript{81} Another study of patients showed insurance coverage for NIPT was the only significant factor associated with acceptance of the test.\textsuperscript{49} Safety was a commonly cited reason in support of the test, with women willing to accept longer wait times and less accurate results for a test which was safe for mother and fetus.\textsuperscript{81,83,84} Patients and members of the public all expressed some reticence about the test in relation to themes of societal implications, discrimination against people with disabilities, and potential eugenic purposes.\textsuperscript{81-83} A recent study of Hong Kong women who had paid privately for NIPT confirmed many of these motivations, finding that most women chose NIPT because of risk factors such as maternal age, previous affected pregnancy, or after a high-risk result from initial screening (>1:250).\textsuperscript{76} The women provided many reasons for undergoing NIPT, including confirmation of uncertain results from initial screening, reassurance after negative screening results, the safety of the procedure compared with amniocentesis, and the ability to gain access to earlier information and potentially earlier termination.\textsuperscript{76}

**EXISTING POLICY GUIDELINES**

NIPT is currently not publicly funded in most jurisdictions in Canada, despite the fact that it has better detection rates and false-positive rates than publicly funded forms of prenatal screening (Table). Although for most Canadian women NIPT is not publicly funded, the SOGC has recommended that NIPT (with confirmatory amniocentesis in the event of a positive result) be “an option available” to women at high risk of trisomy 13, 18, and 21.\textsuperscript{7}

Similar recommendations have been made by the American Congress of Obstetricians and Gynecologists,\textsuperscript{8} the International Society for Prenatal Diagnosis,\textsuperscript{9} and the National Society of Genetic Counselors.\textsuperscript{10} All of these organizations cite the lack of trial evidence in average-risk women as a barrier to recommending NIPT for all pregnant women. This lack of evidence may soon be ameliorated, as there are currently large-scale clinical trials under way in the general population of pregnant women.\textsuperscript{85} The American College of Medical Genetics and Genomics has not limited their recommendation to women at high risk for fetal aneuploidy, a position also taken by the health insurer Blue Cross.\textsuperscript{11,86} The Royal Australian and New Zealand College of Obstetricians and Gynaecologists is working on updating their statements on prenatal screening tests to address NIPT.\textsuperscript{87} In 2009 the Royal College of Obstetricians and Gynaecologists published a scientific paper on the topic, which is currently under review, and commissioned a report from the Foundation for Genomics and Public Health.\textsuperscript{88,89} New scientific and clinical advances in NIPT may necessitate clinical policy to be revised to consider other potential uses of this test, at other points in pregnancy, or for other conditions.\textsuperscript{78,90,91}
ETHICS AND POLICY CONSIDERATIONS

Equity of Access

The ethical implications of recommending NIPT when it is available only to patients who can afford to pay are important for future policy considerations in public health care systems. When NIPT is available only to those who can afford to pay, two types of inequity of access may occur: inequity of access to the NIPT technology itself, and, in some instances, preferential access to related services, typically in the form of access at an earlier gestational age. In simpler terms, patients who can afford to pay for NIPT can access a better test and can also have access to other related services at an earlier gestational age, which typically means less risk (physical and psychological) to the mother and less physical risk to the fetus. Patients who cannot afford to pay for NIPT are excluded not only from the test but also from earlier access to other publicly funded services, such as counselling and pregnancy termination. The relevant ethical principles are equity (fairness), and the Canadian commitment to accessible health care. Early access to publicly funded services after private NIPT means that the health care system implicitly enables different care between patients on the basis of their economic privilege.

We are not arguing that private access to NIPT results in a higher burden to the health care system. In fact, economic and other analyses show that this is not necessarily the case; NIPT may actually save money for the health care system, especially when patients pay for it privately. Rather, we argue that if NIPT is an important and beneficial technology, it should be available to all patients. Additionally, privately procured NIPT should not be used to facilitate preferential access to publicly funded services that are not available without NIPT. For instance, NIPT may facilitate preferential access in the form of longer counselling sessions or pregnancy termination at an earlier gestational age. That is not to say that it is bad for patients to receive more counselling or earlier termination; indeed, this is a significant benefit and should be available to all patients, regardless of their ability to pay for NIPT. This situation is analogous to patients who pay for MRIs at private clinics to expedite the next phase of their care. These patients eventually receive the same treatment as they would have if they had not paid; indeed, they save the health care system money by paying for the MRI and potentially gaining quicker access to treatment, which may result in fewer complications and an easier rehabilitation process. We may sympathize with these patients, as quicker care is preferable to longer waits. However, a commitment to equity means that it is not fair for people with economic means to have access to better or faster health care than those who cannot afford to pay. We do not suggest, however, that clinicians should try to curtail the private use of NIPT. Rather, we suggest that further clinical and funding policy on NIPT is needed, and that policy should consider the principle of equity when determining whether NIPT should be made available to all women.

Informed Decision-Making

Prenatal testing in Canada is grounded on the principle of informed choice, which insists that each woman should have the opportunity to obtain as much information as she needs to make decisions about her pregnancy. Information should be provided in a comprehensive and easily understandable manner, and accompanied by the opportunity to ask questions for clarification. This ethical principle is in keeping with our societal commitment to reproductive autonomy and is often presented as the differentiating factor between choice for genetic testing and eugenics. Informed choices are those that are “based on relevant knowledge, consistent with the decision-maker’s values and behaviourally implemented,” and so require the commitment of adequate resources to ensure that each woman receives the “relevant knowledge” required to make the decision.

NIPT, like other types of prenatal testing, requires consideration of three ethical challenges related to the issue of informed choice. These are:

1. What resources are required to support informed choice about NIPT?
2. What if a woman’s informed choice runs counter to our societal expectations, such as in the case of sex selection? and
3. How do we resolve the tension between individual choice and the public good?

We provide here an overview of each of these ethical issues as it relates to NIPT.

Promoting Individual Informed Choices

When we consider what resources are required to support informed choices, we refer to two categories of resources:

1. informational resources, to ensure that women have sufficient comprehensible information needed to make a decision about whether or not to do the test, and what to do with the results; and
2. material and social resources, to support the choice each woman wishes to make.

There is an extensive literature about promoting informed choice in the context of integrated prenatal screening and invasive prenatal testing (CVS, amniocentesis). Many of
the challenges to informed choice in those contexts are also applicable to NIPT, including lack of information, the most significant source of decision-making difficulty.\textsuperscript{99} Lack of information may stem from insufficient, incorrect, or confusing information given by the clinician offering the test,\textsuperscript{100–103} as a result of time constraints,\textsuperscript{104–106} inadequate clinician knowledge,\textsuperscript{103,107,108} or insufficient effort to include women in the decision-making process.\textsuperscript{109} Facilitating informed choice is not as simple as providing the “right” information. There is not necessarily a correlation between the level of knowledge a woman has about prenatal testing and her report of whether or not the information she received was sufficient for decision-making.\textsuperscript{110–113} This may be explained by other studies showing that, in this context, women and clinicians have different information priorities.\textsuperscript{97,214–217} Given these challenges, it is not surprising that health care providers may find it difficult to facilitate a conversation about informed choice in the context of prenatal testing.\textsuperscript{118}

NIPT does not alleviate these challenges to informed decision-making, and potentially adds further complications.\textsuperscript{119,120} For instance, direct-to-consumer marketing of NIPT typically compares the test with amniocentesis or CVS, but, as emphasized by several authors, NIPT has not demonstrated sufficient accuracy to be deemed fully diagnostic; comparing it directly with amniocentesis or CVS may be misleading.\textsuperscript{12,13} While nuanced discussions of test accuracy pose a challenge to even the most educated patients, there are several features of NIPT which may be easier to explain to patients: there is only one component to the test and it does not use likelihood ratios, which some have described as the “completely random and quite illogical cut-off levels” used in IPS to distinguish between low, average, and high risk of aneuploidy.\textsuperscript{4} An NIPT result is clearer—it either shows extremely low risk of aneuploidy (<1 in 10,000) or very high risk, requiring less time to explain and leaving more time for discussing the suspected condition and options available.\textsuperscript{4,12} While the simplified procedure has positive implications for informed decision-making, it may also have negative implications.\textsuperscript{120} There is reason to believe that women may feel more obligated to participate in NIPT because there is no physical risk.\textsuperscript{121–123} The risk for miscarriage associated with invasive testing is a major concern of women offered invasive diagnostic tests such as amniocentesis\textsuperscript{124}, describing this physical risk is seen as an important part of informed consent for current testing procedures and can be used by some women as a physician-accepted justification to refuse testing.\textsuperscript{120,125–127} Additionally, NIPT complicates the question of when informed decision-making should occur. In the current system of prenatal screening, limited pre-test counselling is offered with more extensive counselling available if a high-risk result is returned. Numerous studies have critiqued this model, pointing out that the current system results in decisions that cannot be considered “informed.”\textsuperscript{99,93,106,112,128–133} With NIPT, if the bulk of counselling takes place before the test, the resources required to conduct this counselling will increase dramatically.\textsuperscript{71,91,121} Because NIPT is a single test rather than a multi-step procedure such as IPS, there may be less time for counselling and for the patient to comprehend and process the implications of the information.\textsuperscript{99} Tischler’s survey of pregnant women showed that nearly all women (95%) indicated interest in talking to a genetics counsellor before (32%), after (48%), or both before and after (14%) NIPT.\textsuperscript{81} Therefore, a key aspect of the ethical implementation of NIPT will be developing approaches to counselling and providing information to facilitate informed choice.\textsuperscript{69,108}

The second component of an informed choice is the opportunity to implement the decision.\textsuperscript{95} As we consider expanding prenatal testing and the concomitant requirement to allocate more resources to this program for the purpose of expanding and supporting informed choice, a critical examination of the concept of choice is warranted. Scholars committed to the ethical theory of relational autonomy ask what informed choice really means when the options available and the context within which these choices will be enacted are constructed by others.\textsuperscript{134,135} In other words, when we provide an individual woman with a set of options, are those all the available options? Are all of these options available to that particular woman, or do her circumstances prevent her from choosing within the full complement of options available to other individuals? Considering the ethics of informed choice through the lens of relational autonomy is useful for drawing attention to the social and political context in which the choices we offer to patients are constructed.\textsuperscript{136,137} Traditional conceptions of autonomy tend to consider the decision-maker as an isolated individual, ignoring the context or situations in which that person makes decisions.\textsuperscript{138} A relational conception of autonomy strives to consider the influence of the social and political structures, as well as personal and public relations, on the availability and feasibility of different options.\textsuperscript{139,140} For example, the decisions made by policy-makers, researchers, and clinicians will affect what information is created, deemed relevant, and made available to women, thereby shaping what constitutes the “relevant knowledge”\textsuperscript{98} used for an informed decision. Likewise, the policy decision to allocate more resources to prenatal screening may mean that there is less pressure to allocate resources to social and medical programs to help people who have the tested-for conditions live to their full potential.\textsuperscript{134,141–143} The theoretical lens of relational autonomy is also useful in guiding clinicians towards...
facilitating conversations of informed choice and shared decision-making, by encouraging the woman to share more information about her family and social situation and how that particular circumstance might affect her decision-making about her pregnancy.\textsuperscript{137,144,145}

**NIPT and Disability**

When prenatal testing programs are predicated on the value of promoting individual choice and encouraging reproductive autonomy, there is an inherent tension between individual interests and societal values. The individual choices that women make regarding prenatal screening affect the make-up of our society, decreasing the visibility of people with certain conditions. Many scholars have argued that a systematic bias against people with disabilities is embedded in the structure and practice of prenatal testing programs, creating a subtle directive to test and terminate.\textsuperscript{134,140,146–149} Given current termination rates for pregnancies found to have aneuploidy, it is reasonable to expect that as prenatal testing options expand, the number of people with the tested-for conditions will decrease, especially when new testing options, such as NIPT, remove existing barriers to termination, such as gestational age.\textsuperscript{150}

As the number of people with disabilities decreases, it is likely that acceptance, support, and resources afforded to these people may also decrease as they (and their families, friends, and advocates) become less visible and less vocal.\textsuperscript{84,112} Indeed, regardless of changing incidence or visibility of people with disability, the authority conferred on prenatal screening programs from increasing availability of testing may contribute to social stigmatization.\textsuperscript{151} The societal effects of prenatal screening programs have been recognized by the public. When members of the public have been asked for their opinions of prenatal and pre-implantation testing, a common opinion has been that the enhancement of individual choice is positive, but society should be cautious of the broader impact of the technology.\textsuperscript{81–83,132–155}

The societal effects of prenatal testing on people with disabilities have been well-covered in the literature on non-invasive prenatal screening and invasive prenatal testing. NIPT poses an additional ethical challenge—for what conditions should we test? Currently, most clinical and commercial applications of NIPT detect conditions that are already included in the existing system of prenatal screening and testing, such as trisomies 13,18, and 21.\textsuperscript{15} However, NIPT has been proven clinically effective for detecting conditions that are not currently included, and it shows promise for detecting many more conditions.\textsuperscript{31} If NIPT continues to be procured through private sources, Canadian policy-makers may have no jurisdiction over regulating the conditions that are included in this test. If some jurisdictions in Canada decide to provide public funding for NIPT, they will likely choose which conditions will be covered for testing. It remains to be seen whether or not patients will be able to pay to detect additional conditions.

**Sex Selection**

NIPT has shown high clinical effectiveness in detecting fetal sex as early as nine weeks’ gestation.\textsuperscript{33,36} This use is already included in most commercially available tests, and clinicians may encounter requests for termination on the basis of fetal sex after a patient has privately obtained an early NIPT.

Individual interests and social values are also in tension around the issue of sex selection. Concerning the rights and interests of the individual patient, ethical principles include respect for an individual’s autonomy, including the right to personal health information (such as genetic information about her fetus) and the right of a woman to terminate a pregnancy for whatever reason she chooses. Following this reasoning, sex selection via NIPT and termination is congruent with reproductive autonomy and informed choice. However, sex selection is not generally congruent with our societal values of equality and non-discrimination on the basis of sex or gender.\textsuperscript{156} This has been codified into the *Assisted Human Reproduction Act*, addressing sex selection of embryos and strongly prohibiting anything “which would ensure or increase the probability that an embryo will be of a particular sex, or that would identify the sex of an in vitro embryo, except to prevent, diagnose, or treat a sex-linked disorder or disease.”\textsuperscript{157} The SOGC has issued two policy statements regarding sex selection. One states that “medical technologies and/or testing for the sole purpose of gender identification in pregnancy should not be used to accommodate societal preferences. . . . The SOGC does not support termination of pregnancy on the basis of gender.”\textsuperscript{158} A second, on the topic of fetal sex determination and disclosure, acknowledges that some women wish to know the sex of the fetus for the purpose of sex selective termination. The policy statement does not prohibit disclosure of this information, nor does it offer any practical guidance for clinicians, suggesting only that this information is a woman’s personal health information and that the issue of sex selection “is best addressed by the health professionals who are providing care for these women.”\textsuperscript{159}

The challenge for clinicians is to navigate requests for terminations on the basis of fetal sex that contravene professional obligations (as described in the SOGC policy statements) but are congruent with a woman’s right to
reproductive autonomy. Some have made suggestions about how this might be done within the existing system of prenatal screening tests, including simply not noting the fetal sex on the ultrasound report and thereby avoiding the obligation to disclose that information to the patient, or not disclosing fetal sex until a “gestational age at which abortion is not permitted.” These suggestions provide a practical “work around” for clinicians, but they do not resolve the ethical tension inherent in this issue, and they will not apply to NIPT because this technology allows pregnant women to pay to obtain information about fetal sex before the end of the first trimester.

CONCLUSION

NIPT offers significant opportunities for patients and clinicians to obtain accurate early information about a pregnancy, with low physical risk to the mother or fetus. Both growing demand and research studies indicate that women are enthusiastic about this new opportunity. The SOGC has issued a position statement supporting the use of NIPT for women at high risk of fetal aneuploidy, to be confirmed with invasive testing. However, as a private-pay service this test is not available to all women, and others may choose to use it in ways not recommended by the SOGC. Ethical issues pertaining to counselling to facilitate informed decision-making, sex-selection, and equity of access will follow the expansion of NIPT. As access to this technology expands (whether it is funded privately or publicly), additional policy guidance will be needed to help clinicians navigate these important issues.

ACKNOWLEDGEMENTS

Meredith Vanstone’s salary is funded by the Ontario Ministry of Health and Long-Term Care through a Health System Research Fund grant entitled “Harnessing Evidence and Values for Health System Excellence.” The views expressed in the article are the views of the authors and should not be taken to represent the views of the Ontario Ministry of Health and Long-Term Care.

The authors thank Kyoko Wada for assistance reviewing international policy statements about NIPT.

REFERENCES


44. Hui L, Bianchi DW. Recent advances in the prenatal interrogation of the human fetal genome. Trends Genet 2012.


