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Prenatal Care Providers' Experience With Pre-test Counselling for NIPT in Ontario: Counselling Challenges and Support Required

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A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Health and Rehabilitation Sciences

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Abstract

Non-invasive prenatal testing (NIPT) is a prenatal test that has experienced unprecedented commercial development and transformed prenatal care. The Ontario Ministry of Health presently funds NIPT as a first-tier prenatal screening option for high-risk singleton pregnancies and all twin pregnancies. Individuals who do not qualify for public funding or would like to screen for additional conditions can pay for NIPT privately, starting at approximately \$495-\$550 (CA) for baseline panels. Prenatal care providers such as family physicians, maternal-fetal-medicine specialists, obstetrician-gynaecologists, residents, midwives and registered nurses have an increasingly important role in offering NIPT in Ontario. Although these healthcare professionals do not have a specific genetic focus to their practice, little research exists exploring their experience of being at the forefront of counselling for this technology. This dissertation explores how these prenatal care providers in Ontario provide counselling for NIPT within their clinical practice.

Charmaz's constructivist grounded theory methodology was used to explore how prenatal care providers have enacted the process of prenatal pre-test counselling since the introduction of NIPT in Ontario. A total of 19 providers who encounter NIPT professionally in the Ontario cities of London, Hamilton, Toronto and Kingston participated in this study. The resulting theoretical model describes how providers experience pre-test counselling considerations for NIPT, including challenges, ethical considerations, and patient engagement in decision-making. To address these issues and effectively counsel patients about this expanding technology requires ongoing education, support and resources.

Findings suggest practical, educational, and ethical inequalities between current NIPT panel options and prenatal care providers' comfort and ability to provide pre-test counselling. Prenatal care providers require ongoing guidance and support as their role in prenatal screening is shifting to involve more complex counselling for NIPT. It is also essential to be proactive and develop supportive strategies to help providers navigate this technology's rapid expansion in the future.

Keywords

Non-invasive prenatal testing, Non-invasive prenatal screening, Pre-test counselling; Prenatal Care Providers, Non-genetic healthcare professionals, Non-genetic healthcare providers

Summary for Lay Audience

Non-invasive prenatal testing (NIPT) is an optional screening test that can tell a pregnant person if they have a high or low chance of having a baby with certain chromosome differences, including trisomy 21 (Down syndrome), trisomy 18, trisomy 13 and Turner syndrome. These chromosomal differences involve changes in a fetus's genetic material, which can lead to serious physical and developmental challenges. NIPT involves a maternal blood draw at 9-10 weeks of pregnancy and is funded in Ontario for all pregnant individuals who meet specific Ministry of Health criteria. Individuals can also pay for this test if they do not qualify for public funding.

Pre-test counselling involves giving information about the benefits and limitations of testing and addressing any potential medical, reproductive, and psychosocial implications of genetic test results. When NIPT in Ontario became publicly funded in 2014, healthcare professionals trained in genetics, such as genetic counsellors, provided counselling to facilitate a patient's decision to undergo NIPT. Since then, many prenatal care providers not specialized in genetics, including family physicians, maternal-fetal-medicine specialists, obstetrician-gynaecologists, midwives and registered nurses, discuss NIPT during a prenatal care visit. However, there is concern that patients are not receiving adequate counselling due to barriers such as time constraints and a provider's lack of knowledge about this technology. In addition, NIPT counselling is becoming more complex as screening expands to include more conditions and is used for non-medical purposes such as sex identification.

This research explores how prenatal care providers in Ontario provide pre-test counselling for NIPT within their clinical practice. I interviewed 19 providers from the Ontario cities of London, Hamilton, Toronto, and Kingston in 2016. From these interviews, I used the methodology "constructivist grounded theory" (as described by Kathy Charmaz) to generate a theoretical model. This model describes the practical, educational, and ethical issues between current NIPT panel options and these prenatal care providers' comfort and ability to provide pre-test counselling. These providers require ongoing guidance and support as their role in prenatal screening is shifting to involve more complex counselling for NIPT.

Co-Authorship Statement

Leichelle Little completed this dissertation under the supervision of Dr. Barbra de Vrijer and Dr. Marilyn Evans.

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Glossary of Terms

Accuracy:	The overall percentage of correct test results. This includes true positives and true negatives (Maxim et al., 2014).
Aneuploidy:	Describes the condition where trisomy or monosomy occurs due to an error in meiosis or mitosis (cell division). The incidence of fetal aneuploidy increases with maternal age (Rink & Norton, 2016).
Autosome	Refers to any of the 22 (numbered) chromosomes, not a sex chromosome (X or Y) (Nussbaum et al., 2007).
Cell-free DNA (cfDNA)	Extracellular DNA that exists in the bloodstream of all individuals (Lo et al., 1997).
Cell-free fetal DNA (cff-DNA)	Extracellular DNA of fetal origin that exists in the bloodstream of pregnant individuals. Used in NIPT screening (Lo et al., 1997).
Chorionic villus sampling (CVS):	An invasive procedure of obtaining a small piece of placental tissue. This tissue contains fetal cells that can be used for diagnostic testing purposes, such as a karyotype . This procedure has a risk of pregnancy loss of about 1% or less (Akolekar et al., 2015).
Chromosome:	Biological structures that are comprised of DNA and proteins and carry genetic information in the cells of living organisms (Nussbaum et al., 2007).

Clinical utility:	To what extent a test improves health outcomes compared to the current alternative (which could be another form of testing or no testing at all) (Lesko et al., 2010).
Clinical validity:	How well the test performs: this is dependent on the test's sensitivity, specificity, positive predictive value, and negative predictive value (Burke, 2014).
Congenital:	Present from birth (Nussbaum et al., 2007).
Deoxyribonucleic acid (DNA):	Deoxyribonucleic acid (DNA) is a chemical that contains within its structure the genetic information needed to specify all aspects of the formation and development of a human (Nussbaum et al., 2007).
Diagnostic test:	Either a test which has 100% sensitivity and 100% specificity , or a test whose performance characteristics are high enough to allow a conclusive diagnosis without causing serious concern for a clinical error (Benn et al., 2012).
Disorders of sex determination:	Congenital conditions associated with abnormal development of internal and external genital structures (Nussbaum et al., 2007).
Enhanced first-trimester screen ((e)FTS):	A prenatal screening test which involves measurements from maternal, fetal, and placental analytes (hormones or proteins) in a pregnant individual's blood and a first-trimester NT ultrasound. Performed between 11 weeks 2 days to 13 weeks 3 days gestation pregnancy, results of this blood work, ultrasound and individual's age at delivery (or the age of the egg donor) provides a risk estimate of having a fetus with trisomy 21 and trisomy 18 (Nussbaum et al., 2007).

False-negative:	When an individual with the disease is misclassified as not having the disease (Maxim et al., 2014).
False-negative rate (FNR):	The proportion of affected individuals with a negative result (Nussbaum et al., 2007).
False-positive:	When an individual without the disease is misclassified as having the disease (Maxim et al., 2014).
False-positive rate (FPR):	The proportion of unaffected individuals who have a positive result (Nussbaum et al., 2007).
Genes:	Functional units of genetic information. Genes are made up of DNA . (Nussbaum et al., 2007).
Gonads:	The reproductive gland that produces an organism's gametes and sex hormones, such as the ovary in females or the testicles in males (Nussbaum et al., 2007).
In vitro fertilization (IVF) with intracytoplasmic sperm injection:	A patient's eggs (oocytes) are surgically removed from the ovaries and fertilized in a laboratory through the injection of live sperm into the oocyte (Nussbaum et al., 2007).
Integrated Prenatal Screening (IPS):	A prenatal screening test which was available in Ontario in 2016. It involved measurements from maternal, fetal, and placental analytes (hormones or proteins) in a pregnant individual's blood and a first-trimester NT ultrasound. IPS required two separate blood tests. Blood was drawn between 11-14 weeks in the first trimester and at 15-20 weeks in the second. IPS results were not released until the second trimester blood draw was analyzed at 16 -

21 weeks (Mt. Sinai Hospital, 2007). In 2018, (e)FTS replaced IPS in Ontario.

- Karyotype:** A procedure which produces an image of an individual's **chromosomes** (Nussbaum et al., 2007).
- Maternal serum screen:** A prenatal **screening test** which analyzes maternal, fetal, and placental analytes (hormones or proteins) in a pregnant individual's blood. Performed between 14 and 20 weeks six days of pregnancy, results of this blood work combined with the individual's age at delivery (or the age of the egg donor) can provide a risk estimate of having a fetus with trisomy 21 and trisomy 18 (Nussbaum et al., 2007).
- Microdeletion:** Smaller deletions in **DNA** that are 1-3 million base pairs in size (the chemical building blocks of genetic material) (Nussbaum et al., 2007).
- Monosomy:** The loss of one member of a pair of **chromosomes** (Nussbaum et al., 2007).

Multiple marker Screening:	Overall term to describe prenatal screening test . These tests measure maternal, fetal, and placental analytes (hormones or proteins) in a pregnant individual's blood and, if the individual is undergoing (e)FTS, an NT ultrasound. Results of this screening, combined with the individual's age at delivery (or the age of the egg donor) can provide a risk estimate of having a fetus with trisomy 21 and trisomy 18. The two maternal serum screening tests available in Ontario are the enhanced first trimester screen ((e)FTS) and maternal serum screen . At the time of this study (e)FTS was not available, and the integrated prenatal screen (IPS) was offered (Nussbaum et al., 2007).
Mutation:	A change in the sequence of DNA (Nussbaum et al., 2007).
Negative predictive value (NPV):	The probability that subjects with a low-risk/negative screening result truly do not have the disease (Mennuti et al., 2013).
Neural tube defects:	Birth defects of the brain, spine or spinal cord (Nussbaum et al., 2007)
Non-invasive prenatal testing (NIPT):	Prenatal screening method that detects the cell-free DNA in the blood of pregnant individuals to determine the risk that a fetus will be born with certain genetic abnormalities (Lo et al., 1997).
Prenatal Care Providers	Professionals who do not specialize in genetics, and have not received advanced training in this field. For this particular study, these professionals are referring to family physicians, maternal fetal medicine specialists, obstetrician- gynaecologists, residents, midwives and a registered nurse.

Nuchal translucency (NT):	A measurement of fluid accumulation between the skin and soft tissue of the fetal neck. An increased nuchal translucency can be correlated with a greater chance of having a fetus with trisomy 21, trisomy 18 or another chromosomal abnormality. Healthy pregnancies can also have increased NT (Nussbaum et al., 2007). The prenatal screening test, (e)FTS , includes the analysis of nuchal translucency (NT).
Penetrance:	The probability that a particular mutation will have any phenotypic expression at all. When there is reduced penetrance, a proportion of individuals who carry a mutation will not exhibit a characteristic phenotype (Nussbaum et al., 2007).
Phenotype:	The observable expression of a person's genetic information in the form of morphological or clinical traits (Nussbaum et al., 2007).
Plasma:	Component of blood that does not contain cells. It contains elements such as water, proteins, clotting factors and nutrients (Nussbaum et al., 2007).
Positive predictive value (PPV):	Probability that subjects with a high-risk/positive screening result truly have the disease (Mennuti et al., 2013).
Prevalence:	The proportion of the population that have a specific disease and/or characteristic in a given time period (Nussbaum et al., 2007).
Screening test:	A medical test or procedure performed on a defined asymptomatic population (or population subgroup) to assess the likelihood that these members have a particular disease (Maxim et al., 2014).

Sensitivity (detection rate):	A test's ability to correctly identify an individual with a disease as positive. If a test is highly sensitive, there are few false-negative results, and therefore it will rarely miss subjects with the disease (Maxim et al., 2014).
Serum:	The clear to yellowish coloured fluid in the blood that does not contain white or red blood cells, but does contains substances such as electrolytes, antibodies and hormones (Nussbaum et al., 2007).
Sex-limited disorders:	Mutations in genes that are not on the sex chromosomes, but whose presentation is influenced by the sex of the individual (Shawky, 2014).
Specificity:	A test's ability to correctly identify an individual who doesn't have a disease as negative. High specificity tests have few false-positive results (Maxim et al., 2014).
Trisomy:	The addition of an extra chromosome (Nussbaum et al., 2007).
True negative:	When the individual with the disease is properly classified as having the disease (Maxim, Niebo, & Utell, 2014).

Chapter 1

1 Introduction

Clinical practice guidelines by the Society of Obstetricians and Gynaecologists of Canada and the Canadian College of Medical Genetics (SOGC-CCMG) recommend that all pregnant people in Canada should be offered, through an informed pre-test counselling process, the option of prenatal screening for common fetal aneuploidies (Audibert et al., 2017). Guidelines recommend that this aneuploidy screening is discussed early in pregnancy (ACOG-SMF, 2020; Audibert et al., 2017). Therefore, patients usually first discuss prenatal genetic screening with their prenatal care provider. These providers can include obstetricians, midwives, family physicians or other primary obstetrical care providers (Minkoff & Berkowitz, 2014; Farrell, Nutter & Agatista, 2015; Farrell et al., 2016; Best Start, 2020). For the remainder of this thesis, the term “prenatal care providers” will denote healthcare professionals who provide care to individuals during their pregnancy but do not specialize in genetics.

Non-invasive prenatal testing (NIPT) is a relatively new form of testing representing a significant evolution of prenatal screening technology. This method includes a single blood draw from the pregnant person and is an alternative screening method for fetal aneuploidy. NIPT can be performed at 9-10 weeks of pregnancy, up until the time of birth (Lo et al., 1997; Wright et al., 2012; Wright & Burton, 2009), with results available within 5-10 working days (Natera, 2021a; Dynacare, 2020a). Since its implementation, there has been a considerable uptake of publicly funded NIPT in Ontario (Dougan et al., 2021), with prenatal care providers becoming more involved in the pre-test counselling process for this test (Larion et al., 2014; McLennan et al., 2016; Gregg et al., 2016). This dissertation presents a constructivist grounded theory study exploring how prenatal care providers experience NIPT pre-test counselling and how they have integrated this technology into their prenatal practice. Insight into the opinions and experiences of providers who do not specialize in genetics can proactively inform what interventions are

required to help these professionals counsel for increasingly complex genetic testing in the future.

1.1 Types of Prenatal Screening

Screening, in general, refers to the process of using specific markers and defined screening cut-off levels to identify individuals in a population at a higher risk for a particular disorder (McCormack et al., 2013). Various prenatal screening tests are available in Ontario (Table 1). These tests screen for different fetal and maternal conditions, depending on what fetal, placental or maternal factors are analyzed. Depending on the test, prenatal screening can be performed during the first trimester, second trimester, or both. Prenatal screening can identify pregnant individuals at risk for having a fetus with three common aneuploidies: trisomy 21 (Down syndrome), trisomy 18 or trisomy 13 (Pandya et al., 2019; Rink & Norton, 2016). For this thesis, individuals who have a “high-risk” screening result refer to those at an increased risk for trisomy 21, 18 or 13 based on certain screening criteria established by the Ministry of Health (MOH) in Ontario (see Appendix A).

Although most of these aneuploid pregnancies are not viable, fetuses with trisomy 21, 18, 13 can survive to term with medical and developmental consequences. These trisomies are associated with growth retardation, intellectual disability, and multiple congenital anomalies (Nussbaum et al., 2007). Trisomy 21 is the most common trisomy and the single most common genetic cause of moderate intellectual disability with an average life expectancy of over 50 years. Approximately 1 in 850 children are born with trisomy 21 (Nussbaum et al., 2007). Table 2 summarizes the prevalence and common features of these aneuploidies.

1.1.1 Multiple Marker Screening

Enhanced first-trimester screening ((e)FTS) and maternal serum screening are examples of multiple marker screens. (E)FTS is performed between 11 weeks two days and 13 weeks three days gestation, while maternal serum screening is performed between 14 and 20 weeks six days of pregnancy (Audibert et al., 2017). These prenatal screens include

the analysis of maternal, fetal, and placental analytes (hormones or proteins) in a pregnant individual's blood (Nussbaum et al., 2007). Concentrations of these analytes can be correlated with an increased chance of having a fetus with trisomy 21 or trisomy 18. (E)FTS also includes the analysis of nuchal translucency (NT) using prenatal ultrasound. NT is a measurement of the fluid accumulation between the skin and soft tissue of the fetal neck. An increased NT (above 3.5 mm) can also be correlated with an increased chance of having a fetus with trisomy 21 or trisomy 18. Results of either the (e)FTS or serum screen, in combination with the individual's age, are used to determine the risk of someone having a fetus with trisomy 21 and 18 (Audibert et al., 2017). Certain thresholds determine if the final result is reported as a "screen positive" or "screen negative." For example, a "screen negative" result for multiple marker screening in Ontario means the chance that a pregnancy is affected with trisomy 21 is less than 1 in 350 (PSO, 2019a).

Multiple marker screens can also give information that guides pregnancy management, as abnormal screening results can also be a marker for fetal and obstetric complications (Dugoff, 2010). For example, abnormal analyte readings alone can be associated with fetal loss (Duric et al., 2003), fetal growth restriction, preeclampsia (increased blood pressure during pregnancy), placental abruption, preterm delivery (Dugoff et al., 2005; Dugoff et al., 2004; Chandra et al., 2003; Audibert et al., 2017; Katz et al., 1990). In addition, increased nuchal translucency is associated with fetal cardiac defects (Hyett et al., 1996). However, the performance metrics of abnormal analyte readings (such as sensitivity and positive predictive value, discussed below) are not high enough for any serum analyte to be recommended as a screening test for adverse pregnancy outcomes (Dugoff, 2010; Heazell et al., 2015).

It is important to note that the analytes used in second trimester marker screening can identify neural tube defects, whereas first trimester marker screening (e)FTS does not. Neural tube defects are birth defects of the brain, spine, or spinal cord (Nussbaum et al., 2007). These defects are a leading cause of stillbirth, death in early infancy and disability in surviving children (Nussbaum et al., 2007). If abnormal markers do identify a risk for fetal or obstetric complications, follow-up ultrasound examination for growth or further monitoring of fetal heart rate may be considered (ACOG-SMFM, 2020).

1.1.2 Prenatal Ultrasound

1.1.2.1 First Trimester Ultrasound

Ultrasound has a vital role in prenatal screening. Regardless of screening choice, guidelines recommend offering all pregnant individuals a first-trimester ultrasound (optimally between 11-14 weeks) in order to confirm details such as fetal viability, gestational age and number of fetuses (Audibert et al., 2017; ACOG, 2016; Norton et al., 2017). First-trimester ultrasound provides an early anatomic assessment and, therefore, could detect major structural anomalies (Nussbaum et al., 2007). These fetal abnormalities can be associated with the common aneuploidies or occur as isolated findings in a chromosomally normal fetus (Nussbaum et al., 2007). First trimester ultrasound can detect neural tube defects (Engels et al., 2016; Meller et al., 2017).

The first trimester ultrasound also includes an NT scan (PSO, 2018). In addition to trisomy 21 and 18, an increased NT can also be associated with structural malformations such as congenital heart defects, abdominal wall defects, and fetal akinesia (impaired fetal movement) (Audibert et al., 2017). An increased NT can also be observed in fetuses with Noonan syndrome, a condition characterized by heart defects, unusual facial features, skeletal malformations and possible developmental delays (Suskin et al., 2016). Many guidelines recognize the importance of measuring NT due to these clinically adverse conditions (Lee et al., 2015; Audibert et al., 2017; ACOG-SMFM, 2020; Salomon et al., 2017; Gregg et al., 2016). If a patient declines (e)FTS, they can still choose to have an NT ultrasound performed, where available (PSO, 2018).

1.1.2.2 Second Trimester Ultrasound

A second trimester ultrasound between 18-22 weeks is a routine part of prenatal care in Ontario. It provides an assessment of fetal organ systems, including the heart, kidneys, bladder, stomach, brain, sex organs, the amniotic fluid levels, location of the placenta, and fetal heart rate (Audibert et al., 2017; Rink & Norton, 2016). SOGC-CCMG guidelines recognize the second trimester ultrasound as the primary screening test for detecting fetal structural abnormalities (Audibert et al., 2017). Guidelines recommend

that all pregnant individuals be offered a second trimester ultrasound to screen for fetal structural defects regardless of first trimester prenatal screen results (Audibert et al., 2017; Gregg et al., 2016; American College of Obstetricians and Gynaecologists, 2016). Second trimester ultrasonography is the least effective primary screening test for trisomy 21, as it detects only 50-60% of affected fetuses. Therefore, ultrasonography alone should not be used to screen for trisomy 21 (Audibert et al., 2017).

Importantly, this ultrasound also includes detailed fetal cranial and spinal imaging and assessment to detect neural tube defects, such as spina bifida, which occurs when the spine and/or spinal cord doesn't close properly (Nussbaum et al., 2007). Spina bifida includes gradual loss of nerve function, which can present as bladder, bowel and sexual dysfunction and loss of motor function in the lower extremities (Gotha et al., 2020). This condition is one of the most common congenital anomalies, with an incidence of 1 in 3,000 to 4,000 pregnancies (De Wals et al., 2008).

1.1.3 Cell-free DNA Screening

NIPT is a prenatal screening test that detects cell-free DNA (cfDNA) in the plasma of pregnant individuals. As genomic DNA is released from dying cells into the bloodstream, DNA fragments from placental cells are detectable in the plasma of pregnant individuals during pregnancy. Cell-free fetal DNA (cff-DNA) is abundant, stable, and stays in maternal circulation for a few days after each pregnancy (Sayres & Cho, 2011). Therefore, maternal plasma contains the entire fetal genome (Kitzman et al., 2012), originating from apoptotic trophoblasts (placenta cells undergoing programmed cell death) from the embryo (Tjoa et al., 2006; Alberry et al., 2007). Circulating cfDNA of fetal origin comprises approximately 13% of the total cfDNA found in plasma (Nygren et al., 2010). Different companies offering NIPT will report aneuploidy risk in diverse ways. For example, some report risks as “positive” or “negative” while others report “>99%” as high-risk and “<1/10,000” as low-risk (Skrzypek & Hui, 2017).

Table 1*Comparison of available prenatal screening tests in Ontario*

Screening test	NIPT (Provincially funded labs)			
	Multiple Marker Screening (e)FTS	MSS	Panorama™ by Natera	Harmony™ by Roche
Gestational age at time of screen	11 weeks 2 days - 13 weeks 3 days	14 weeks - 20 weeks 6 days	9 weeks to term	10 weeks to term
Time to result	~5 business days	~5 business days	5-7 calendar days	7-10 business days
Components of screen	Maternal blood work First-trimester U/S	Maternal blood work only	Maternal blood work only	Maternal blood work only
Conditions screened	T21 T18 NT	T21 T18 NT ONTD	<u>Basic panel</u> T21 T18 T13 SCAs (no opt-out) Fetal sex (opt-in) Triplody (no opt-out)	<u>Basic panel</u> T21 T18 T13 SCAs (opt-in) Fetal sex (opt-in)

Table 1 (continued)*Comparison of available prenatal screening tests in Ontario*

Screening test	NIPT (Provincially funded labs)			
	Multiple Marker Screening		Panorama™ by Natera	Harmony™ by Roche
	(e)FTS	MSS	<u>Additional Options</u>	<u>Additional Options</u>
Conditions screened (continued)	Fetal and obstetric complications		22q11.2 deletion syndrome Microdeletion extended panel*	22q11.2 deletion syndrome
Overall sensitivity	T21: 86.3% T18: 76.8%		T21: 99.8% T18: 94.4%	
Specific sensitivities based on test type/provincial lab	T21: 88.8% T18: 78.2%	T21: 80.6% T18: 60.0%	T21: >99% T18: 98.2% T13: >99% Monosomy X: 94.7% 22q11.2 deletion syndrome: 90% Microdeletion extended panel*: 93.8% to >99%	T21: >99% T18: 97.4% T13: 93.8% Monosomy X: 94.3% 22q11.2 deletion syndrome: None given

Table 1 (continued)*Comparison of available prenatal screening tests in Ontario*

Screening test	NIPT (Provincially funded labs)			
	Multiple Marker Screening (e)FTS	MSS	Panorama™ by Natera	Harmony™ by Roche
False-positive rates**	T21: 5.1%	T21: 6.7%	T21: 0%	T21: <0.1%
	T18: 0.5%	T18: 0.2%	T18: <0.1%	T18: <0.1%
			T13: 0%	T13: <0.1%
			Monosomy X: <0.1%	
			Each	22q11.2
			Microdeletion	deletion
			syndrome:	syndrome:
			<1%	None given

Note. The data for the gestational age at time of screen, time to result, components of screen, conditions screened for, specific sensitivities and false-positive rates for multiple marker screening tests (including MSS and (e)FTS) are from Ontario’s Birth Outcome Registry Network (BORN) PSO, 2019 (<https://www.bornontario.ca/en/pso/results-and-next-steps/multiple-marker-screening-mms-results.aspx>). Data for the Panorama™ NIPT test are from Natera™, 2021 (<https://www.natera.com/womens-health/panorama-nipt-prenatal-screening/>). Data for the Harmony™ NIPT test are from Roche, 2021 (<https://www.harmonytest.com/global/en/nipt-test-for-expecting-parents-cell-free-dna.html>). The overall sensitivity data is adapted from “Performance of a universal prenatal screening program incorporating cell-free fetal DNA analysis in Ontario, Canada, 2021” by S. D. Dougan, N. Okun, K. Bellai-Dussault, L. Meng, H. E. Howley, T. Huang, J. Reszel, A. Lanes, M.C. Walker and C.M. Armour, 2021. *Canadian Medical Association Journal*, 193(30), E1156–E1163. (<https://doi.org/10.1503/cmaj.202456>).

MSS= Maternal serum screen, T21=trisomy 21, T18= trisomy 18, T13= trisomy 13 NT= Nuchal Translucency, ONTD= Open neural tube defects, U/S= Ultrasound, SCA =Sex chromosome aneuploidy.

*Panorama extended panel includes 1p36 deletion, 15q11–q13 deletions (Angelman syndrome and Prader-Willi syndrome) and 5p deletion.

** Systematic reviews suggest a higher false-positive rate than those reported by the manufacturers (Badeau et al., 2017; Varela-Lema et al., 2018; Iwarsson et al., 2017; Taylor-Phillips et al., 2016).

In addition to trisomy 18 and 21, NIPT can screen for trisomy 13 and sex chromosome aneuploidies (SCAs) involving the X or Y chromosome. Trisomy 13 occurs in approximately 1 out of 10,000 newborns (Driscoll & Gross, 2009), with a clinical presentation (phenotype) that includes central nervous system malformations and congenital heart defects. Survival beyond the first year is rare (Nussbaum et al., 2007; Gregg et al., 2013).

Individuals with SCAs can have variable phenotypes, with some not even receiving a diagnosis due to a lack of any overt clinical features or receiving a diagnosis (Skuse et al., 2018; Luthardt & Keitges, 2001; Demaliaj et al., 2018). Examples of SCAs include Turner syndrome (monosomy X) and Klinefelter syndrome (XXY). Turner syndrome occurs in approximately 1 in 2500 to 4000 female births and may cause up to 10% of all first trimester miscarriages (Morgan, 2007). This syndrome is associated with short stature, a webbed neck, and an increased risk of cardiac abnormalities. Features can also include gonadal dysgenesis, the complete or partial loss of gonadal development, delayed maturation, impaired social adjustments, and infertility (Morgan, 2007; Demaliaj et al., 2018). Klinefelter syndrome is the most commonly occurring SCA, with an incidence of approximately 1 in 600 male births (Ross et al., 2012). Features of Klinefelter syndrome can include tall stature, reduced verbal IQ, educational difficulties, infertility, hypogonadism (a decreased function of the testes), and azoospermia (the absence of sperm) (Ross et al., 2012; Demaliaj et al., 2018).

NIPT can also determine fetal sex as early as seven weeks gestation (Devaney et al., 2011; Finning & Chitty, 2008; Costa et al., 2002). NIPT for fetal sex determination has been used to ascertain the risk of transmission of X-linked genetic disorders, such as Duchenne muscular dystrophy (Parks et al., 2016) and hemophilia (Hudecova et al., 2017; Tsui et al., 2015). NIPT's determination of fetal sex also has implications for screening individuals at risk for sex-limited disorders and disorders of sex determination. Sex-limited disorders are conditions where the sex of the individual influences the clinical presentation; however, the changes (mutations) in genes responsible for these conditions are not located on the sex chromosomes (Shawky, 2014). Disorders of sex determination are congenital conditions associated with abnormal development of internal and external genital structures (Nussbaum et al., 2007).

In addition to aneuploidy screening, some laboratories provide expanded NIPT options for microdeletion syndromes. A microdeletion is the deletion of a small piece of a chromosome. These deletions are 1-3 million base pairs, the chemical building blocks of DNA, in size (Nussbaum et al., 2007). These deletions' exact size and location can vary, but a specific critical region involving a particular gene(s) is usually involved (Nussbaum et al., 2007). The phenotype of these individuals is due to the absence of these critical regions.

Microdeletion syndromes are inherited, occur randomly during gamete development, or occur early in fetal development (Nussbaum et al., 2007). Microdeletion syndromes can have severe clinical presentations, including developmental delay, intellectual disability, seizures and congenital heart defects (Nussbaum et al., 2007). However, like SCAs, microdeletion syndromes can result in phenotypic variability and uncertain clinical significance (Wapner et al., 2012). Some conditions may be undetected until adulthood or completely remain undetected (Gillentine et al., 2018). Clinically relevant microdeletions and duplications overall occur in 1.7% of all structurally normal pregnancies (Wapner et al., 2012).

Common microdeletion syndromes include 22q11.2 (DiGeorge syndrome), 1p36 deletion, 15q11–q13 deletions (Angelman syndrome and Prader-Willi syndrome), and 5p

deletion (Cri-du-chat syndrome) (Hall, 2015). These microdeletions are individually rare, but the combined at-birth incidence of these five syndromes is approximately 1/1,000 (Buiting, 2010; Dagli et al., 1998; Driscoll et al., 2017; McDonald-McGinn et al., 2020, 2021). The potential to provide early interventions for individuals affected by these five syndromes are the primary considerations for choosing them for expanded testing (Hu et al., 2019; Benn, 2016). Table 2 summarizes the common features of the conditions that NIPT can screen for.

Table 2

Frequency of chromosomal abnormalities included on commercial NIPT screening tests

Condition	Prevalence in newborns	Common features (Present from birth)
<i>Autosomal chromosome aneuploidies:</i>		
Trisomy 21 (Down syndrome)	1 in 800 Most common autosomal chromosome aneuploidy in live births Frequency strongly dependent on maternal age	Intellectual and developmental disabilities, neurological features, heart defects, gastrointestinal abnormalities, characteristic facial features
Trisomy 18 (Edwards syndrome)	1 in 5,000 More common in fetuses that do not survive to term Frequency increases with maternal age	Growth deficiency, characteristic craniofacial features, distinctive hand posture, short sternum, heart malformations

Table 2 (continued)*Frequency of chromosomal abnormalities included on commercial NIPT screening tests*

Condition	Prevalence in newborns	Common features (Present from birth)
Autosomal chromosome aneuploidies		
Trisomy 13 (Patau syndrome)	1 in 16,000 Frequency increases with maternal age	Cleft lip and/or cleft palate (inappropriate formation of lip or roof of mouth), cerebral defects, anophthalmia (missing one or both eyes), polydactyly (extra fingers)
Monosomy X (Turner syndrome)	1 in 2,000-2,500 (females) More common in fetuses that do not survive to term	Short stature, webbed neck, heart defects, impaired social adjustments, gonadal dysgenesis, delayed maturation, infertility
XXY syndrome (Klinefelter syndrome)	1 in 500-1,000 (males) Most common sex chromosome aneuploidy	Tall stature and reduced verbal IQ (low to normal range), educational difficulties, infertility, hypogonadism, azoospermia
Sex chromosome aneuploidies		
XXX syndrome	1 in 1,000 (females)	Earlier growth, auditory processing disorders, disorders in language development and problems in forming stable interpersonal relationships

Table 2 (continued)*Frequency of chromosomal abnormalities included on commercial NIPT screening tests*

Condition	Prevalence in newborns	Common features (Present from birth)
Sex chromosome aneuploidies		
XXY syndrome	1 in 1,000 (males)	Tall stature, macrocephaly (large head), macroorchidism (increase of testicular volume), hypotonia (decreased muscle tone) and tremor
Microdeletion syndromes		
15q11-q13 deletion of genes in regions on chromosome 15 (Prader-Willi syndrome)	1 in 10,000-30,000	Obesity, delayed motor and language development, cognitive impairment, hypogonadism (incomplete pubertal development and infertility), short stature, characteristic facial features
15q11-q13 deletion of gene UBE3A on chromosome 15 (Angelman syndrome)	1 in 12,000-20,000	Severe developmental delay, intellectual disability, severe speech impairment, gait ataxia (uncoordinated walking), unique behaviour of frequent laughing, microcephaly (small head), seizures
22q11.2 deletion syndrome (DiGeorge)	1 in 4,000	Congenital heart disease, immune deficiency, characteristic facial features, learning difficulties, hearing loss

Table 2 (continued)*Frequency of chromosomal abnormalities included on commercial NIPT screening tests*

Condition	Prevalence in newborns	Common features (Present from birth)
Microdeletion syndromes		
5p deletion syndrome (Cri-du-chat)	1 in 20,000-50,000	High-pitched cry, microcephaly, broad nasal bridge, micrognathia (lower jaw is smaller than normal) and severe psychomotor, mental retardation
1p36 deletion syndrome	1 in 5,000-10,000	Developmental delay, intellectual disability, seizures, vision problems, hearing loss, short stature, distinctive facial features, brain anomalies, cleft lip and/or cleft palate, heart defects, renal anomalies

Note. Adapted from “Genetics home reference”, by the U.S. National Library of Medicine, 2021 (<https://medlineplus.gov/genetics/>).

The landscape of NIPT is rapidly evolving. Commercial laboratories already provide expanded testing beyond the microdeletion syndromes mentioned above, including testing larger deletions and trisomies 16 and 22 (Dynacare, 2020b). These conditions can lead to complex, severe fetal anomalies (Bianchi & Chiu, 2019). NIPT has also been used to detect genetic abnormalities such as achondroplasia, the most common nonlethal skeletal dysplasia (prevalence of 1/26,000- 1/28,000 births) (Waller et al., 2018). This testing has also been used to screen for single-gene conditions such as sickle-cell anemia (Barrett et al., 2012; Tsui et al., 2015), β -thalassemia (Lam et al., 2012) and cystic fibrosis (Bustamante-Aragones et al., 2008). NIPT is not currently clinically offered for these conditions; however, its use will likely expand to include additional chromosomal

abnormalities as future studies support the clinical validity of this application (Devers et al., 2013; Ngan, 2018).

Sequencing of the fetal genome indicates that NIPT could detect a more comprehensive range of genetic disorders, including the detection of milder conditions and traits (Fan et al., 2012; Blumenthal-Barby et al., 2015; Hui & Bianchi, 2013; Benn & Chapman, 2016; Lo et al., 2010). Private testing is also becoming more affordable. For example, Invitae™ offers NIPT for approximately \$125 (CA) (Invitae, 2021) and companies such as SneakPeak® offers NIPT for fetal sex screening for \$80 (US) (SneakPeak, 2021).

1.2 Benefits and Limitations of Prenatal Screening

When evaluating whether a prenatal screening test is appropriate, stakeholders, including clinicians, healthcare policymakers and patients, must balance the benefits and harms of prenatal screening (Dondorp et al., 2015). These aspects are directly affected by the performance measures of the test itself (clinical validity) and whether the test is reliable and useful to patients (clinical utility) (Gregg et al., 2016; Burke, 2014).

Clinical validity of the screening test is the extent to which a test measures what it is supposed to measure; essentially, it is the accuracy with which a laboratory test identifies individuals with a clinical condition (Holtzman & Watson, 1999). Clinical validity is defined by sensitivity and specificity and is independent of the prevalence of the condition being screened (Gregg et al., 2016). Sensitivity and specificity are helpful when determining which test to implement and for ensuring a quality screening system with high performance (Dougan et al., 2021). For example, sensitivity, or detection rate, is the proportion of affected individuals (or pregnancies) with a positive test result; this is considered a “true positive” (Burke, 2014). Specificity is the percentage of unaffected individuals who have a negative result, or “true negative.” (Burke, 2014). The false-positive rate (FPR) is the proportion of unaffected individuals with a positive result. The false-negative rate (FNR) is the proportion of affected individuals with a negative result (Nussbaum et al., 2007). A highly sensitive test will identify a high percentage of affected individuals and not generate many false-negative results. For example, a test

with 90% sensitivity will correctly return a positive result for 90% of affected individuals and return a false-negative result for 10% of affected individuals (Parikh et al., 2008).

In the decision-making process towards NIPT, patients and providers bestow great importance on the accuracy of testing (Beulen et al., 2015; Carroll et al., 2013; Chen et al., 2017; Chen et al., 2018; Farrell, Agatista & Nutter, 2014; Lewis et al., 2014; Lewis et al., 2016a; Lund et al., 2018; Seror et al., 2019; Skutilova, 2015; van Schendel et al., 2016; Lewis et al., 2012a; Lewis et al., 2013; van Schendel et al., 2014; Kibel & Vanstone, 2017; Lau et al., 2016; Farrell, Agatista, Mercer, et al., 2015; Vanstone, Yacoub, Giacomini, et al., 2015). NIPT has a high detection rate for trisomy 21 compared to other forms of prenatal screening. For example, the overall sensitivity of multiple marker screening for trisomy 21 is approximately 86.3% (Dougan et al., 2021). Conversely, the sensitivity for detecting trisomy 21 for NIPT is greater than 99% (Dougan et al., 2021). It is important to note that different sensitivity rates exist depending on the condition screened. For example, the overall sensitivity for trisomy 18 is 77% for maternal serum screen, and 94% for NIPT (Dougan et al., 2021). The FPR of (e)FTS for trisomy 21 is approximately 5.1% (PSO, 2019b) and the FPR for trisomy 21 is lower for NIPT than other prenatal screening tests at <0.1% (Roche, 2021). The sensitivities of the various microdeletion extended panels varies from 94% to greater than 99% (Lifelabs, 2019). Table 1 lists additional performance measures for these tests.

There is a chance that the results of an NIPT screen would not solely represent the genetic makeup of the fetus, which may lead to false-positive results (Amant et al., 2015; Pandya et al., 2019). As the fetal DNA tested originates mainly from the placenta, there could be a discrepancy between the DNA of the cells in the placenta and the fetus's cells, an anomaly known as confined placental mosaicism (CPM) (Nussbaum et al., 2007). The presence of a chromosome abnormality in the placenta with normal fetal DNA occurs in approximately 1-2% of NIPT cases (Audibert et al., 2017).

Studies have shown a 0.9- 5.6% chance that the initial NIPT test performed reports a “no result,” which means the test has failed and requires a repeat blood draw (Bianchi et al., 2014; Langlois et al., 2017; Nicolaides et al., 2013; Norton et al., 2015; Palomaki et al.,

2017; Quezada et al., 2015; Song et al., 2013). A repeat screen has shown to be successful in 45% to 77% of these cases (Langlois et al., 2017; Palomaki et al., 2017; Quezada et al., 2015). A no result outcome is unique to NIPT, as traditional prenatal screening tests rarely report out a failed result (Benn et al., 2013). An NIPT test may fail for several reasons, such as insufficient cf-DNA in the maternal sample, often referred to as a low “fetal fraction.” A low fetal fraction is one of the most common reasons for failure (Health Quality Ontario, 2019a). NIPT test failure may occur due to maternal obesity or if the test is performed too early in pregnancy (Lyons et al., 1988; Health Quality Ontario, 2019a). Fetal aneuploidy is also associated with low fetal fraction and failed NIPT results (Pergament et al., 2014). Therefore, patients with failed NIPT screens are at an increased risk (approximately 5%) for fetal aneuploidy (Norton et al., 2012; Pergament et al., 2014; Norton et al., 2015).

Clinical utility includes considering the test metrics positive predictive values, negative predictive values, cost, and a patient’s value system towards testing (Gregg et al., 2016). Positive predictive values (PPV) and negative predictive values (NPV) of a test are important measures of clinical utility. These measures are helpful when determining how reliably a test can confirm or refute a suspected diagnosis and the chances of returning a correct result (Audibert et al., 2017; Burke, 2014). PPV is the proportion of individuals with a positive test result who are true positives. Conversely, NPV is the proportion of individuals with a negative test result who are true negatives (Burke, 2014). Importantly, the disease prevalence in the population tested strongly influences the predictive values. Therefore, a test with high sensitivity could still have low positive predictive values and yield a greater number of false-positive results when screening individuals with a low likelihood of disease (Burke, 2014; Audibert et al., 2017). As the prevalence of trisomy 21, 18 and 13 varies in a high-risk population, the PPV will be variable for each condition. For example, the chance that a positive screening test result is true positive for NIPT screening in trisomy 21 has been reported to be 93% compared to 64% for trisomy 18 and 44% for trisomy 13 in a high-risk population (Wang et al., 2015).

The positive predictive value is especially relevant when considering the benefits and limitations of prenatal screening in a population at low risk for aneuploidy. The lower

prevalence of the aneuploidy leads to a lower PPV in the general population. Thus, fewer individuals with a positive result in the general population will have an affected fetus, and there will be a greater number of false-positive results (Audibert et al., 2017). For instance, a 40-year-old individual has a 1/100 chance of having a live-born child with trisomy 21. Assuming the sensitivity and specificity of NIPT are over 99%, the PPV, in this case, is 93%, with a 7% chance that the test is a false-positive. In comparison, for a 20-year-old individual whose chance of a live-born child with trisomy 21 is lower at 1/1400, the PPV is 48%. Therefore, if a 20-year-old has an NIPT test result “positive” for trisomy 21, there is a 52% chance that the fetus is not affected (Gabriel & Diskin, 2018). Therefore, PPV can be significantly different for a “high-risk” pregnancy versus a “low-risk” pregnancy. Conversely, for individuals who receive a negative result, the negative predictive value will also depend on many factors but is overall very high (>99%) (Sachs et al., 2015). A high NPV means that a negative result for someone in this population is very reliable and could offer them reassurance. However, there is limited follow-up genetic testing to confirm outcomes and accurately assess test performance.

Although NIPT has substantially higher performance measures for identifying aneuploidies than (e)FTS and maternal serum screen, it is still considered a screening test. As such, a positive or high-risk result from NIPT, or any prenatal screening test, requires confirmation by diagnostic testing before making any decision about the pregnancy (Audibert et al., 2017; Gregg et al., 2016; Dondorp et al., 2015; Benn et al., 2015; Salomon et al., 2017; Royal College of Obstetricians & Gynaecologists, 2014). Some individuals consider the uncertainty of prenatal screening to be a disadvantage as they cannot use the test to make confident decisions about their pregnancy (Crombag, van Schendel, Schielen, et al., 2016; Seror et al., 2019; Floyd et al., 2016; Farrell, Agatisa, Mercer, et al., 2015). For example, patients accessing testing later in pregnancy may place more emphasis on test accuracy and may be more inclined to opt for invasive, diagnostic testing (Lewis et al., 2016a).

Prenatal diagnostic testing includes invasive procedures like chorionic villus sampling (CVS) or amniocentesis. CVS is performed between 11 and 14 weeks of pregnancy and involves obtaining a small piece of placental tissue. Amniocentesis can be offered

starting at 15 weeks gestation and consists of a needle removing a small amount of amniotic fluid (Audibert et al., 2017; Nussbaum et al., 2007). Both procedures provide fetal cells for diagnostic testing, such as karyotyping, which produces an image of the fetal chromosome (Nussbaum et al., 2007). Both CVS and amniocentesis are invasive tests with about 1% or less (Akolekar et al., 2015). A benefit of receiving screening results earlier in pregnancy is patients have a longer time to make decisions regarding diagnostic testing (Gregg et al., 2016).

For many pregnant individuals, the most important benefit of NIPT was that it poses no physical risk to the fetus (Farrell, Agatisa & Nutter, 2014; Floyd et al., 2016; Haidar et al., 2018; Lewis et al., 2016a; Lewis et al., 2016b; Reese et al., 2018; Kibel & Vanstone, 2017; Lau et al., 2016; Farrell, Agatisa, Mercer, et al., 2015; Vanstone, Yacoub, Giacomini, et al., 2015; Chen et al., 2017; van Bruggen et al., 2018). Despite the understanding that an invasive diagnostic test is required to confirm results of NIPT, some individuals identify the non-invasive nature of testing to be their main decision-making factor between tests (Floyd et al., 2016; Haidar et al., 2018; Lewis et al., 2012a; Farrell, Agatisa, Mercer, et al., 2015; Vanstone, Yacoub, Giacomini, et al., 2015). For some, especially individuals who do not intend to terminate their pregnancy, the risk-free aspect of NIPT is vital, as they considered test results accurate enough to decline confirmation through diagnostic testing (Haidar et al., 2018; Lewis et al., 2016a; Farrell, Agatisa, Mercer, et al., 2015; Mozersky, 2015).

Another benefit to NIPT screening, compared to multiple marker screening, is the early timing of testing. Obtaining screening results early in pregnancy provides individuals with more time to make decisions about pregnancy management, giving them greater control and satisfaction with their decisions (Farrell, Agatisa & Nutter, 2014; Lewis et al., 2012a; Lewis et al., 2012b; How et al., 2019; Yi et al., 2013). Early access to information for those individuals considering termination made the process much easier physically and emotionally. For those who are not considering termination, obtaining information earlier enables them and their partners to consider pregnancy management and prepare emotionally, physically and financially for raising their child (Yi et al., 2013; Farrell, Mercer, Agatisa, et al., 2014; Floyd et al., 2016; Haidar et al., 2018; Crombag, Boeije,

Iedema-Kuiper, et al., 2016; Chen et al., 2017; Reese et al., 2018; Kibel & Vanstone, 2017; van Schendel, Kater-Kuipers, van Vliet-Lachotzki, et al., 2017; How et al., 2019; Agatisa, Mercer, Mitchum, et al., 2018).

It is important to emphasize to patients that no prenatal screening test will pick up all chromosome abnormalities (Audibert et al., 2017), and the conditions identified by these tests are highly dependent on the screening markers used. Although NIPT is highly efficient, its role and performance must be considered alongside and combined with other screening modalities (Salomon et al., 2017). For example, unlike NIPT, multiple marker screening can give information about fetal and obstetric complications (Dugoff, 2010). In addition, prenatal screening such as NIPT does not replace routine fetal anatomic screening (Gregg et al., 2016). Therefore, a second trimester ultrasound at 18-20 weeks gestation is still recommended for all pregnancies, regardless of initial screening results (Audibert et al., 2017; Gregg et al., 2016). Comprehensive diagnostic testing should be offered to patients when a second trimester ultrasound identifies a fetal malformation (Audibert et al., 2017; Gregg et al., 2016; Bianchi & Chiu, 2019).

As NIPT targets a mixture of DNA fragments of maternal and fetoplacental origin (total circulating cfDNA), it can also disclose unexpected maternal, fetal, or placental results known as incidental findings (Orta, 2016). For example, NIPT results could detect residual cfDNA from an unrecognized twin spontaneously lost during pregnancy (vanishing twin) (Curnow et al., 2015; Grömminger et al., 2014). Also, chromosomal mosaicism of maternal, fetal or placental origin can be identified (Lau et al., 2013; Hall et al., 2013; Pan et al., 2014; Mao et al., 2014; Zhang et al., 2015; Choi et al., 2013; Pan et al., 2013). Chromosomal mosaicism is when an individual has two or more populations of cells consisting of different genetic makeup (Nussbaum et al., 2007).

NIPT can also reveal incidental maternal findings such as aneuploidy, microdeletions or cancer (Amant et al., 2015). For example, NIPT has identified maternal chromosome abnormalities (Lau et al., 2013; Wang et al., 2014; Flowers et al., 2015; Snyder, Simmons, Kitzman, et al., 2016), including maternal SCAs such as Turner syndrome (Wang et al., 2014; Bianchi et al., 2015; Mcnamara et al., 2015). Snyder, Curnow, Bhatt,

et al. (2016) reviewed 79 cases where NIPT results included monosomy, trisomy, SCAs, or multiple aneuploidies. Of these cases, seven (9%) were of maternal origin; one attributed to maternal mosaicism, and six to maternal cancer. Lastly, 42 (53%) of these cases were discordant with fetal results and remained unexplained; however, the authors suggested these results may be due to placental mosaicism, vanishing twin, or a maternal chromosome abnormality in cases where maternal results were not available (Snyder, Curnow, Bhatt, et al., 2016). As DNA from an individual's cancer cells sheds into the bloodstream, NIPT could also reveal maternal cancer (Bianchi et al., 2015; Osborne et al., 2013). Maternal cancers identified through NIPT includes maternal non-Hodgkin lymphoma, acute T-cell lymphoblastic leukemia, anal cancer, and colorectal cancer (Bianchi et al., 2015). Grace et al. (2017) used data from previous studies to suggest a 20-40% risk of maternal cancer when multiple aneuploidies are detected using NIPT screening.

The clinical utility determines the usefulness of the test to the patient, including the affordability of testing, what a patient will do with the test results, and how this information may shape their prenatal care (Gregg et al., 2016). These decisions are all framed by the patient's unique value system and can be complicated and emotionally distressing (Lobel et al., 2005). A negative prenatal screen may ease a patient's anxiety. However, a positive test may cause increased anxiety and create difficult decisions about diagnostic testing and subsequent questions surrounding the continuation of pregnancy. For example, using NIPT early in pregnancy allows earlier diagnosis of a fetus affected by a condition than what is possible with traditional prenatal screening methods. Earlier diagnosis is beneficial as it can give individuals more time to decide on termination or plan the clinical management of pregnancy and birth of a disabled child. Those wishing to terminate can do so earlier, in a time that may be less physically and psychologically traumatic in pregnancy (Hall et al., 2009). The benefits and limitations of prenatal screening are essential for health providers to be aware of and discuss with their patients during pre-test counselling to help them make informed decisions about screening (Dondorp et al., 2015; Audibert et al., 2017; ACOG-SMFM, 2020).

1.3 Prenatal Screening in Ontario

1.3.1 Evolution of NIPT

NIPT became clinically available in Ontario in 2011 (Vanstone, Yacoub, Giacomini, et al., 2015), and private diagnostic laboratories began marketing this as a self-funded test across Canada by 2012 (Dougan et al., 2021). Ontario operates a publicly funded single-payer health care system: Ontario's publicly funded Health Insurance Plan (OHIP). In 2014, OHIP began financing this test in high-risk pregnant individuals on a case-by-case basis (Gamma Dynacare, 2014; Huang et al., 2018). Initially, there was no written or publicized announcement regarding the policy to fund NIPT on an individual basis (Gamma Dynacare, 2014) and OHIP circulated referral forms detailing the risk criteria required for reimbursement to specialist genetics and obstetrics clinics and to prenatal care providers (Vanstone, Yacoub, Giacomini, et al., 2015). By 2018, funding criteria were codified and case-by-case approvals by the MOH were no longer required (MOH, 2018; Burgess et al., 2020).

Since 2016, Ontario began contributing NIPT data to the Better Outcomes Registry and Network (BORN). BORN is a registry that collects health data about every pregnancy, birth and newborn in Ontario (BORN, 2022). Therefore, NIPT screening results can now be linked to other pregnancy and birth encounters within this archive. In 2017, prenatal screening Ontario (PSO) was created, a prenatal screening oversight organization within BORN Ontario. Funded by the MOH, its purpose is to enhance access to prenatal screening, provide education, undertake ongoing quality assurance, and facilitate the integration of technologies or screening options (PSO, 2020). The MOH eventually codified funding for NIPT in 2018 (MOH, 2018; Burgess et al., 2020).

1.3.2 NIPT in Ontario from 2016 to Present

1.3.2.1 The Integrated Prenatal Screen

As interviews for this dissertation were conducted in 2016, it is essential to situate the research within the context of prenatal screening practice in Ontario at this time. For

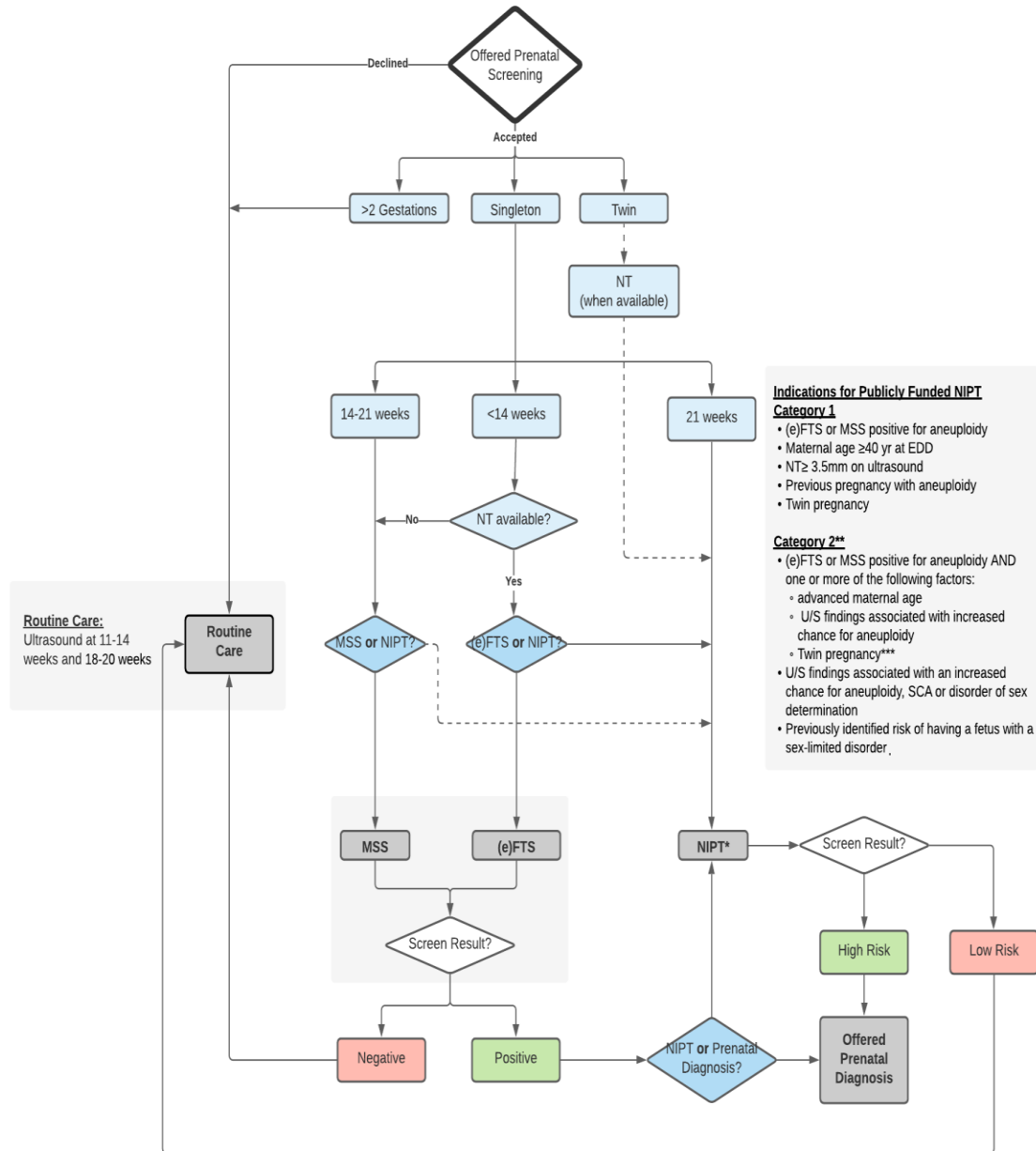
example, in 2016, patients had the option of choosing between three multiple marker screening tests. These tests include the (enhanced) First Trimester Screen” (e)FTS and the “Maternal Serum Screen”, which are still offered presently. The “integrated prenatal screen” (IPS) was still available in 2016 and combines measurements from the first and second trimester screening tests (Wald et al., 1999). At the time, individuals could choose IPS, which was more effective than first trimester screening at detecting trisomy 21 and 18 (Rink & Norton, 2016). Blood was drawn between 11-14 weeks in the first trimester and 15-20 weeks. However, IPS results were not released until the second trimester blood draw had been analyzed at 16 -21 weeks (Mt. Sinai Hospital, 2007). Consequently, waiting until the second trimester for results meant patients could not consider earlier follow-up diagnostic testing if the first-trimester screening results indicated a high-risk of fetal aneuploidy. Some authors suggest that withholding first trimester results were unethical as patients have the right to know this information (Copel & Bahado-Singh, 1999; Spencer & Aitken, 2004). In addition, individuals who did not follow up in the second trimester or chose not to continue to the second step of IPS have no risk assessment available (Rink & Norton, 2016).

In 2018, (e)FTS replaced IPS in Ontario, giving patients two options for multiple marker screening tests: (e)FTS, and maternal serum screen. (e)FTS performs just as well as IPS with earlier results (PSO, 2018, 2019b). The patient's gestational age, the number of fetuses, and the availability of screening tests in their geographical area will determine which of these two tests is possible for that individual. (e)FTS is considered the optimal multiple marker screen for singleton pregnancies (PSO, 2019b). Maternal serum screening is only offered to individuals with singleton pregnancies if the patient presents after 14 weeks or an NT ultrasound is unavailable. In addition, the SOGC has stated that the primary use of maternal serum screen for neural tube defects should be discontinued, and the primary screening test for the detection of neural tube defects and other structural abnormalities should be second trimester anatomical ultrasound with detailed fetal imaging and assessment (Wilson et al., 2014). In December 2021, (e)FTS was discontinued for twin pregnancies in Ontario. NIPT is now covered by OHIP for patients pregnant with twins regardless of gestational age, maternal age, or other factors. A nuchal translucency ultrasound is still recommended for twins where available (PSO, 2021b).

Figure 1 outlines a current comprehensive prenatal screening process map of Ontario. All prenatal screening and diagnostic tests are optional, and a patient may decline testing at any point in this process. If a patient declines (e)FTS, they can still have an NT ultrasound performed.

1.3.2.2 Increase in NIPT uptake

There has been an increase in uptake of NIPT in the low-risk population since 2016. The clinical diagnostic laboratory, which offers Harmony™, reported a significant uptake of NIPT use in the low-risk population between the years of 2014 (47.3%) and 2017 (60.3%) (n=903,789) (Chen et al., 2019). An increased uptake in NIPT has also been observed in Ontario. A retrospective, population-based, descriptive cohort study reviewed BORN data for all pregnant individuals in Ontario who received NIPT from January 2016 to December 2017. In addition to reporting uptake of NIPT in the high-risk population, this review also noted a statistically significant increase in NIPT for the low-risk populations over this study period (Bellai-Dussault et al., 2020). An increase in low-risk pregnant individuals undergoing NIPT has been described as a “trend that is gaining momentum” (Agatisa, Mercer, Coleridge, et al., 2018, p.1375).

Figure 1*Prenatal screening process map of Ontario in 2022*

Note. Prenatal screening options available in Ontario (PSO, 2019b). NT=nuchal translucency, MSS=maternal serum screening, (e)FTS=enhanced first trimester screening, NIPT=non-invasive prenatal testing, EDD=estimated due date. 1st tier: NIPT performed instead of traditional prenatal screening.

*If 1st Tier NIPT: Recommended that NT ultrasound still be performed

**Genetics or Maternal-Fetal Medicine (MFM) specialists are the only providers allowed to submit for NIPT funding for category two.

An uptake in NIPT could be due to increasing health care provider and public awareness of this testing over time, especially as commercial laboratories are undertaking pervasive marketing to increase awareness and uptake of this testing (Farrell, Agatisa, Mercer & Coleridge, 2015; Bellai-Dussault et al., 2020). After these interviews were conducted in 2016, updated clinical guidelines were released that recommend discussing NIPT with all pregnant individuals, regardless of risk status (Audibert et al., 2017; Gregg et al., 2016; ACOG-SMFM, 2020). Additionally, as of December 2021, any physician or nurse practitioner can now order OHIP-funded NIPT for patients pregnant with twins as (e)FTS was discontinued for twin pregnancies in Ontario (PSO, 2021b). Therefore, since 2016, awareness of NIPT has become more widespread in Ontario and an increasing variety of prenatal care providers are using this technology, including more community-based clinicians (Dragojlovic et al., 2021; Burgess et al., 2020).

Importantly, many experts in prenatal care speculate that prenatal care providers will increasingly become involved in genetic testing (Carroll, Grad, Allanson, et al., 2016; Harding et al., 2019; Filoche et al., 2017). This may be primarily due to a limited number of genetic counsellors or trainees available to meet the demand of all patients considering undergoing genetic testing (Devers et al., 2013; Sachs et al., 2015; Alexander et al., 2015; Tamminga et al., 2015; Suskin et al., 2016; Agatisa, Mercer, Coleridge, et al., 2018). In 2018, for example, there was an estimated one genetic healthcare professional per 100,000 people in Canada, with only 109 medical geneticists and 293 genetic counsellors (Berberich et al., 2018). Specifically, as NIPT demand increases, more prenatal care providers are counselling and providing NIPT to an expanding patient population (Larion et al., 2014; McLennan et al., 2016; Gregg et al., 2016). Indeed, many genetic clinics no longer accommodated low-risk NIPT patients who could be managed in primary care in Ontario by 2016 (Burgess et al., 2020).

It has been noted that most individuals prefer NIPT counselling to come from the first care provider they saw during pregnancy, which in many cases was their primary care provider (Lewis et al., 2014). In semi-structured telephone interviews by Benseid et al. (2014), genetic counsellors discussed the benefits to individuals receiving genetic services from these providers, such as improved access to services, convenience, and local availability. Even if prenatal care providers referred their patients to genetics, participants in the Benseid et al. (2014) study mentioned the referring doctor's influence in creating expectations regarding testing before a patient's appointment to genetics. In addition, prenatal care providers have a trusting relationship with their patients, including their knowledge of patients' medical and personal histories. This background knowledge is something that patients value during the decision-making process (Carroll, Makuwaza, Manca, et al., 2016; Benseid et al., 2014).

As prenatal care providers become further entrenched in genetic testing, they must perform adequate pre-test counselling as their role changes to accommodate increased prenatal screening demands. However, pregnant individuals have expressed a critical concern about the lack of valuable informed-choice conversations with their prenatal care providers (Health Quality Ontario, 2019b). Cernat et al. (2019) performed a systematic review of individuals' experiences and preferences for informed decision-making around NIPT. They noted that most pregnant individuals had been disappointed by the counselling they have received from non-genetic professionals, including family physicians, general practitioners, and obstetricians (Cernat et al., 2019). Individuals have expressed that the quality and type of information about NIPT needs to be improved and expanded to better facilitate informed decision-making (Cernat et al., 2019). They desired more information about the benefits and limitations of screening (Agatisa et al., 2015; Floyd et al., 2016; Daley et al., 2017) and the potential next steps in the care pathway following NIPT results (Farrell, Mercer, Agatisa, et al., 2014; Floyd et al., 2016).

1.3.2.3 Conditions Screened

Since 2016, the MOH has had an agreement with two companies to provide provincially funded NIPT screening in Ontario: Harmony™ by Roche (Harmony, 2021) and

Panorama™ by Natera (Natera, 2021a). Panorama is available as early as nine weeks gestation, with results available within seven days (Lifelabs, 2019). Harmony™ is available at ten weeks gestation, and results are available within ten days (Harmony, 2021). Both Harmony™ and Panorama™ have basic prenatal panels that OHIP covers. The basic prenatal panel offered by Harmony™ includes screening for common trisomies (13, 18, and 21), sex chromosome aneuploidies, and fetal sex. Screening for fetal sex and sex chromosome aneuploidies are opt-in options and only covered by OHIP for individuals who meet criteria in category two (Dynacare, 2020c). Alternatively, Panorama™ offers a basic prenatal panel that includes screening for the common trisomies, sex chromosome aneuploidies, and triploidy (three copies of every chromosome). An individual will only qualify for screening for sex chromosome aneuploidies and triploidy if they meet criteria in category two. For those who qualify for category two for this basic prenatal panel, there is no opt-out option for reporting sex chromosome abnormalities and triploidy; fetal sex is an opt-in option (Natera, 2021a). These are considered baseline testing options and were available to individuals in 2016 when these interviews were conducted.

Since 2015, Panorama™ provides expanded testing in Ontario for five microdeletion syndromes: 22q11.2, 1p36 deletion, 15q11–q13 deletions (Angelman syndrome and Prader-Willi syndrome), and 5p deletion (Cri-du-chat syndrome) (Hall, 2015). The performance data for microdeletion screening using NIPT is still limited (Vora & O'Brien, 2014; Health Quality Ontario, 2019a; Wapner et al., 2015; Allyse et al., 2015). In addition, these conditions have variable expression and penetrance. Based on these concerns of clinical utility and validity, clinical guidelines still do not recommend using NIPT to screen for microdeletions in the low-risk population (Audibert et al., 2017; Dondorp et al., 2015; Gregg et al., 2016; ACOG-SMFM, 2020). Despite this, many people have ordered this testing, with Natera™ reportedly performing over 400,000 NIPT screening tests for the 22q11.2 microdeletion in 2020 (Natera, 2021b). MOH in Ontario does not fund these expanded tests, and an “expanded prenatal” panel option is available for \$185-245\$ more (Panorama, 2020; Dynacare, 2020d).

1.3.2.4 Funding for NIPT

Apart from twin pregnancies, Ontario has maintained the same funding model for NIPT since 2014. Clinicians are reimbursed for counselling about NIPT at the same rate as counselling for other prenatal screening options (MOH, 2021). NIPT is publicly funded in Ontario as a first-tier screen test (performed instead of traditional prenatal screening) for all patients with twin pregnancies and singleton pregnancies at high-risk for fetal aneuploidy and SCAs (PSO, 2021a). According to the MOH, a pregnancy is considered “high-risk” if it meets any criteria in two specific categories. Individuals with singleton pregnancies qualifies for the first category (“Category I”) if they meet any of the following criteria: are of advanced maternal age (greater than or equal to 40 years of age at expected time of delivery), have a positive multiple marker screen test for aneuploidy, have had a fetal NT measurement greater than or equal to 3.5 mm and/or had a previous pregnancy or child with trisomy 13,18 or 21. Pregnant individuals with a screen positive prenatal screening result qualify for publicly funded NIPT for the investigation of trisomy 21, 18 or 13 only (Dynacare, 2020c). Any physician or nurse practitioner can order NIPT for individuals who qualify for Category I testing or for individuals who will pay for screening themselves. Midwives in Ontario are independent prenatal clinicians who provide care to low-risk individuals. They have never been able to order NIPT in Ontario and must refer their patients to a physician for counselling and follow-up (PSO, 2021a).

An individual qualifies for Category II testing if they have congenital fetal anomalies identified on ultrasound that are associated with an increased risk of trisomy 13, 18, or 21. Other criteria in this category soft markers, ultrasound markers that are not congenital anomalies per se, that indicate a risk of trisomy 13, 18 or 21. Lastly, individuals are eligible for this category if they request NIPT for sex chromosome determination based on a previously identified risk of a sex-limited disorder or ultrasound findings are suggestive of a sex chromosome aneuploidy or disorder of sex determination (Dynacare, 2020c). Genetics or maternal-fetal medicine (MFM) specialists are the only providers allowed to submit for NIPT funding for Category II. See Appendix A for the Ministry of Health guidelines for funding of NIPT. The Prenatal Screening Ontario Advisory

Committee (PSO, 2019b) recommends this criterion to optimize performance and costs (Okun et al., 2014; Bellai-Dussault et al., 2020).

In 2019, Health Quality Ontario published a holistic assessment of NIPT's use in the average population. This review included evaluating clinical benefits and harms, cost-effectiveness, and patient preferences related to NIPT screening for trisomies 21, 18, 13, SCAs and microdeletions. Compared with NIPT, offered as a second-tier test, contingent to a high-risk status or increased risk (e)FTS, IPS or maternal serum screen result, NIPT offered as a first-tier screening test detected more chromosomal anomalies but resulted in a considerable increase in the total budget. As an increased uptake of NIPT is not necessarily associated with a decrease in cost associated with the care for a pregnancy, child or adult with aneuploidy, first-tier NIPT has not been deemed cost-effective for the average-risk population in most provinces (Audibert et al., 2017; Health Quality Ontario, 2019a), including Ontario (Okun et al., 2014; Dougan et al., 2021). In addition, this assessment found that patients who underwent NIPT discussed the need for improved pre-and post-test counselling for NIPT and were concerned about the quality of information they received from their clinicians about the conditions NIPT can screen for (Health Quality Ontario, 2019b). Therefore, Health Quality Ontario concluded that NIPT should remain a publicly funded screening test only for high-risk pregnancies. However, unlike other prenatal screening and diagnostic testing, individuals who do not qualify for public funding or would like to screen for additional conditions can purchase NIPT as a first-tier test through private pay (PSO, 2021a). Testing begins at \$495-\$550 (CA) for the baseline panels (Panorama, 2020; Dynacare, 2020d).

1.4 Pre-test Counselling for NIPT

Professional societies and expert groups recommend pre-test genetic counselling to ensure individuals make well-informed decisions about pursuing NIPT (Audibert et al., 2017; Gregg et al., 2016; ACOG-SMFM, 2020; Salomon et al., 2017; Devers et al., 2013). Informed decision-making refers to the decision-making process, and informed choice refers to the actual decision made (Hall et al., 2009). Informed consent is the legal agreement by the patient under the conditions that they made a voluntary decision, were

appropriately informed and could make said decision (Deans & Newson, 2011). In Canada, informed choice is a key principle of prenatal screening (Audibert et al., 2017; Chitayat et al., 2017; Summers, 1994). An informed choice in the context of prenatal screening is made when an individual is effectively and sufficiently informed about their screening options. This choice includes considering how their pre-existing values and beliefs influence their decisions about managing their pregnancy (Marteau, 2009; Kater-Kuipers, de Beaufort, Galjaard, et al., 2018; Deans & Newson, 2011). An informed decision allows a person to act autonomously, which is a core principle for prenatal testing (Lewis et al., 2017).

The specific features of NIPT technology raise ethical concerns, such as the erosion of informed choice. For example, due to the simplicity of this procedure, there is a risk that pregnant individuals will view NIPT as just “another blood test” and choose testing without fully understanding its importance or implications (Cernat et al., 2019). Many researchers also fear that NIPT may be routinized, as this simple blood test could become a standardized part of the prenatal care pathway (Lewis et al., 2016a; Lewis et al., 2013; van Schendel et al., 2014; Yi et al., 2013; Mozersky, 2015). Correspondingly, an individual’s acceptance of the test is highly correlated to institutional and provider support, rather than the individual making autonomous decisions about testing (Press & Browner, 1997). In addition, this “easy and risk-free” (Farrell, Mercer, Agatista, et al., 2014; van Schendel et al., 2014; van Schendel, Kater-Kuipers, van Vliet-Lachotzki, et al., 2017), early and highly accurate test may mean pregnant individuals feel external pressures to undergo prenatal screening, as it is perceived as a responsibility of doing the right thing (Farrell, Agatista & Nutter, 2014; Ngan et al., 2020; Salema et al., 2019). From a different perspective, selective abortion of affected fetuses expresses negative or discriminatory attitudes towards the disability and those who carry it (Parens & Asch, 1999). Society may become less supportive of affected children based on the “easy” and accurate NIPT test, giving people an option to avoid the birth of a child with a particular condition, which leads to increased discrimination and stigmatization of these individuals in society (Parens & Asch, 1999; Kater-Kuipers, de Beaufort, Galjaard, et al., 2018; Health Quality Ontario, 2019a; van Schendel, Van El, Pajkrt et al., 2017; van Bruggen et al., 2018).

1.5 Significance of Study

Despite their increasing importance and role in discussing NIPT with pregnant individuals, more studies are required to explore how prenatal care providers experience being at the forefront of this counselling. The premise of this study centers around the novel features of this technology, such as its unprecedented commercial development (Chitty & Kroese, 2015) and early timing in pregnancy. Understanding how prenatal care providers navigate the complexities and nuances of counselling for NIPT within their practice could identify specific barriers in this process and subsequently inform what further support is required so these clinicians can provide the highest quality of care. Support could include improvements to best practice guidelines to specifically support prenatal care providers' needs. In addition, results from this study could inform policies that further clarify how NIPT is used in practice (Khoury et al., 2007; Lobb & Colditz, 2013).

This research explores Ontario prenatal care providers' experiences and perceptions of using NIPT to screen for expanded conditions. In addition, a broad range of common and rare diseases with known and uncertain clinical significance could be prenatally screened for soon, due to the technological advancements of this methodology. Understanding prenatal care providers' opinions on the development of increasingly complex genetic screening can proactively inform what interventions are required to help prenatal care providers navigate prenatal testing in the future. More broadly, findings can inform the creation of supportive environments for patients being offered genetic tests by prenatal care providers in an era where genomics is being used more commonly in healthcare.

1.6 Purpose

This constructivist grounded theory study aims to generate a substantive theory to explain the processes involved with prenatal care providers' pre-test counselling of pregnant individuals. Specifically, it explores how these professionals have integrated NIPT in their clinical practice in Ontario, identifies potential counselling barriers, and explores their experiences with expanded prenatal screening options.

1.7 Research Questions

The research question that guided this constructivist grounded theory study was: From the perspective of prenatal care providers delivering care to pregnant individuals in 2016, what has been their experience with pre-test counselling for NIPT in Ontario?

Sub-questions include:

- 1) What challenges and barriers have prenatal care providers experienced when pre-test counselling people about NIPT?
- 2) What support is available to improve pre-test counselling of NIPT by prenatal care providers?
- 3) What are prenatal care providers perspectives on using NIPT to offer and counsel for additional indications such as fetal sex, expanded testing (for trisomy 16 and 22, and microdeletion/microduplication syndromes) or potential monogenic disorders? Furthermore, what are their perceptions about incidental findings and NIPT?

1.8 Declaration of Self

The methodology used in this study was constructivist grounded theory as formulated by Kathy Charmaz (Charmaz, 2000, 2007, 2014). Constructivist grounded theory purports that researchers hold prior ideas and skills that play a role in the co-construction of theory. Charmaz (2014) suggests that researchers examine how their personal and professional experiences can influence how they see the world and data and give researchers starting points for initiating the research and analysis of the data. To declare the self, I will state my past experiences that influence the depth of my exploration.

I completed my Master's degree in Genetic Counselling in 2011. My research skills have been developed by studying as a doctoral candidate at Western University, London, Ontario and working as a research coordinator, research assistant, and research genetic counsellor. Currently, I work as a laboratory genetic counsellor at CHEO Hospital, Ottawa, Ontario.

This research was motivated and influenced by my experience and training as a genetic counsellor; this included my involvement as a genetic counselling student in a prenatal clinic where I counselled patients about their various prenatal testing options. I experienced an emotional counselling session that affirmed the importance of pre-prenatal counselling during my training. I provided post-test counselling for a couple whose physician ordered multiple marker screening. They were given a “high-risk” result for having a child with Down syndrome. They were upset, claiming to have known nothing about the full consequences of the screening test. They saw the test as routine blood work during one of their clinical visits. This information led them down a new decision-making pathway and changed their pregnancy experience. The emotional effects of their inadequate pre-test counselling resonated with me as a student genetic counsellor. As such, my research interests focus on how prenatal counselling issues may become more pronounced with NIPT, which can screen for a greater variety of genetic conditions than traditional prenatal screening.

Genetic counsellors receive training in counselling individuals about the medical, psychological, and familial implications of genetic diseases (Resta et al., 2006). My genetic counselling education has provided foundational knowledge surrounding ethical principles and considerations occurring in clinical practice. As a counsellor, I see myself as a bridge between two very different worlds, moving back and forth between the very objective world of genetics research and the complex and highly emotional social world of the families affected by this science.

In addition, my current work as a laboratory genetic counsellor has influenced the analysis of this research. Part of my job includes responding to inquiries and providing information and support to healthcare providers who do not specialize in genetics and advising them regarding the appropriate use of genetic tests, limitations/accuracy of tests, possible testing outcomes, sample requirements, interpretation of results, and general genetics-related questions. I liaise between clinical professionals and genetic laboratories to ensure continuity of care through counselling, testing, and follow-up. As genetic professionals, I believe it is crucial to educate prenatal care providers who may be struggling with the counselling for genetic tests. Providing such support allows genetic

counsellors to ensure that patients receive the best possible care. These guiding interests, experiences, and disciplinary perspectives have helped form the research questions of this study and guide the research process itself (Charmaz, 2006).

1.9 Organization of the Dissertation

This dissertation is in a monograph format and contains six chapters, including the first chapter, which provides the introduction, background information, significance, purpose and research questions for this research study. Chapter two presents a review of the current literature on healthcare providers' views and experiences with counselling patients for NIPT. Chapter three presents the methodology, constructivist grounded theory, used in this study. Chapter four presents the data findings. Chapter five presents a discussion of the findings, followed by Chapter six, which summarizes the study's strengths limitations, and presents implications and directions for future research.

Chapter 2

2 Literature Review

The following chapter reviews the literature on healthcare providers' views and experiences on NIPT pre-test counselling and their thoughts regarding future testing. Several studies explore pregnant individuals' and their family's views and experiences surrounding NIPT (Agatisa et al., 2015; Farrell, Agatisa, Mercer, et al., 2015; Floyd et al., 2016; Haidar et al., 2018; Lewis et al., 2012a; Lewis et al., 2012b; Lewis et al., 2014; Lewis et al., 2016a; Lewis et al., 2016b; Reese et al., 2018; van Schendel et al., 2014). However, fewer studies exist which examine healthcare professionals' experiences with pre-test counselling for NIPT, including prenatal care providers who are at the forefront of offering this test (McLennan et al., 2016). As per Charmaz's (2006) recommendations, a preliminary literature review should identify and discuss the most significant findings in the area to inform study design without forcing data into preconceived categories. Therefore, a narrative review was conducted to identify and summarize what has been previously published in this specific area to avoid duplication, determine what areas of study need strengthening and, importantly, highlight gaps in the literature (Derish & Annesley, 2011; Pautasso, 2013; Grant & Booth, 2009).

2.1 Search Strategy

For this review, a search was conducted using Scopus, PubMed, Google Scholar, CINAHL and Western Libraries databases for genetic counselling, genetics and medical literature conducted between 2014 and 2021. This timeframe was chosen because NIPT became publicly funded for those at high-risk for fetal aneuploidy in Ontario in early 2014 (Vanstone, Yacoub, Giacomini, et al., 2015). The key search terms, which were first searched on their own, include: cell-free DNA, cfDNA, non-invasive prenatal testing, non-invasive prenatal screening and clinicians, providers, professionals, and genetic counsellors. These two results were combined with the terms: thoughts, perspectives, beliefs, attitudes, behaviours, expectations, or experiences. The references for all included articles were searched to include papers not found through the initial searches.

I reviewed the articles and identified the following thematic areas: ‘advantages and limitations of testing,’ ‘scope of testing,’ ‘pre-test counselling considerations,’ and ‘support required.’ Prenatal care providers discuss various ethical considerations for using NIPT in their clinical practice throughout these themes.

2.1.1 Advantages and Limitations of Testing

2.1.1.1 Advantages

It is well established that providers believe the accuracy of NIPT is a major advantage over other screening methods (Gammon et al., 2016; Horsting et al., 2014; Brewer et al., 2017; Alexander et al., 2015; Beulen et al., 2015; Hill et al., 2012; Yotsumoto et al., 2012). Providers have discussed how higher levels of accuracy are reassuring for both themselves and their patients, noting this advantage as a key driver for their patients choosing NIPT for aneuploidy (Agatista, Mercer, Coleridge, et al., 2018; Yi et al., 2013; Lewis et al., 2014; Brewer et al., 2017). These studies involved healthcare professionals commenting on the accuracy of NIPT overall when compared to conventional screening methods. However, other performance measures, such as positive predictive value (PPV) and false-positive rates affect patient and provider’s perspectives about NIPT testing have been less investigated. For example, measures such as the PPV for common aneuploidies in low-risk individuals are lower than PPVs reported in high-risk individuals.

Consequently, fewer individuals with a positive result in the general population will have an affected fetus, leading to higher false-positive results (Audibert et al., 2017). Although these performance measures have been an essential part of prenatal screening for decades, they are important to NIPT screening as it is increasingly being used among the low-risk obstetric population (Suskin et al., 2016; Palomaki et al., 2017).

The fact that NIPT can be offered at an earlier stage in pregnancy compared to other prenatal screening options has been mentioned as a major advantage by several healthcare professionals (Bennett et al., 2016; Brewer et al., 2017; Ngan et al., 2017; Yotsumoto et al., 2012; Ahmed et al., 2017; Barrett et al., 2017; Kim et al., 2018; Hill et al., 2013). Earlier testing is seen as an advantage because it could enable more time for

decision-making regarding pregnancy management, including more time to prepare for raising a child with a disability or earlier termination, which could be both physically and psychologically easier to undergo (Gammon et al., 2016; Hill et al., 2013, Ngan et al., 2017). During interviews conducted by Hill et al. (2013) regarding NIPT for single-gene disorders, various healthcare professionals state that the earlier results of NIPT meant pregnancy termination could occur earlier and could be performed by vacuum aspiration. This method is safer for surgical abortion and can be completed in a primary care office, abortion clinic, or hospital (World Health Organization, 2012). Providers in the Hill et al. (2013) study also indicated that earlier testing was beneficial for couples considering a termination of pregnancy as the pregnancy was not physically obvious and recognizable features of the fetus were not visible on ultrasound (Hill et al., 2013). However, what has not been explored is how providers incorporate pre-test counselling for NIPT into an early pregnancy visit. Insight into this process may illuminate specific challenges and barriers they may face during this busy time. Most importantly, this knowledge could inform what additional guidance and support is required for prenatal care providers juggling multiple topics early in pregnancy.

Although NIPT is not diagnostic, many genetic counsellors and other prenatal care providers have indicated that the non-invasive nature of this screening test is its major advantage over invasive diagnostic tests such as amniocentesis and CVS (Sayres et al., 2011; Kim et al., 2018; Ahmed et al., 2017; Hill et al., 2013). Providers view NIPT as an emotionally easier test that can reduce anxiety and stress for patients compared to diagnostic options. They believe that patients can focus on whether the information gained from this blood test would be valuable to them without the need to weigh the risk of miscarriage into the decision (Hill et al., 2011; Hill et al., 2013; Agatista, Mercer, Coleridge, et al., 2018; Yotsumoto et al., 2012; Ngan et al., 2017; Ngan, 2018; Bennett et al., 2016). Clinicians noted that the simplicity of NIPT made it easier to explain to patients (van Schendel, Van El, Pajkrt et al., 2017; van den Heuvel et al., 2010). However, providers are also concerned that the ease of testing may lead to NIPT becoming a routine part of prenatal care and accepted by pregnant individuals without proper consideration (van den Heuvel et al., 2010; Hill et al., 2011; Hill et al., 2013; Skirton & Patch, 2013; Alexander et al., 2015; Tamminga et al., 2015; Bennett et al.,

2016; Ahmed et al., 2017; Haidar et al., 2018). For example, in interviews with U.K. genetic counsellors, respondents felt that diagnostic testing involves a more complex and riskier procedure; the risks involved act as a “safeguard” in prenatal testing, making both patients and professionals consider the implications of the test compared to a blood draw (Alexander et al., 2015). Therefore, the low-risk nature of this test has been explored as a possible risk to a patient’s informed decision-making. However, further investigation is required into how the simplicity of testing has impacted prenatal providers’ pre-test counselling. This inquiry includes whether clinicians believe patients are being counselled adequately by other prenatal care providers in the community. Investigating this aspect of counselling can provide further insight into how this process can be improved to enhance the decision-making of patients who may not consider the full implications of NIPT results.

2.1.1.2 Limitations

A limitation of NIPT includes the additional conditions that it cannot screen for, such as conditions identified by other prenatal screening methods, including ultrasound (Kim et al., 2018; Hill et al., 2013; Suskin et al., 2016). To compensate for these shortcomings, providers commented on the value of information taken from other screening tests (Horsting et al., 2014) and reported using NIPT in conjunction with another form of traditional screening in the first trimester (Suskin et al., 2016; Martin et al., 2018; Kim et al., 2018; Brewer et al., 2017; Tamminga et al., 2015; Suskin et al., 2016; Filoche et al., 2017). For example, to investigate the clinical implementation of NIPT by members of the Australian Association of Obstetrical and Gynaecological Ultrasonologists, Hui et al. (2015) conducted an anonymous online survey with its members (n=54). The main reasons for performing traditional first-trimester screening alongside NIPT were to detect structural anomalies (100%), to predict adverse obstetric outcomes such as preeclampsia (45%) as well as to reassure patients (24%) (Hui et al., 2015). It is important to investigate if prenatal care providers experience difficulties conveying the confines of what NIPT can test for and why these obstacles may exist. If providers face difficulties conveying these limits, it can set unrealistic expectations for testing and ultimately prevent patients from making an informed choice.

There is a consensus from providers that it is imperative to inform patients that follow-up diagnostic testing is recommended for a positive NIPT result (Ramdaney et al., 2018; Weingarten, 2016; Ngan, 2018; Geeter, 2015; Tamminga et al., 2015; Hill et al., 2013; Kim et al., 2018; Chan et al., 2018; Brewer et al., 2017; Haidar et al., 2020). However, some prenatal care providers worry that this message is lost, and some patients and providers misperceive NIPT as a diagnostic test (Hui et al., 2015; Haymon et al., 2014; Chan et al., 2018; Brewer et al., 2017; Haidar et al., 2020). Consequently, providers are worried that patients are making pregnancy decisions, such as termination, without performing follow-up diagnostic testing after a positive NIPT result (Begleiter & Finley, 2014; Mennuti et al., 2013; Hui et al., 2015). This major limitation should not be missed in the pre-test counselling process (ACOG-SMFM, 2020; Audibert et al., 2017; Gregg et al., 2016). A more in-depth exploration of what factors perpetuate this misconception in providers and patients is required, including providers' perspectives. Further investigation of these perspectives may identify barriers and challenges that could inform additional education and support required to provide adequate pre-test counselling that addresses this misperception.

2.1.2 Scope of Testing

Many providers believe NIPT should be offered to low-risk individuals as a first-tier test (Horsting et al., 2014; Musci et al., 2013; Hui et al., 2015; Benn et al., 2014; Silcock et al., 2015; Tamminga et al., 2015; Weingarten, 2016; Ahmed et al., 2017; Martin et al., 2018; Kim et al., 2018; Ngan, 2018; Di Gioacchino et al., 2019; Suskin et al., 2016; Ngan et al., 2017; Haymon et al., 2014). A small portion of these clinicians, through interviews, discussed why they were willing to offer NIPT to all individuals, regardless of risk status. Some believed it was important to provide access to a superior screening test (Suskin et al., 2016; Ngan et al., 2017). Others felt that it was important to consider patient preference (Haymon et al., 2014) and allow patients to make their own decision towards testing (Di Gioacchino et al., 2019). In practice, providers who both do and do not specialize in genetics are offering NIPT screening to individuals in the general population as a first-tier test (Horsting et al., 2014; Musci et al., 2013; Haymon et al., 2014; Buchanan et al., 2014; Weingarten, 2016; Hui et al., 2015; Brewer et al., 2017; Suskin et

al., 2016). As those individuals who are not eligible for any universal or subsidized government funding must pay out of pocket for NIPT, clinicians raised concerns about equity issues involved in providing a superior technology to only those who can afford it (Sayers et al., 2012; Horsting et al., 2014; Suskin et al., 2016; Haidar et al., 2020). Some prenatal care providers have noted that a patient's ability to pay for testing influenced their decision to offer NIPT to that individual (Birko et al., 2019; Burgess et al., 2020; Filoche et al., 2017). A more in-depth analysis is required to investigate Ontario prenatal care providers' perceptions of offering NIPT for aneuploidy testing and expanded conditions through private pay. This information is especially relevant as NIPT screening options expand. Understanding these views and concerns may help with future regulations and directives between private and public testing and address disparities in access. This knowledge can also inform future guidance and support for prenatal care providers offering this counselling.

It has been well documented that healthcare professionals are concerned that NIPT is being used for non-medical sex identification or sex selection, which many feel is an improper use of this technology (Hill et al., 2013; Allyse et al., 2015; Swaney et al., 2016; Alexander et al., 2015; Ahmed et al., 2017; Agatisa, Mercer, Coleridge, et al., 2018; Flynn, 2018; Gammon et al., 2016; Geeter, 2015). Providers noted that a patient's interest in learning fetal sex is an important motivation to undergo NIPT, especially for individuals at low fetal risk for common aneuploidies (Agatisa, Mercer, Coleridge, et al., 2018; Flynn, 2018). General obstetricians, MFM specialists, specialists in reproductive endocrinology and infertility, and genetic counsellors in a U.S. study reported that an advantage to NIPT is obtaining results early in the pregnancy, as patients often wanted to know the sex of the baby as early as possible (Gammon et al., 2016). As more individuals use NIPT, it is also predicted that the number of patients who intend to use NIPT for non-medical sex selection will also increase (Orr-Ferdinand, 2021).

Although patients use NIPT for non-medical sex determination and selection, there is a significant gap in the literature on prenatal care providers' in-depth thoughts and experiences with counselling patients who intend to use NIPT for this purpose. Some genetic counsellors in the U.S. have noted that screening for fetal sex has caused

difficulty in pre-test counselling as some individuals prioritize using NIPT for this purpose (Agatisa, Mercer, Coleridge, et al., 2018; Geeter, 2015). Counsellors described experiences where patients only wanted to know the fetal sex and declined to view fetal aneuploidy results (Agatisa, Mercer, Coleridge, et al., 2018) or didn't understand the possibility that an SCA could also be identified (Geeter, 2015). Orr-Ferdinand (2021) conducted an anonymous online survey of open-ended questions to learn about U.S. genetic counsellors' experience counselling patients who intended to use NIPT towards non-medical sex selection. Counsellors reported ethical dilemmas, emotional distress, and cognitive dissonance from encountering patients using prenatal tests for fetal sex identification and non-medical sex selection (Orr-Ferdinand, 2021). Exploring prenatal care providers' perspectives on this topic is also important as a major part of their patient population could include low-risk individuals interested in using NIPT for this indication. Examining this process could reveal prenatal care providers' comfort with encountering these cases and their potential ethical concerns. As prenatal care providers face situations in the future where patients request NIPT for non-medical fetal sexing, this information could serve as practical guidance for what additional support is necessary to help prenatal care providers navigate this ethically charged topic.

Some providers have expressed positive attitudes toward broadening prenatal screening results to gain more information about the fetus (Kim et al., 2018; Gammon et al., 2016). However, genetic counsellors and other prenatal care providers have voiced concerns about using NIPT for conditions such as SCAs based on the uncertainty of their clinical significance, especially in the context of prenatal testing, where not all clinical data is available (Agatisa, Mercer, Coleridge, et al., 2018; Geeter, 2015; Flynn, 2018; Gammon et al., 2016). A survey by Geeter (2015) given to prenatal genetic counsellors (n=163) from the National Society of Genetic Counsellors' (NSGC) listserv included closed and open-ended questions regarding their views on using NIPT to screen for SCAs. Some counsellors thought NIPT was only clinically useful in detecting Turner syndrome but not for other SCAs, which they felt had little clinical significance. Many providers believe that NIPT should only be used for severe early-onset disorders (Benn et al., 2014; Yotsumoto et al., 2012; Tamminga et al., 2015) and for disorders characterized by

neonatal death or death within the first year of life (Tamminga et al., 2015; Filoche et al., 2017).

Genetic counsellors and prenatal care providers have expressed concern that NIPT will expand to screening for adult-onset conditions or non-medically relevant traits that are not currently tested for invasively (Haidar et al., 2020; Bennett et al., 2016). The potential for expansion of scope could promote the use of NIPT to screen for the “perfect” child (Haidar et al., 2020; Alexander et al., 2015). As NIPT expands its testing options, it is essential to explore what prenatal care providers believe are appropriate boundaries for this testing and why. These values are essential to review as these healthcare professionals may have to provide counselling on conditions available to screen for but go beyond their comfort level professionally and ethically. This input is essential in developing guidance for counselling patients for current expanded options and creating future policies and guidelines.

Providers have agreed that the decision to offer NIPT for other disorders in the future should be based on factors such as clinical utility and clinical validity (Sayres et al., 2011; Hill et al., 2013; Skirton & Patch, 2013; Yotsumoto et al., 2012). However, some genetic counsellors have shown concern for the lack of validation data currently available for microdeletion syndromes, given the rarity of these conditions (Flynn, 2018). For example, Agatisa, Mercer, Coleridge, et al. (2018) conducted interviews in 2016 with 25 prenatal genetic counsellors in the U.S. to understand their experience with the continued expansion of NIPT screening. These counsellors felt that more validation studies are required, with improved positive predictive values and detection rates, before offering NIPT for microdeletions (Agatisa, Mercer, Coleridge, et al., 2018). More investigation is needed regarding how the accuracy, false positive rate, and PPV affect providers' and patients' views towards microdeletion syndrome screening using NIPT. This area may not be explored due to a lack of knowledge and awareness of this testing availability. With the growing number of low-risk individuals interested in NIPT and manufacturers including more rare disorders on their test menus, it is imperative to explore the prenatal care providers' understanding of this validation data. How these measures are understood and applied can influence people's confidence and decision-making (Health Quality

Ontario, 2019b). Therefore, an exploration into the impact of this information could influence a provider's pre-test counselling session.

2.1.3 Pre-test Counselling Considerations

Many clinicians recognize the importance of pre-test counselling in general, and many emphasize how the process should provide patients with accurate and comprehensive information about NIPT (Benachi et al., 2019; Filoche et al., 2017; Alexander et al., 2015; Hill et al., 2011; Suskin et al., 2016). Many clinicians emphasized various topics to cover during the pre-test counselling session to aid decision-making. These topics include the range of conditions screened for, the performance of testing (including test accuracy, the possibility of false-negative and false-positive results), the need for a diagnostic test in the event of a high-risk screen, cost and waiting time for results (Buchanan et al., 2014; Weingarten, 2016; Ngan, 2018; Geeter, 2015; Tamminga et al., 2015; Hill et al., 2013; Kim et al., 2018; Filoche et al., 2017).

Providers have expressed concerns regarding patients' lack of understanding of NIPT and their subsequent ability to make informed choices towards screening (Alexander et al., 2015; Yotsumoto et al., 2012; Ngan et al., 2017; Agatisa, Mercer, Coleridge, et al., 2018; Yi et al., 2015; Ngan, 2018). Some genetic and non-genetic professionals from Canada and other countries are concerned that other prenatal care providers are not delivering adequate pre-test counselling (Horsting et al., 2014; Alexander et al., 2015; Agatisa, Mercer, Coleridge, et al., 2018; Ngan, 2018). It is essential to explore prenatal care providers' perspectives on NIPT's pre-test counselling practices in Ontario. These viewpoints could identify barriers they may encounter in the decision-making process. This perspective could proactively identify potential challenges in pre-test counselling for expanding NIPT testing in the future.

Prenatal care providers have reported that time constraints of a clinical encounter as a major barrier in providing informed consent for NIPT and other prenatal testing options (Farrell et al., 2016; Kim et al. 2018; Gammon et al., 2016; Ngan, 2018. Burgess et al., 2020; Filoche et al., 2017; Farrell et al., 2016; Benachi et al., 2019). In interviews conducted with genetic counsellors in the U.K., respondents expressed concerns about

other prenatal care providers' abilities to provide adequate counselling within the context of an already overstretched service (Alexander et al., 2015). Some providers have reported using pre-prepared notes or brochures about prenatal testing or NIPT (Kim et al., 2018) or propose using educational videos (Gammon et al., 2016) to overcome these time restrictions. More investigation is required on how prenatal care providers in Ontario maneuver counselling for NIPT within busy, time-pressured prenatal visits. Such analysis could provide more information about the potential barriers these non-genetic specialists face when undergoing pre-test counselling in a routine prenatal visit. In addition, these perspectives can inform what additional support is needed for clinicians who may be struggling to provide adequate pre-test counselling in their practice.

Genetic counsellors and prenatal care providers from the U.S. have discussed how screening for expanded conditions introduces pre-test counselling challenges. Due to the variety of different genetic conditions and phenotypes associated with each microdeletion available, providers were apprehensive about the uncertainty, volume, and complexity of information they may have to discuss during the counselling process (Gammon et al., 2016; Agatista, Mercer, Coleridge, et al., 2018). Of the 111 genetic counsellors from the U.K. surveyed by Alexander et al. (2015), almost half (46%) purported that if NIPT-based screening is introduced for a broader range of disorders, it should be made available as a fixed list rather than having individuals choose from a catalogue of disorders. Tamminga et al. (2015) agree that health professionals may raise objections to allowing patients to choose from a list of disorders, as counselling would become a complicated and time-consuming task. With the current list of expanded conditions offered with NIPT, and the potential to expand to more tests, it is important to investigate how providers integrate these options into pre-test counselling. However, very little research has explored prenatal care providers' perceptions on delivering pre-test counselling for these expanded conditions, despite these options being available to pregnant individuals for private pay in Ontario. An investigation into what barriers these professionals may face in offering this testing could reveal where possible support is required to help prenatal care providers deliver better pre-test counselling for these expanded options.

2.1.4 Support Required

Prenatal care providers have consistently reported about their inability to provide adequate pre-test counselling for NIPT based on their lack of knowledge and confidence in the test (Hill et al., 2011; Horsting et al., 2014; Alexander et al., 2015; Gammon et al., 2016; Suskin et al., 2016; Filoche et al., 2017; Weingarten, 2016; Yi et al., 2015; Ngan, 2018). For example, a survey was distributed online through SOGC in 2016 to assess obstetrical provider knowledge and attitude toward this testing. Providers, including obstetricians, MFM specialists, general practitioners, and midwives (n=207) were unsure of NIPT details, such as the capabilities of what NIPT can test for and when the earliest gestation age at which this screening can be offered (Chan et al., 2018). Healthcare professionals have reported a need for more updated education and training about NIPT (Weingarten, 2016; Gammon et al., 2016; Suskin et al., 2016; Alexander et al., 2015; Horsting et al., 2014; Weingarten, 2016; Gammon et al., 2016; Agatisa, Mercer, Coleridge, et al., 2018). Importantly, more recent studies report that clinicians, including genetic counsellors, are requesting more education and training for NIPT screening for conditions beyond aneuploidy, such as sex chromosome abnormalities (Fleddermann et al., 2019; Benachi et al., 2019). As recent as 2018, prenatal care providers in Canada have expressed a need for education about NIPT and they have shown a lack of awareness of testing (Burgess et al., 2020; Haidar et al., 2020). As NIPT migrates from specialized healthcare providers to primary care prenatal practice, these providers must receive additional education. Importantly, ongoing education is crucial as the knowledge gap will widen as NIPT's test menu expands. Therefore, an in-depth exploration into what may be causing educational challenges for prenatal care providers is required. This investigation can inform strategies for filling this current knowledge gap and can help ensure these providers are kept up-to-date on the continual expansion of NIPT.

Providers have stated the methods they use to learn about NIPT, including formal education activities such as presentations, workshops, or seminars. Others have said they learn through a review of the literature, society's recommendations or guidelines, word of mouth and discussion with peers or genetic counsellors as educational resources (Yi et al., 2015; Swaney et al., 2016; Weingarten, 2016; Kim et al., 2018; Ngan, 2018). More

explicitly, clinicians have expressed the desire for this information to come from definitive, trustworthy and unbiased sources (Horsting et al., 2014; Gammon et al., 2016; Filoche et al., 2017; Alexander et al., 2015; Suskin et al., 2016). Genetic counsellors have suggested spending time creating educational resources for prenatal care providers (Suskin et al., 2016; Agatisa, Mercer, Coleridge, et al., 2018). In addition, genetic counsellors in the Agatisa, Mercer, Coleridge, et al. (2018) study emphasized a greater need to collaborate with obstetricians to optimize the counselling and decision-making process during a pre-test counselling session. However, these educational efforts will all take significant time and resources (Gammon et al., 2016); therefore, it is essential to understand what targeted education prenatal care providers need in order to provide this support as sufficiently as possible.

2.2 Conclusion

The literature reveals that clinicians recognize the importance of pre-test counselling in general and emphasize that patients receive accurate and comprehensive education surrounding NIPT during this process. Providers identified challenges and barriers such as the time-pressured counselling, complex discussions, and concerns regarding current and future expanded test options. However, a more in-depth examination of how prenatal care providers in Ontario provide pre-test counselling for NIPT is required. Exploring this process from the perspectives and experiences of these clinicians can bridge the gap between practice and research and identify any challenges and barriers this particular group may experience when providing pre-test counselling for NIPT.

Chapter 3

3 Methodology and Methods

This chapter presents the methodology and methods used to investigate prenatal care providers' experience of offering NIPT during pre-test counselling. I begin the chapter with a brief overview of the methodology used to guide this study, constructivist grounded theory by Charmaz, and the philosophical perspectives that influenced this choice. I also describe the research sample, setting, recruitment strategies, data collection and management, data analysis strategies and ethical considerations. Lastly, a discussion regarding rigour is presented. The study's purpose supported using a qualitative approach, as these methods are useful when focusing on the subjective human experience, capturing a phenomenon from an individual's perspective. In this case, the qualitative approach was used to develop a framework that describes providers' experience of counselling for NIPT in their practice (Polit & Hungler, 1993).

3.1 Grounded Theory Methodology and Philosophical Underpinnings

Methodology is the process or strategy behind the methods chosen to obtain the desired outcomes (Crotty, 1998). The methodology used in this study was constructivist grounded theory as formulated by Kathy Charmaz (Charmaz, 2000, 2003, 2006, 2014). Grounded theory was developed in 1967 by two sociologists, Glaser and Strauss. They proposed that theory can be generated from data (Charmaz, 2000) rather than comparing data to preconceived logically deduced hypotheses (Glaser & Strauss, 1967). Grounded theory involves conducting inquiry through a systematic, inductive, and comparative approach to bridge the gap between research and theory (Glaser & Strauss, 1967; Bryant & Charmaz, 2007). The final theory arises from real-life observations and enables the researcher to be guided directly by the actual research process and data.

Grounded theory, as defined by Glaser and Strauss, Strauss and Corbin, and finally Charmaz, will be discussed. Grounded theory has several distinct methodologies, each with some variations in their philosophical underpinnings. Although Glaser and Strauss never distinctly defined their philosophical paradigm, classical grounded theory is considered to be rooted in the positivist paradigm (Kenny & Fourie, 2015). Paradigms are “a basic set of beliefs that guide action” (Guba, 1990, p. 17). Positivism assumes that reality is objective and described by measurable properties, independent of the researcher or instruments (Myers, 1997). Correspondingly, Glaser has said that the theory generated by classic grounded theory should be as “objective as humanly possible” (Glaser, 2002, p.5), providing a formal theoretical explanation of fundamental social processes. Verification of this theory occurs after quantitative analysis (Glaser & Strauss, 1967). According to Glaser & Strauss (1967), the role of the researcher should be a distant and detached observer to minimize bias. The literature review should be delayed until after data analysis to prevent the researcher from developing preconceived ideas (Glaser & Strauss, 1967). Previous literature should only be used to “challenge emergent theory and locate the emergent theory within the current body of knowledge” (Heath, 2006, p. 527). Classical grounded theory aims to arrive at a core category that denotes a central phenomenon that connects all other categories. Once a core category is discovered, the researcher hypothesizes its relationship with the remaining categories (Glaser & Strauss, 1967).

Some of the methods utilized by classical grounded theory are central to all versions of this methodology. For example, data collection, analysis, and theory construction occur iteratively. In addition, data analysis for all grounded theory approaches first involves breaking data into smaller segments (word-by-word or line-by-line) and labelling it based on their characteristics or properties. The “constant comparative method” is also a core concept of all grounded theory studies, which involves finding patterns within data by comparing data against one another (Glaser & Strauss, 1967; Corbin & Strauss, 2008; Charmaz, 2014). All forms of grounded theory utilize theoretical sampling. This method involves taking theoretical ideas previously developed from early analysis and using these concepts to guide additional data collection. This data could include new participants, new questions in subsequent interviews, and/or seek out recent literature to

elaborate the developing theoretical categories and address conceptual gaps (Glaser & Strauss, 1967; Corbin & Strauss, 2008; Charmaz, 2014). All grounded theory also involves the researcher engaging in memo writing, preliminary analytic notes about their thoughts regarding the data, and data analysis process to develop theoretical ideas and direct theoretical sampling (Glaser & Strauss, 1967; Corbin & Strauss, 2008; Charmaz, 2014). Lastly, a core concept of all grounded theory is to remain theoretically sensitive, which involves balancing an open mind with the ability to identify what is theoretically significant during data collection and analysis (Birks & Mills, 2015).

Strauss worked with Corbin in the 1990s to develop an interpretivist grounded theory methodology. This version rejects positivist thinking and is grounded in the subjectivist paradigm, which assumes that reality is dependent on how people perceive and understand it (Strauss & Corbin, 1990; Strauss & Corbin, 1994). This second genre is founded on symbolic interactionism, a sociological perspective that assumes people think about their actions rather than respond mechanically to stimuli (Park & Burgess, 1921). Furthermore, symbolic interactionism is focused on the subjective meaning people place on objects, behaviours, or events based on what they believe is true. Corbin states: “meaning does not come out of an interplay between subject and object but is imposed on the object by the subject” (Corbin & Strauss, 2008, p.9). The researcher’s role in this version of grounded theory is acknowledged as a subjective interpreter of data. Corbin states that it is not possible to “separate who I am as a person from the research and analysis that I do” (Corbin & Strauss, 2014, p. 11). In contrast to classical grounded theory, a review of the literature is encouraged before data collection and during this process in order to inform research questions; increase theoretical sensitivity; stimulate reflections, data comparisons and observations; and confirm or explain results (Corbin & Strauss, 2014). Therefore, Strauss & Corbin's (1998) version also incorporates deduction in the analysis process, which involves testing abstract ideas against emerging data (Singh & Estefan, 2018).

Interpretivist grounded theory emphasizes a very structured approach to coding and analysis, and the researcher intervenes intensively using analytical tools and questions (Strauss & Corbin, 1998; Walker & Myrick, 2006). Coding also involves breaking down

and rebuilding codes to create more significant and descriptive categories, leading to a formal theoretical explanation. Like classic grounded theory, the aim is to arrive at a core category that connects all other categories. Verification occurs when multiple perspectives confirm the same data (Strauss & Corbin, 1994).

3.1.1 Constructivist grounded theory

A student of Glaser and Strauss, Kathy Charmaz's constructivist grounded theory also centers around a subjectivist paradigm. Charmaz's methodology embraces symbolic interactionism and has roots in constructivism (Birks & Mills, 2015; Charmaz, 2006). Constructivism focuses on how and why individuals construct meanings, actions, and processes when in specific situations (Charmaz, 2003, 2006, 2014). Charmaz maintains that the iterative data collection and analysis processes, alongside the intimate connection researchers and participants have with the data and the emerging theory, make grounded theory development a co-constructed endeavour (Charmaz, 2014). This version assumes that the researcher's values, priorities, positions, and actions impact views and interpretations. Charmaz states: "we [as researchers] are part of the world we study and the data we collect. We construct our grounded theories through our past and present involvements and interactions with people, perspectives, and research practices" (Charmaz, 2006, p.10). Constructivist grounded theory promotes researchers to be reflexive about these influences and how they may affect their interpretations of the data and emerging theory development (Charmaz, 2006).

Before data analysis, a preliminary literature review is performed to examine and understand how previous research and theories influence their research (Charmaz, 2014). Charmaz advocates for using the current literature to inform all phases of the project (Charmaz, 2014; Kenny & Fourie, 2015); this includes a comprehensive literature review to inform the discussion of the findings/theory and place the study within the current research context of the phenomenon studied (Charmaz, 2014). Both induction and deduction are used when and where needed to make sense of the grounded data.

3.2 Rationale for the Constructivist Grounded Theory Approach

Research methodology and methods must suit the research question (Beeson, 1997). This study aimed to describe prenatal care providers' perspectives and clinical experiences with prenatal counselling since the introduction of NIPT in Ontario. Qualitative inquiry was chosen as a method to describe, discover, and document aspects of a process that cannot necessarily be anticipated (Beeson, 1997). This technology's implementation in clinical settings have unexpected consequences on clinicians' practices, including the pre-test counselling process (Vanstone, Yacoub, Giacomini, et al., 2015; Burgess et al., 2020). Grounded theory is a qualitative research design to which an explanation (theory) of a process is generated from participants who have experienced the process. This methodology is useful in studying a process "...where there are major gaps in our understanding, and where a new perspective might be beneficial" (Schreiber, 2001, p. 57). Although prenatal care providers are increasingly becoming involved in genetic counselling for NIPT, little is known about the process they experience when counselling. Therefore, constructing a theory "grounded" in data will provide new knowledge about what experiences and psychosocial processes occur in practice (Grubs & Piantanida, 2010) and will inform what future research is needed.

In addition, "to ensure a strong research design, researchers must choose a paradigm that is congruent with their beliefs about the nature of reality" (Mills et al., 2017, p.26). Before starting this study, I was deeply embedded in this field of research as a genetic counsellor with prior experience in health professional education and prenatal counselling. Therefore, the emphasis on distance from a phenomenon in classic grounded theory and Strauss & Corbin's approach did not seem achievable. I chose constructivist grounded theory as its methods emphasized the importance of being reflexive of my own experiences in order to remain open to the data and enhance theoretical sensitivity (Charmaz, 2006).

3.3 Sampling

A purposeful sampling strategy involves identifying and selecting information-rich cases (Patton, 2002) by identifying and recruiting individuals who are knowledgeable about and experienced with the phenomenon of interest (Cresswell & Clark, 2011). Initially, purposive sampling was conducted in this study to recruit professionals who do not specialize in genetics (prenatal care providers) who have experience with counselling patients about NIPT in a clinical setting. To be eligible for the study, participants met the following criteria: prenatal care providers who have experience with counselling clients about NIPT in a clinical setting, are currently licensed and practicing in Ontario, are at least 18 years of age, and can communicate in English. These individuals worked in various settings, from community-based practices to academic hospitals and specialty clinics, providing services to individuals experiencing low-risk or high-risk pregnancies. High-risk pregnancies involved pregnant individuals with a higher-than-average chance of developing complications. These complications include existing health conditions, obesity, multiple births, and young or old maternal age (UCSF, 2019). Obstetrician gynecologists (OB/GYNs) provide prenatal care for low and medium-risk patients at an office or hospital (Best Start, 2020). Maternal-Fetal-Medicine (MFM) specialist are obstetrician-gynecologists who have received additional education, practical experience, and certification in the management of high-risk pregnancies, and work in hospitals or specialty clinics (uOttawa, 2022). Residents are physicians who have completed their Doctor of Medicine program and are undergoing further training under the direct or indirect supervision of clinicians in different specialties of care. These providers are often involved in a patient's first medical contact in teaching hospitals and clinics (PARA, 2022). These healthcare professionals were purposefully sampled as they counsel patients for NIPT in both high- and low-risk settings. They have a range of length of time in practice and have received different training dependent on their place in practice at the time of implementation of NIPT, which is essential to collect a range of experiences and perspectives from providers who have been counselling in a prenatal setting. Therefore, an emphasis was placed on identifying a variety of healthcare professions to understand how these different groups experienced NIPT in their own practices. Clinicians or health

professionals were excluded if they did not encounter NIPT professionally. Participants were limited to those who gave informed consent to have their interview audio recorded. Dr. Barbra de Vrijer and Dr. Meredith Vanstone initially identified eligible participants based on their knowledge of prenatal care providers in the community.

Theoretical sampling, which involves simultaneous data collection and analysis, was also utilized in this current study to ensure the final developed theory is grounded in the data (Grubs & Piantanida, 2010; Mills et al., 2014). This technique consists of the researcher following leads in the data to sample new participants, asking new questions in subsequent interviews, and/or seeking out recent literature to understand further what is being shared or interpreted throughout the research process (Charmaz, 2014). Initially, prenatal care providers recruited for this study included residents, obstetrician-gynaecologists, and MFM specialists. These professionals expressed concern that family physicians may have additional barriers that prevent them from providing adequate pre-test counselling for NIPT. Primary care providers, including a nurse practitioner, midwives, and several family physicians, were recruited to investigate these barriers further. The primary care providers who were subsequently interviewed were able to finalize a significant theme from this study, which was the need for more support for family physicians, including better pre-test counselling strategies and dissemination of updates and guidelines for NIPT.

This ongoing, non-random sampling technique is meant to obtain a representation of the variants of contexts, events, and situations rather than obtain a statistical representation of a group (Glaser et al., 1968; Strauss & Corbin, 1990; Corbin & Strauss, 2008). I engaged in theoretical sampling until theoretical saturation was reached. Theoretical saturation refers to the point in data collection when no new theoretical understandings emerge from the data and when all relevant theoretical concepts have been identified, explored, and exhausted (Charmaz, 2006). Therefore, the quality of the data in theoretical saturation is more important than the frequency with which it recurs (McCann & Clark, 2003). The data was verging on theoretical saturation after collecting and analyzing 15 participant interviews. However, primary care providers, including midwives, family physicians and one nurse practitioner, were sought to investigate what support they may require in

delivering adequate pre-test counselling for NIPT. This additional recruitment was based on earlier data suggesting primary care providers may face additional counselling barriers. A final sample size of 19 participants was reached for this study when theoretical saturation was determined.

3.4 Recruitment

Dr. Barbra de Vrijer and Dr. Meredith Vanstone initially identified potential participants and reached out to them by email. If interested, these clinicians provided their emails to our research team. A standard email script outlining the study (see Appendix B) was emailed to interested contacts. The email gave a brief overview of the study, including an official letter of information and consent form (see Appendix C). Interested clinicians responded directly to me by email. I subsequently emailed back, answered any questions, and, for those who met eligibility criteria, set up an interview time and location based on their availability. Snowball sampling was used as the recruitment method for this study, which involved initial participants referring our research team to other colleagues who have relevant but different experiences with NIPT. These participants then referred us to other eligible colleagues, which continued until theoretical saturation occurred. Participants were from London, Hamilton, Toronto, and Kingston. At the beginning of all interviews, I answered questions and obtained informed consent from all participants.

3.5 Data Collection

This study used semi-structured one-to-one interviews; the most common form of data collection used in grounded theory studies. These types of interviews allow the researcher to guide the interview in a general direction while being flexible enough to generate and explore new insights about the topic that may not have been previously predicted (Willig, 2008). Data was collected from March 20 to July 15, 2016. Each participant was interviewed once. Interviews were scheduled at a time and place agreed on by the participants and took place in an available private room in their hospital, private office, or over the telephone. Participants had a choice as to whether they would like to be interviewed in person or over the phone. A total of 10 participants decided to be

interviewed by phone. The interviews lasted approximately 30-60 minutes and ended when the participant felt they had nothing more to add. CMBusiness and Transcription Services performed the verbatim transcription of each interview. After receiving completed transcripts from the transcriber, I read each one while listening to the audio interview to ensure accuracy and completeness.

At the beginning of each interview, demographic data were collected from each provider, including years of professional practice and what type of patients they see (individuals experiencing high or low-risk pregnancy), which could affect a participant's feelings or attitudes about NIPT. The interviews were conducted using an interview guide (see Appendix D). The questions were open-ended to facilitate discussion and elicit valuable data (Charmaz, 2014). An example of an open-ended question was: "How do you typically encounter NIPT in clinical practice?" Prompts were used to facilitate the conversation and elicit more in-depth descriptions from participants. For example, when discussing pre-test counselling to patients, one provider noted that they "...think that people understand" prenatal screening, but wondered "...if they really get the whole thing...". I probed further and asked, "What gives you those indications that [patients] might not understand?"

Field notes were taken throughout the data collection process. Field notes are written records of observational data that provide contextual information, including descriptions of the sights and sounds of the physical environment and any non-verbal reactions of the participants during interviews (Hammersley & Atkinson, 2002; Jackson, 1990). These notes supplement language-focused data to provide essential context to inform data analysis (Montgomery & Bailey, 2007). An example of a field note I wrote involved how the participant spoke; it was labelled "What they aren't saying" and included the comment "The last interview (OB/GYN-010) had a lot of pauses and seems like she was filtering what she was saying" (Field note, April 11, 2016).

3.6 Data analysis

Coding is the backbone of the analysis process in grounded theory (Charmaz, 2000) and includes defining what the data is about and seeking conceptual abstraction of the data (Bryant & Charmaz, 2007; Charmaz, 2000). Utilizing QUIRKOS™ qualitative analysis software to help manage the analysis, as per Charmaz (2000), I engaged in three types of coding: initial, focused, and theoretical.

Before any coding occurred, I read the transcript in its entirety to get a sense of what was shared and reviewed the field notes to remind me about the interview. I then conducted initial line-by-line coding by fracturing data into small blocks of text to remain close to the data. At this stage, all codes created were expressed as gerunds, which identify actions and processes within the data, such as ‘relying on genetic professionals’ or ‘facing difficulties with educating patients.’ Initial coding generated as many ideas as possible from the early data and allowed me to look at processes without imposing preconceptions and gain insights about what kinds of data to collect next (Charmaz, 2014).

Next, focused coding was used to condense and sharpen the splintered data to highlight significant or frequent codes. Focused coding allowed me to synthesize and explain larger segments of data. I decided on what initial codes were most prevalent or important and contributed the most to the analysis. Throughout this process, the constant comparative method was used to compare codes and processes within each informant's data and across informants to form categories and subcategories. It was an emergent, iterative process of comparing new codes or concepts to existing ones to look for similarities, differences, patterns, relationships, refinements, and dimensions. This comparative analysis provided a way to see which codes were related conceptually (Charmaz, 2006). Coding during this phase was more selective and directed towards developing a theory, and therefore I identified codes that were more analytical than others to categorize the data (Charmaz, 2004, 2014). Through this comparison of codes, categories and subcategories were eventually developed. The terms “categories” (themes) and “subcategories” (subthemes) were adopted from Charmaz and used to describe the

model that was developed from the data analysis (Charmaz, 2014). For example, I related the codes ‘facing difficulties with educating patients,’ ‘struggling with managing expectations,’ and ‘difficulty with prioritization of information,’ to create the subcategory: ‘difficulties experienced with counselling.’ Charmaz (2006) notes that the literature can illuminate theoretical categories and expand on ideas in the field. In previous studies, a lack of time was identified as a barrier to counselling patients about NIPT (Gammon et al., 2016; Farrell et al., 2016). In my interpretation, I related this data with ‘difficulty with prioritization of information’ and eventually ‘difficulties experienced with counselling.’

I then engaged in theoretical coding, which is the process of refining the final categories of a developing theory and relating them to one another (Charmaz, 2006). This process, for example, allowed me to see how the subcategory ‘engaging patients in decision-making’ is affected by ‘difficulties experienced with counselling,’ which is also linked to the ‘ethical considerations’ subcategory. These subcategories all relate to ‘pre-test counselling considerations,’ which became a major category in this model. Meetings with my advisory committee were held intermittently throughout the research process to discuss the emerging theory and inform the prospective analysis. Eventually, two major categories were derived, which explored how the process of prenatal screening has been enacted since the introduction of NIPT.

3.7 Reflexivity

Reflexivity plays an important role in qualitative research (Finlay & Gough, 2003). Although a diversity of definitions and theoretical positions on reflexivity exist, many transpire beyond the breadth of this study. I used the following definition of reflexivity as proposed by Charmaz (2014, p.344):

[reflexivity is] ...the researcher's scrutiny of the research experience, decisions, and interpretations in ways that bring him or her into the process and allow the reader to assess how and to what extent the researcher's interests, positions, and assumptions influenced inquiry. A reflexive stance informs how the researcher conducts his or her research, relates to the research participants, and represents them in written reports.

Although constructivist grounded theory recognizes the researcher as a co-constructor of data and theory, Charmaz warns against forcing data into preconceived codes, categories, and/or theories (Charmaz, 2014). To prevent this from happening, she suggests constantly engaging in the reflexive process throughout all phases of research (Charmaz, 2014).

Reflexivity in this sense allows the researcher to scrutinize their decisions and understand how these affect the research process and, ultimately, their findings (Burr, 1999; Charmaz, 2014; Finlay & Gough, 2003). In doing so, reflexivity can also improve rigour in grounded theory methodology (Finlay & Gough, 2003, p.28). A researcher's willingness to identify these factors is essential (Charmaz, 2014). As such, I continually reflected, examined, and explored my relationship with the data through this research process to develop self-awareness of these subjective factors (Denzin & Lincoln, 2005).

Reflexivity was essential in this study to examine various aspects of conducting research, including my preconceptions about the topic, my experiences during interviews, and the analysis process. These factors influenced how I planned the study, conducted the interviews, analyzed data, and wrote throughout this process. I wrote reflective notes after interviews and analysis to examine my feelings towards each participant's comments and their ideas towards NIPT in a prenatal setting in order to uncover my values and assumptions.

After each interview, I wrote a reflexive note which assessed my performance as both an interviewer and participant and assessed any biases or feelings I may have had throughout (Mauthner & Doucet, 2003). An example of a reflexive note I wrote was regarding how I revealed my profession as a genetic counsellor (GC) after an interview: "... [when I] mention that I'm a GC- that surprises them, and then they seem immediately conscious about whether or not they spoke well of our profession" (reflexive note, March 31, 2016). In this note, I was reflecting on my co-construction of reality with this participant and how, as described by Charmaz, "...research participants...pursue purposes that influence their respective views and actions in the presence of [the researcher]" (Charmaz, 2006, p.15). I was concerned about "social desirability bias," where respondents in qualitative research respond in a way that they perceive to be acceptable but not entirely reflective of their reality (Bergen & Labonté, 2020). In this

case, I was worried that prenatal care providers would not respond truthfully about their relationship with genetic counsellors and interactions with genetics if they were aware of my professional background. Based on this reflection, I did not reveal that I was a genetic counsellor until the end of the interviews.

I also wrote reflexive notes throughout the research process. For example, I wrote a reflexive note involving my background as an educator: “In analyzing this paper - I realize as an educator at heart - I am looking for the misconceptions of providers- and trying to find a critical view of what needs to be corrected from a provider's perspective as well as a patient's perspective, which is tough because this is not always what's happening here...” (Reflexive note, April 19, 2018). In this case, being reflexive about the nature of the analysis prevented me from forcing superficial categories from my data. Although I coded openly, I acknowledged that my background in education and genetic counselling might make me sensitized towards specific factors in the area of prenatal screening and decision-making that have been previously developed.

I constructed memos throughout the analysis process to bring the data to a conceptual level, develop the characteristics or properties of the categories, and fine-tune my subsequent data-gathering. Memos were written using Microsoft OneNote™ software. Early memos were more tentative and less theoretically developed to uncover processes in the data. An example of an early memo that I wrote was labelled “timing” and was very short. After my 9th interview, I had noted that an MFM specialist discussed how “time-consuming” pre-test counselling was for NIPT. As a genetic counsellor whose entire visit can involve pre-test counselling only, this was something I had not thought about prenatal counselling from the perspective of a prenatal care provider, who saw this counselling as a competing priority in a larger prenatal session. Afterwards, I wrote a memo: “Ask about expanded testing opportunities- ask how this will change timing: will this influence the way [providers] pre-test counsel?” (Memo, April 8, 2016). Later memos written further into analysis had more conceptual ideas to identify incomplete categories and gaps in data analysis (Charmaz, 2014). I noted the concept of timing showing up in various areas in my analysis: “timing is really important: time to think about testing time to make an informed decision, time to create this concept of “baby” in

[a patient's] head: this experience can be transformative: the experience of testing, and changing [their] thoughts of pregnancy: what does that do to [their] concept of "baby" what changes for these women?" (Memo, November 22, 2017). Gradually, memos shifted to categorizing the data and became more analytical. These advanced memos framed the idea of prioritizing information shared during a counselling session, and eventually, this idea fits into the subcategory of 'difficulties experienced with counselling.' See Appendix E for an example of how this category was generated from the data.

3.8 Quality Criteria of Constructivist Grounded Theory

Scholars have no consensus about standards and guidelines for conducting and evaluating qualitative work (Ravenek & Rudman, 2013; Caelli et al., 2017). However, I believe that quality criteria should be congruent with the research's underlying paradigm(s), aims, and goals. As such, I used specific quality criteria related to constructivist grounded theory. Charmaz provides guidelines for grounded theory studies centred around credibility, originality, resonance, and usefulness (Charmaz, 2014).

Credibility is ensured by providing enough evidence for your claims to allow your reader to assess whether the data supports the findings (Charmaz, 2014). One way this was achieved was by involving my supervisors in discussing developing categories. I also completed memos and field notes throughout the data collection and analysis process; these were written after conducting and coding each interview and during each round of coding. This reflexivity enhances credibility by allowing the reader to evaluate how my experience, decisions, and interpretations influenced inquiry. Furthermore, credibility is achieved if the researcher is intimately familiar with the topic (Charmaz, 2014). This closeness is accomplished by conducting all data collection by myself. In addition, I engaged in a constant comparative analysis which kept my analysis close to the gathered data. Member checking is when researchers seek participant feedback on previous data, analyses, interpretations, and conclusions regarding the accuracy and credibility of the account (Creswell & Poth, 2018). I engaged in member checking by asking participants about developing categories based on preliminary analysis. For example, I asked a

provider whether they discuss expanded testing options with their patients: "... what we're hearing so far is it's not really discussed. What are your thoughts about offering NIPT screening...for [the expanded panel]?"

In addition, a thorough literature review strengthens the credibility of a constructivist grounded theory study (Charmaz, 2006). An initial scan of the literature was conducted at the onset of the study to inform the study design and identify sensitizing concepts (see Chapter 1). A formal literature review was also conducted (see Chapter 2), which focused on providers' perspectives on NIPT after completing the data collection and analysis to avoid stifling the creative process during data analysis, as per Charmaz's recommendations (Charmaz, 2014). The literature is subsequently used to inform the discussion of the newly formed theory (Kenny & Fourie, 2015).

Concerning originality, Charmaz emphasizes the need for one's research to have social and theoretical significance and provide fresh insights and a new conceptual rendering of the data (Charmaz, 2014). As such, study questions arise from providers' perspectives and are developed around pre-test counselling for NIPT, a new and rapidly expanding prenatal test. The findings are described in relation to the practical and applicable aspects of the medical literature, such as the bioethical literature and psychosocial process models discussed in genetic counselling and prenatal literature. Few studies exist which examine providers' experiences with incorporating NIPT in their practice.

According to Charmaz (2006, 2014), a study achieves resonance by having categories that portray the studied experience's fullness, drawing links between larger groups, institutions, and individual lives to offer deeper insights about a population's lives. My study addresses these links by drawing connections between the various healthcare workers who can be involved with prenatal care and how offering NIPT impacts the process of prenatal screening, including counselling, in practice settings. Resonance is also achieved, according to Charmaz, by focusing on the statements, intentions, interpretations, and words taken for granted to ensure that each category suitably explains the participants' experiences. Thus, the developed theory appears relevant from the participant's viewpoint (Charmaz, 2014). I tried to summarize the participants' overall

statements to understand what they wanted to describe their experience during the interviews. I provided in-depth descriptions and used direct quotes to illustrate the themes that describe the providers' experience. I also asked participants to clarify particular descriptions during the interview whenever I felt opaqueness or wanted them to describe a topic further. For example, to understand providers' beliefs regarding who should be involved in the future directions of NIPT, I asked, "who should decide?" or "who do you think should be choosing these limitations [to testing]?" For some of the issues where I noticed a lack of clarity after the interview was completed, I tried to provoke a response from subsequent participants by adjusting the interview guide and using prompts.

Usefulness is achieved when the analysis offers interpretations that people can use in everyday life and sparks further research in other substantive areas (Charmaz, 2014). Despite their increasing importance and role in offering NIPT to pregnant individuals, few studies have explored how prenatal care providers experience being at the forefront of this counselling practice. Therefore, this overall research contributes to our understanding of how Ontario prenatal care providers are experiencing pre-test counselling for NIPT and its expanding test options. These findings have implications for future research in prenatal screening and NIPT. More broadly, practical links can be made between this research and prenatal care providers who are becoming more involved in providing genetic testing in their practice.

3.9 Ethical Considerations

Ethics approval was obtained from the Health Sciences Research Ethics Board (HSREB) of Western University (Original McMaster University REB #14-056, reciprocal Western University REB#106393) to conduct this study. The approval demonstrates that ethical requirements stipulated in the Tri-Council Policy Statement of Canada (2nd edition) were satisfied (Government of Canada, 2014). The key ethical considerations of this study will be addressed in this section: informed/process consent, protection from harm, privacy, confidentiality, and anonymity. Informed consent was obtained from all participants prior to the interview. Written consent was obtained from the interviewed participants face-to-face, and oral consent was obtained and documented for the interviewed participants over

the telephone. The letter of information included details such as the purpose of the research, what is expected of the research informant, anticipated risks and benefits, and how confidentiality and privacy will be protected (see Appendix C). A master list of participants was created to link names with an identifier code if participants wanted to withdraw all or part of the data after the interview. Participants were given a physical copy of the consent document or emailed an electronic version to refer to at any time.

Chapter 4

4 Results

The following chapter describes the findings of the constructivist grounded theory study, which explored prenatal care providers' experiences of offering NIPT. The theoretical model was generated from the empirical data of semi-structured interviews with 19 clinicians. Providers described their thoughts and experiences on pre-test counselling for traditional aneuploidies, fetal sex, SCAs, microdeletion syndromes and incidental findings. The model explains how prenatal care providers enact pre-test counselling for NIPT, including challenges faced and support required when offering NIPT to patients. Through iterative data collection and analysis, I constantly compared codes, memos and field notes with each other and emerging categories to the point of theoretical saturation which was when no new themes emerged. After 15 participants were sampled, I approached additional primary care providers to confirm the counselling barriers identified by this group. A final sample size of 19 participants was reached for this study when theoretical saturation was determined.

4.1 Participants

A total of 19 prenatal care providers who encounter NIPT professionally in their clinical settings in London, Hamilton, Toronto, or Kingston participated in this study (Table 3). The final sample included family physicians (FP), maternal-fetal-medicine specialists (MFMs), two senior residents in obstetrics and gynaecology, obstetrician-gynaecologists (OB/GYN), midwives and one registered nurse. These individuals worked in various settings, including community-based practices, academic hospitals, and specialty clinics, and provided services to individuals at low- or high-risk for maternal or fetal complications in pregnancy. The number of years of independent practice for these physicians varied from less than one year to 39 years, with a median of eight years. Additional participant demographics such as age and gender were not included as it was not relevant to the purpose of the current study.

Table 3

Characteristics of participating healthcare professionals

Number of individuals interviewed	Study group	Average number of years in independent practice
7	FP	13
4	MFM	18
3	OB/GYN	19
2	R	<1*
2	MW	6
1	RN**	10

FP= Family physician, MFM= Maternal-fetal medicine specialist, OB/GYN= Obstetrician-gynaecologist, R=OBGYN Resident, MW=Midwife, RN =Registered nurse

* Participants in their 4th and 5th year of their OBGYN residency

**Registered nurse working with individuals with maternal or fetal complications in pregnancy

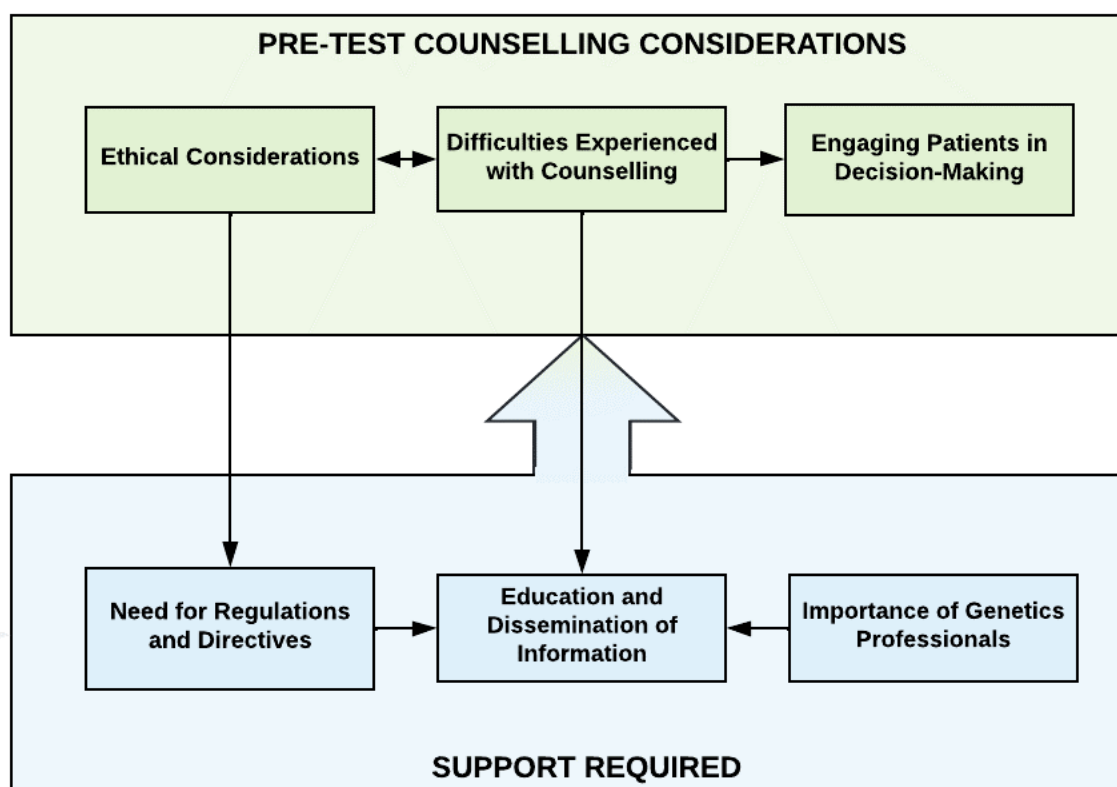
4.2 The Model: Prenatal Care Providers' Involvement with Pre-test Counselling for NIPT in Ontario

The theoretical model, 'prenatal care providers' involvement with pre-test counselling for NIPT in Ontario', explains how prenatal care providers navigate the process of prenatal pre-test counselling since the introduction of NIPT in Ontario. The model shown in Figure 2 consists of two main categories, 'pre-test counselling considerations' and 'support required,' and six interconnected subcategories. The category 'pre-test counselling considerations' illustrates the difficulties faced by prenatal care providers when counselling patients for NIPT. This category also demonstrates how their ethical concerns about testing impact their ability to engage patients in decision-making about this test. Prenatal care providers also described the ongoing education, professional

support, and regulations necessary to successfully undergo pre-test counselling for NIPT, as reflected in the second category, ‘support required.’ For example, providers discussed how ethical concerns regarding pre-test counselling for NIPT must be addressed through regulations and directives. They emphasized the importance of disseminating these guidelines to prenatal care providers. In addition, some of the difficulties experienced with counselling for NIPT are a product of deficits in prenatal care provider education, and genetics professionals were mentioned as an important link in providing this education. Lastly, the large arrow in the model shows how the two main categories relate to each other: the support required by prenatal care providers influences all aspects of pre-test counselling considerations. Supporting evidence for the main categories and subcategories are presented in detail below.

Figure 2

Prenatal care providers’ involvement with pre-test counselling for NIPT in Ontario



4.2.1 Category #1: Pre-test Counselling Considerations

4.2.1.1 Ethical Considerations

The subcategory ‘ethical considerations’ encompasses the ethical aspects of pre-test counselling for NIPT that providers have identified. Some of these ethical concerns made pre-test counselling difficult for prenatal care clinicians to provide and have influenced additional regulations and directives they believe are needed to support this process. For example, many providers expressed concern that individuals are not making fully informed decisions when considering NIPT. Some participants attributed this ethical concern to patients not receiving sufficient information about NIPT during pre-test counselling. As individuals are not “...fully counselled...[they] don’t always understand what they’re getting into” [OB/GYN-04]. Some providers discussed their own experiences with patients who have been negatively affected by inadequate counselling from other prenatal care providers:

I find in practice the most frustrated women that I see...are usually the ones that have sort of been guided down one path, such as genetic testing, and then being sort of blind-sided by a result, and then kind of wishing they had never gone down that road in the first place because it was just not what they expected. [MW-015]

Other providers said their patients had misconceptions about prenatal screening, such as the difference between a screening and diagnostic test: “...we get a lot of our referrals from the community, so sometimes their referring doctor has already planted it in their head... I’d probably say the most common misconception is that it is a diagnostic test” [RN-013]. Specifically, a few providers were worried that a family physician’s pre-test counselling “gets rushed” [MW-015] based on the limited time they have with their patients to provide this service:

...again, again, again, we have to explain the difference between a screening and a diagnostic test. I had one patient that came back really, really, really upset for counselling ... it was a false-negative. Nobody had time to explain...[NIPT] is a screening [test]... [MFM-009]

Prenatal care providers also discussed the importance of equal access to NIPT as an effective first-trimester screening test. Some providers stated accessibility to testing is a

social responsibility, their professional duty was to stay current with the technology, and their professional obligation was to offer the test. Some also mentioned that offering NIPT as a private-pay (self-paid) option was a viable way for individuals to have access to screening even if they may not qualify for public funding. One provider commented on patients' rights: "as a consumer able to buy a product commercially, it's their right to purchase [NIPT]" [MFM-003]. Similarly, one provider believed that patients had the right to pay for NIPT for the indication of sex selection even "if the public system feels that it's inappropriate to cover it... [but]...they want to pay out of pocket, I'm fine with that" [OB/GYN-002]. Others discussed the ability to pay for expanded screening as "...a great resource for [patients] to have" [RN-013] for those individuals who would like to pay for "reassurance" [FP-011] but do not qualify for public funding.

Conversely, many providers raised concerns regarding equal access to NIPT, including the discrepancy between testing services across provinces and the affordability of the test for individuals who do not qualify for public funding in Ontario. One provider noted that at the time of interviewing, NIPT was "...a rich person's test" [FP-008]. Another mentioned the moral conflict they had with individuals having access to expanded disorders through private pay with something that would otherwise not be funded through public testing: "It doesn't seem right that someone with money can get more information, for me...I don't know what the right answer is, but that's a quagmire as well..." [FP-16].

Providers discussed the ethical challenges that can be associated with offering NIPT for conditions beyond the traditional aneuploidies of trisomies 21, 18 and 13. For example, many participants were conflicted with offering screening for conditions with variable clinical presentations, such as Turners or Klinefelter syndrome. This concern was amplified when discussing the expanded use of NIPT to screen for microdeletion syndromes, such as 22q11, cri-du-chat, Prader Willi/Angelman syndrome and 1p36 deletion syndrome. These syndromes can: "have a much more variable appearance, much more variable effect on what's going on with the fetus..." [MFM-006]. One clinician has not offered expanded testing for microdeletions because "the only thing that comes with bringing that up is more questions" [OB/GYN-004]. One provider compared these uncertain phenotypes to something such as: "...a major structural anomaly, there could be

some fairly significant physical restrictions, health issues that go forward with that. The microdeletions, I think, are even worse in terms of that broadness” [MFM-006]. Ultimately, providers were concerned that NIPT would be used for screening for conditions in which the clinical severity was uncertain. However, some participants thought it was appropriate to use NIPT to screen conditions beyond the traditional aneuploidies in order to gain more information about the fetus. They emphasized the importance of properly educating patients before deciding to go forward with testing and ensuring “transparency” [MW-015] regarding the potential range in phenotypes that could occur for some conditions. One OB/GYN discussed the nuances involved in pre-test counselling for sex aneuploidies:

To do that kind of counselling properly takes a lot of time and a clear understanding of the ethical issues that arise when you counsel for something that is non-lethal, variable expression, that’s a lot of stuff to bring forward...
[OB/GYN-004]

Many participants raised ethical concerns regarding the “slippery slope” [FP-014; FP-018; MW-019] that could result from offering NIPT for disorders beyond common aneuploidies. Providers used phrases like “opening the floodgates” [R-001] and opening up “a can of worms” [OB/GYN-004; MFM-003; MFM-006] to describe the issues they faced about expanding testing. Some providers were enthusiastic about the prospect of accessing information they had never seen before. In contrast, others were concerned about the implication of not necessarily knowing how to interpret that information: “... it’s one of those things that, the horse might be able to get out of the barn and then you actually lose the ability for it to be done well” [OB/GYN-004].

Participants also expressed concerns about using NIPT to screen for indications that they considered to be inappropriate. There was a concern that NIPT could go into “scary territory” [MW-015], and providers wondered what the limits to testing should be. They mentioned that it was a matter of ethical debate of whether this test is going to “be used or abused” [OB/GYN-002], with the extreme end leading to patients undergoing genetic selection for the “perfect baby” [OB/GYN-002], “designer babies” [MFM-005] or to “grow [the] perfect race” [OB/GYN-010]. One provider noted: “maybe someday we will

be selecting our baby's hair colour and eye colour and gender... it's kind of a fear...in terms of the risks and benefits of more knowledge and more information" [FP-011].

Participants were very concerned about the use of NIPT for sex selection, as many considered this an inappropriate indication for screening: "...you don't want to do this [NIPT] willy-nilly. Hopefully, we're not doing it just for gender" [OB/GYN-002].

Another participant was unsure how to respond if the request for NIPT for sex selection alone surfaced: "... that's one of my big worries...I don't even know how you would approach that or try to prevent that from happening..." [FP-014]. Another physician discussed how they felt "lucky" to practice in a city where this does not take place but noted that it could occur: "in a different city [in Canada] where there might be different cultural norms..." [FP-012]. In practice, some providers discussed counselling their patients on how NIPT reveals fetal sex in conjunction with other results of this screen. However, one provider explicitly withholds this information from patients based on their fear of sex selection: "... I don't tell [my patients] about the gender selection, so I'm already sort of withholding some information as far as in their decision to make the test right, to do the test because I'm worried about gender selection..." [FP-016].

Feelings about offering NIPT for conditions beyond traditional aneuploidies were obfuscated with the importance of a patient's right to know available information. In terms of sex selection, one provider stated that "...this is something for ethical debates in terms of all or nothing... I believe that we have to tell them, and I agree it's indefensible not to" [R-007]. In terms of offering NIPT for microdeletions, providers stated that they would struggle with providing patients with this information and controlling what testing should be offered: "I don't think that it's my job to say which things should and shouldn't be offered because it's health information that truly is the patient's. It's not our information, so I don't know" [MFM-003]. Many providers stated it was also important to disclose any incidental findings, and it was unethical to withhold this information. However, one provider expressed the dilemma of a patient possibly having this incidental information on their permanent medical records and the potential insurance implications in the future [RN-013].

4.2.1.2 Difficulties Experienced with Pre-test Counselling

The subcategory ‘difficulties experienced with pre-test counselling’ describes the challenges providers face while counselling patients about NIPT. Some of these difficulties contribute to the ethical concerns of testing. In addition, these difficulties ultimately affect how prenatal care providers engage patients in decision-making about this test. For example, many providers mentioned the time constraints, including pre-test counselling for NIPT and prenatal testing in an already busy session. One family physician described pre-test counselling for prenatal screening to be “more challenging than any other counselling” they do in their office, as “...there is so much to tell somebody who knows so little in such a short amount of time” [FP-017]. Counselling about NIPT itself was described as a “time-consuming” [MFM-009] process by one provider. This struggle was emphasized by family physicians who grappled with the competing priorities of other topics to discuss during a patient’s prenatal session, especially if it was the first visit:

I’m talking about...their nausea, and how they’re coping with their fatigue...about their regular blood test, and how they have to come back for a physical and all that stuff. So it’s a lot to talk about. Talking about the minutia of what a particular test might find...is probably not going to happen realistically. Unless I’m there for two hours, which I don’t have time for... [FP-012]

In contrast, one midwife discussed how they had more time to provide pre-test counselling compared to family physicians:

I think that [pre-test counselling for NIPT] gets rushed, because in the physicians’ world they have a lot more clients and patients than I do, so I understand that their time is limited and they don’t have as much of it. [MW-015]

Providers were balancing this conversation while still acknowledging the importance of early prenatal screening with NIPT: “it is a long visit in addition to all the stuff, are you eating well, are you happy you’re pregnant...And you really have to do it early because the screening time is so early. So it’s difficult” [FP-106]. One family physician noted that they bring patients back for a separate visit for prenatal counselling, as their appointments are usually only 15 minutes and there is a lot of information to cover: “...when the

patient comes in initially telling me they're pregnant... there's too much in that visit to go through their whole medical history, coordinate their obstetrical care and provide pre-test counselling" [FP-017].

Family physicians see patients the first prenatal visit when patients have "a lot to think about" [FP-011]. Consequently, physicians noted that individuals might not be receptive to discussing prenatal testing early in pregnancy due to competing priorities. "[My patients] are probably more interested in hearing 'who is going to deliver my baby' and 'which hospital is it at' and 'do I need to take my vitamins' " [FP-016]. Family physicians described the tonal shift that occurs once NIPT is brought up in the session: "[The patient is] more worried about losing the baby than something being wrong with the baby, and then it shifts, okay now is everything okay with the baby" [FP-011].

Another provider was not sure whether discussing NIPT was a welcomed conversation at the initial prenatal visit: "I [say to them] 'I know you're pregnant, and it's happy news, but we also have to discuss this...in a timely fashion' ... it's sort of like a very serious conversation that they have to...bend their mind around" [FP-016]. Providers also explained having difficulties with balancing how much information they should give to patients regarding the potential for NIPT test to reveal incidental findings:

I don't want to tell [my patients] too much information right off the bat because most people come back with a normal result, but I also have to leave them prepared that there could be unexpected things that will be picked up. [MFM-003]

Participants discussed how they struggled to manage patient expectations surrounding prenatal screening in general, and how this can prevent patients from making fully informed decisions. As one provider noted, "[When it] comes to any screening test, it's often challenging to find a way to describe to patients what the test can and cannot do for them" [R-001] including the expectation that a negative screening test means the fetus is "healthy" [OB/GYN-004; OB/GYN-010; FP-011]. Screening tests were described as "confusing" [R-001, FP-018] in nature, as the average individual's concepts such as false-positives and false-negatives are unfamiliar and hard to understand. According to some providers, NIPT is often viewed as a diagnostic procedure by patients, and a positive result did not need any additional follow-up testing. As discussed previously, this

misconception can be particularly problematic if the patient does not receive appropriate pre-test counselling.

Providers mentioned how pre-test counselling for conditions such as Turner syndrome and Klinefelter syndrome could be challenging based on the range in phenotypic variation, making it difficult to counsel patients based on the uncertainty of outcomes in pregnancy. In addition, difficulties experienced with pre-test counselling for NIPT are “multiplied exponentially” [R-001] if NIPT is used to screen for rare microdeletion syndromes. Providers felt that the phenotypic variability of these disorders was not as well defined as the aneuploidies that NIPT currently tests for and may therefore make informed decision-making more difficult. One provider thought that screening should be kept “specific” in order to reduce the risk of “...counselling difficulties that are going to be less than if we start expanding...” [MFM-005]

Some providers compared the difficulty of informed decision-making to the same phenomenon that already occurs with microarray testing: “... there are all kinds of differences in microarray ... that have no clinical significance. But you still have to counsel the couple on ‘well, your baby has this difference...but we don’t know what it means’ ” [MFM-003]. Although these are difficult concepts to understand and counsel patients about, providers suggested that the lessons learned with pre-test counselling for microarray testing could serve as a guide for expanded testing in NIPT:

Hopefully, genetics will learn how we’re managing, how we’re dealing... We’ll have an opportunity to kind of have some counselling about more surreal and more kind of esoteric concepts, potentially, and that may help guide how we would talk about that in an NIPT setting with some of those more expanded testing options. [MFM-006]

Individual expectations of expanded testing were mentioned as especially problematic when patients pay for the tests themselves. One family physician discussed misconceptions that their patients who pay out of pocket have had: “... I think that they felt that they were getting more than what they got. I think that they thought the microdeletions were included in it ...” [FP-008]. Another provider noted the complexities

that would arise from different needs for pre-test counselling: “The private sector would say, if I can pay for it, I want to pay for anything possible. But if you have two different tiers, you have two different needs for counselling.” [OB/GYN-004]

4.2.1.3 Engaging Patients in Decision-Making

Participants discussed how they engaged their patients in decision-making during pre-test counselling for NIPT. This activity was affected by the challenges they faced while counselling. First and foremost, participants described the importance of allowing patients to explore whether prenatal screening, including NIPT, is appropriate for them based on their attitudes, values, expectations, and perceptions:

[This conversation] ...can be very illuminating. It can...shed a lot of light on how that client is as a person...what their values are, what their biggest concerns are, as well as what their baseline level knowledge is around their pregnancy. [MW-015]

Providers stated how highly anxious patients might want to undergo prenatal screening, such as NIPT, based on the information it can provide. One OB/GYN, who provides care for both low-risk and high-risk patients, noted how prenatal screening might not be an appropriate choice for individuals who are highly anxious about fetal health and wellbeing, and need reassurance: “They have anxieties, but their anxieties are more about, is the baby put together normally, not around the genetics so much” [OB/GYN-010]. Providers mentioned that their patients’ current perceptions, goals and expectations might be influenced by their previous pregnancy experiences, such as facing challenges with becoming pregnant or having experienced a perinatal loss. They stated that these individuals might not want additional risks associated with some prenatal screening tests, such as amniocentesis. In addition, providers mentioned that genetic testing results would not alter pregnancy management for some people, and therefore genetic testing may not be appropriate for them.

Participants also described what information they share with patients about NIPT to enhance informed decision-making. They review the benefits and limitations of NIPT with patients, often in the context of other prenatal tests. Specifically, many providers

explain that NIPT is not a diagnostic test, and confirmatory diagnostic testing is required after positive results. Some also emphasize that NIPT cannot replace all prenatal screening, as the test does not screen for placental insufficiency, intrauterine growth restriction, or congenital anomalies, such as spina bifida. Of note, very few report discussing with their patients that there is a possibility of placental mosaicism [FP-014; MFM-005; MFM-009, R-001], inconclusive results [RN-013], or false-positive results [MFM-003; FP-011].

Participants discussed how pre-test counselling involves reviewing several benefits of NIPT with patients, including that NIPT has higher accuracy than the conventional prenatal screening test offered at the time of this study. Although most providers did not mention that this technology is not as accurate for aneuploidies beyond trisomy 21, many tell patients that NIPT is non-invasive. The non-invasive nature of NIPT was considered a benefit compared to an invasive procedure like an amniocentesis: “NIPT definitely can save some of those women the risk of exposure to an invasive procedure like an amniocentesis and give us a little bit more of that yes or no answer” [MFM-006].

Some providers also tell their patients that NIPT is an earlier screening test than IPS, and they noted that early results provide patients more time to make decisions regarding follow-up testing if desired. One provider thought that the decision to terminate a pregnancy if an anomaly was detected: “...would be much more difficult after you’ve seen a couple of ultrasounds [at 21 weeks] than...to terminate a pregnancy at 12 weeks” [FP-011]. When these interviews were conducted in 2016, (e)FTS was not yet available. Instead, IPS was offered as the most superior prenatal screen (Rink & Norton, 2016); however, results were not available until second trimester at 16-21 weeks (Mt. Sinai Hospital, 2007). During this time, a patient may have undergone a detailed anatomical second trimester ultrasound offered in the second trimester between 18-22 weeks (PSO, 2019b).

In contrast, (e)FTS is now offered instead of IPS and performed during the first trimester between 11-13 weeks (PSO, 2018, 2019b). This earlier screening option makes termination possible before the second trimester detailed ultrasound. Despite this, NIPT

can be performed starting at 9 weeks, which is earlier than (e)FTS and IPS. Participants felt this early screening may improve decision-making not only from the perspective of a patient, but also as a decision that they can make about the pregnancy “before the world knows about [it]” [FP-008].

Participants also discussed with their patients how NIPT involves the analysis of fetal DNA for specific chromosome aneuploidies. Some providers mentioned informing patients that NIPT could reveal fetal sex, but very few reveal that NIPT could screen for specific SCAs. Most said they do not discuss expanded testing options with their patients, and none address the potential for incidental findings. The decision to not discuss these additional results with patients was by choice or by being unaware these results were possible or available.

4.2.2 Category #2: Support Required

4.2.2.1 Need for Regulations and Directives

Participants expressed the need for regulations and guidelines regarding prenatal genetic counselling and specified what that would mean for expanding NIPT. Many of the ethical concerns described above by providers inform the type of regulations and directives they believe are necessary to develop. Some providers mentioned that the pressure from industry had initiated the rapid development and implementation of NIPT, and that this specific test had been adopted quickly in practice settings as a result. With this pressure, a few providers were concerned that other prenatal care providers were ordering NIPT in a way that was not cost-effective nor morally appropriate. One provider explained their personal experience during a conference where other providers were discussing ordering NIPT for patients:

I heard people in the room say, ‘yeah, but if you only have this, you get it covered’... it’s almost like people are looking for those little signs to just get it covered. And I don’t think that it’s completely fair for some people to say, ‘oh we’re going to stretch’...so [the patient’s age] is greater than 40, it can be covered...[some providers]...just order it...[and]...say there is a soft sign and it’s

covered...And that's what ... the companies who are doing the test, are telling you because it's their marketing to get more testing...I tend to be thinking about economics as well and that bothers me a lot. [FP-008]

There was also a fear that NIPT would be misused for expanded testing unless stricter regulations were implemented.

With the technological advances of screening, many questioned the limit to NIPT. Current policies and guidelines about expanded testing were considered “patchy” [R-001] and needed to be updated to mirror current options. One provider noted, “technology might be moving faster than policy” [R-001]. Prenatal care providers noted that it was essential to develop additional regulations and directives as the conditions offered by NIPT continued to expand and become more clinically and ethically complex. This need was felt by providers who struggled with ethical questions of offering NIPT for sex selection and expanded disorders with variable phenotypes. These additional regulations were fundamental to address increasing industry pressure to offer expanded testing. Some also discussed the importance of distinguishing what conditions should be publicly provided for NIPT versus the privately available screening. One clinician also mentioned the importance of regulating how pre-test counselling occurs for both public and private screening: “...if it's not streamlined in the way it's rolled out and how the counselling is provided, then I think that becomes very messy” [OB/GYN-004].

When discussing what conditions are appropriate to offer NIPT for, a few providers did not know or have an opinion on what should be included. Many providers mentioned that a disorder might be appropriate to screen for if it is clinically significant, especially when considering the general population: “I think there's going to need to be a lot more discussion, a lot more upper-level genetics...what is the utility of screening for this in the general population” [MFM-006]. In addition to clinical utility, many would approve of screening for a disorder if screening would yield high rates of performance measures such as accuracy, specificity, false-negative and/or false-positive rates. Genetic counsellors, geneticists, MFMs, midwives, nurse practitioners, family physicians, OB/GYNs, pediatricians and researchers were identified as essential stakeholders in creating policies and guidelines on expanded testing.

In 2016, many prenatal care providers were still becoming familiar with NIPT. Many providers in this study were unaware that NIPT could yield unexpected fetal or maternal findings. Some also mentioned the importance of providing more standardized information about NIPT and additional guidelines on counselling patients for any condition other than the commonly known chromosome abnormalities. One provider described feeling uncomfortable offering pre-test counselling or ordering expanded NIPT testing for a patient:

... if anybody asks me about ordering the 22q deletion or the microdeletions... I wouldn't feel comfortable counselling somebody on that and ordering the microdeletion panel, because that's definitely out of my scope of practice...as a family physician to be educating our patients on things that are so, so specific.
[FP-017]

Providers also described their discomfort between the available conditions offered with private-pay NIPT, compared to what they feel comfortable counselling: "...people can pay for whatever they want, but ...I only feel comfortable ordering a test if I feel comfortable and capable of interpreting the results and discussing those results with the patient" [FP-017].

4.2.2.2 Education and Dissemination of Information

Providers mentioned that they learned about NIPT through various methods, including conferences, meetings, information through their genetics department, continuing medical education, the Ministry of Health, companies offering the test, specialty organizations such as the SOGC and word of mouth from other professionals. However, some of the difficulties prenatal care providers were experiencing with counselling can be attributed to a lack of dissemination of information. In 2014, OHIP did not publicly announce its policy to fund NIPT for high-risk women in Ontario. Instead, referral forms detailing the risk criteria necessary for reimbursement were circulated to specialist genetics and obstetrics clinics and providers in obstetrical care. This initial dissemination of information was considered suboptimal by some participants. They described this dissemination process as "haphazard" [MFM-005]:

... It's only by emails... not very widely, through genetics that we were able to figure out initially that they were covering it for certain indications. Now it's fairly clear, but when we were first starting it wasn't clear what they were covering and what they weren't covering... [MFM-005]

Participants discussed experiencing information delays about how new technology is implemented into practice:

...I always think that it's sort of something that happens a lot where sometimes we don't catch wind of a new change that's happening. And we don't adopt it until a year or two later it seems, for various things, depending on who you work with, what their interests are, how up-to-date they are. [FP-012]

By 2016, the funding process was more publicized and streamlined in Ontario as MOH no longer required preapproval for every patient. All participants reflected on how important it was to have specific information about NIPT readily available in order to successfully integrate this technology into clinical practice. This information included NIPT in general, information about expanded testing, and any newly generated regulations and directives.

Many providers expressed concern that family physicians are not well-versed in NIPT, and the need for better dissemination of information was emphasized for this group. Better dissemination strategies were deemed especially important to develop as there is a "...push to have more family doctors understanding it and offering it..." [R-007]. Indeed, some participants, including family physicians, discussed how they had expanded their role in offering NIPT based on the limited resources currently available in genetics. One family physician described a change in practice in response to this increased demand:

... I think a lot of family docs are just referring. But that's what I was doing at the beginning when NIPT was first available, I was referring all my patients. But then I realized, okay, the genetics clinic cannot accommodate every single person that's interested in NIPT because there's just too many of them, and then that's when a lot of the OBs just started ordering it themselves. So, then I realized, okay, this is something I have to become comfortable with myself as well. [FP: 017]

Since 2016, many more prenatal care providers are offering pre-test counselling for NIPT as specialist clinicians are rejecting referrals from cases managed in primary care.

Another obstetrician discussed the importance of family physicians in the initial pre-test counselling phase: “I don’t do the initial screening, where the family doctor does all the groundwork... they’re going to be doing the bulk of the counselling, the IPS testing, etcetera...” [OB/GYN-002]. If any expanded testing was requested from patients, one family physician noted that he would refer that patient to a genetics professional: “That’s something that, again, my information, what I need to know is to refer to somebody who knows more about it and appropriate testing” [FP-011]. Even after the initial conversation with their patients about NIPT, some family physicians emphasized the importance of knowing when to make the correct referral.

There was an expressed need for current regulations and directives to be made more transparent and easily accessible to providers. Providers also emphasized a need for more transparency with the development of policies and guidelines surrounding NIPT:

To some extent, it seems like a big black box to those of us who aren’t privy to how it all comes out. And it just seems weird. You’re like, I know why I’m not involved ... this is actually a conversation family doctors, in particular, are having every day. I think it just seems a little bit more cloaked than it needs to be. Just a bit more transparency, I guess, is what I’m saying. [OB/GYN-004]

Providers noted how difficult it was to remain updated about ongoing NIPT policies and guidelines changes. One provider noted that clinical guidelines for NIPT have: “...no clear indication of where to go for newer information or the best place for new information...,” which was important, “especially with something so rapidly changing like this” [Resident-007]. This provider recommended that a “fantastic addition” to the SOGC website would be the indication of where to go for NIPT's newest, most up-to-date information. Another provider used Cancer Care Ontario as an example of an organization that effectively disseminated information. New screening guidelines were distributed via a pamphlet in paper-based and electronic formats [FP-017].

Ongoing education was an essential piece that providers relied on to counsel their patients about NIPT and its ever-changing landscape. Some participants described their knowledge surrounding NIPT as being at a “surface-level” [MW- 015] and admitted having limited knowledge about specific information on this technology, such as the testing’s limitations and how well NIPT performs in comparison to other prenatal tests.

I think I have enough of a knowledge base that I’d be able to say something coherent to a patient in a way that they would leave feeling a little bit understood. But in terms of the sensitivities and expressivity of those tests and what that means, I was very honest with the patient yesterday, and I said, ‘I don’t know much about that,’ but she still wanted to go ahead and order the test. [FP-17]

This inadequate knowledge is especially relevant as participants expressed concern that family physicians were not well-versed in NIPT and that better dissemination of information to this particular group could enhance the inadequate counselling observed.

Providers revealed a preference for in-person educational methods and electronic formats to receive up-to-date information about NIPT. Those who could attend conferences and other educational opportunities within their professional organizations appreciated these forms of ongoing education. Others suggested creating outreach programs for primary healthcare providers or using pre-existing ones (annual clinical days or pharmaceutical days) to inform a larger portion of providers about NIPT in the community: “...So then you can reach a lot of people, and even if you don’t reach everybody, well, you’re reaching a colleague of those other people who will then talk about it” [FP-012]. Other providers wanted more electronic forms of communication, especially for those colleagues who are unwilling or unable to attend educational sessions in person.

4.2.2.3 Importance of Genetic Professionals

Some participants described how genetic professionals were integral in educating and disseminating information about NIPT and emphasized how ongoing support is required as testing options continue to expand. Some participants would refer their patients to a genetic professional, such as a genetic counsellor, for further information on NIPT. The time of referral to a genetics professional differed between providers. Some participants

would automatically refer any patients interested in NIPT (it is important to note that this represents practice at the time of these interviews, in 2016. Genetic clinics in Ontario no longer accept referrals for cases that meet criteria for NIPT set by the MOH (Category I)). Other providers would only refer if a patient had a positive screening result and/or adverse findings on ultrasound. Others said they would only refer to genetics if the result revealed something beyond common aneuploidies or outside their scope of practice. For example, when discussing pre-test counselling for fetal SCAs, one obstetrician stated the importance of specialized counselling for this indication:

I think it speaks to why it thus far has been in the hands of a very sub-group... I think it becomes very challenging for parents to understand that information, certainly in a small amount of time, and make educated decisions. It would be very dependent on the practitioner sharing the information with them. [OB/GYN-004]

Another provider discussed the logistical reasons as to why genetic professionals should be involved with these kinds of cases: "...I think for something like Klinefelters, for instance, that would be something more that genetics should follow up with because there may be additional testing for the child as they get older that needs to be done through paediatrics" [MFM-003].

Many providers discussed that in addition to taking referrals, genetic professionals play an important role in providing education about NIPT to providers in other medical disciplines. Some of them discussed personal experiences in which they received information about NIPT rollout from the genetics department. Many providers who worked in locations in close proximity to a genetics department appreciated having the support:

I don't think I would change the way we're educated on it because we're very lucky that we have that good ... that they're right down the hallway, and we can talk to them about it, and stuff like that. Because they know what's going on, on a daily basis, in terms of changes... [RN-013]

Some participants felt that genetic professionals play an important role in the ongoing education of NIPT for many prenatal care providers and could offer guidance on NIPT

regulations. Another provider noted that "...hallway consults...[were] very helpful" [OB/GYN-010] to be kept informed. The next chapter will discuss the results, followed by implications for practice and future research.

Chapter 5

5 Discussion

The model “prenatal care providers’ involvement with pre-test counselling for NIPT in Ontario” describes the unique pre-test counselling process experienced by Ontario prenatal care providers and the ongoing support required to fulfill their expanding role in prenatal genetics. Providers discussed how they engage patients in decision-making about NIPT and the ethical and practical challenges that created barriers to counselling on NIPT. In turn, these barriers inform regulations, guidelines, education and support required to improve this counselling process. This chapter describes how the study contributes to the existing body of knowledge on prenatal care providers’ experience with NIPT in clinical practice and details implications for clinical practice and future research.

5.1 Pre-test Counselling for NIPT Considerations

Prenatal care providers discussed navigating pre-test counselling as a frontline healthcare professional in a landscape where NIPT is rapidly evolving. In this study, prenatal care providers discuss ethical conflicts and difficulties with providing counselling in an already busy prenatal session while struggling to remain educated and informed of ongoing updates. This study also provides an in-depth analysis of prenatal care providers’ experience with pre-test counselling for NIPT for conditions beyond traditional aneuploidies, a process traditionally outside their scope of prenatal counselling. Although there has been an increase in the number of prenatal care providers who offer NIPT since these interviews were conducted in 2016 (Dragojlovic et al., 2021; Burgess et al., 2020; Bellai-Dussault et al., 2020), many of these ethical considerations remain.

5.1.1 Ethical Considerations

A significant finding of this study is the tension prenatal care providers feel towards offering NIPT for screening beyond traditional aneuploidies, such as non-medical sex determination, sex selection, SCAs and microdeletion syndromes. Providers feel unease about using NIPT for these additional purposes due to conflicting personal and

professional values and ethical principles. For example, many participants were worried that NIPT would be used for sex identification or sex selection, which they considered inappropriate use of this technology. Other providers and medical ethicists have expressed concerns that NIPT is being used for these purposes as well (Alexander et al., 2015; Mozersky et al., 2017; Toews & Caulfield, 2014; Chapman & Benn, 2013; Nuffield Council on Bioethics, 2017; Allyse et al., 2015; Benn, 2014; Bowman-Smart et al., 2020; Chapman & Benn, 2013; Bennett & Whiting, 2018; Agatisa, Mercer, Coleridge, et al., 2018; Orr-Ferdinand, 2021).

The use of NIPT to determine fetal sex may be in focus for some of these participants as they could encounter low-risk patients motivated to use NIPT for this reason alone. NIPT for sex determination is attractive to low-risk patients as fetal sex can be reported earlier than ultrasound and it is safer than invasive techniques such as CVS (Colmant et al., 2013; Agatisa, Mercer, Coleridge, et al., 2018; Flynn, 2018). This strong desire to know the sex of the fetus among patients may be due to bonding and planning purposes, as previous studies have shown that knowing the fetal sex helps strengthen the parental bond with the fetus early in pregnancy (Shipp et al., 2004; Burke, 1992). As an example of people's interest, NIPT's use for sex determination is a featured frequently asked question on the Lifelabs website for Panorama™ (LifeLabs, 2021). Indeed, companies like SneakPeak® have capitalized on this interest and offer NIPT screening for fetal sex early in pregnancy and marketed towards low-risk individuals (SneakPeak, 2021).

Canada specifically does not have any law prohibiting abortion, including abortions for sex selection (Law Library of Congress, 2020). Two providers in this study noted that individuals in Canada might have cultural beliefs favouring sex selection. A strong preference for a male child could be due to religious reasons in some cultures (Borooah & Iyer, 2004; Arnold & Zhaoxiang, 1986), a belief that there is better treatment available for the mother and son, or a son would have higher status within the family (Rogers et al., 2007). Patients report that they would choose, and have utilized, NIPT solely for non-medical sex determination and sex selection (Farrell, Agatisa & Nutter, 2014; Sahlin et al., 2016; Crabbe et al., 2019; Bennett & Whiting, 2018; Bowman-Smart et al., 2020). In addition, there is evidence that abortions have occurred for sex selection in specific

communities in Canada (Solomon, 2007; Urquia et al., 2016; Yasseen & Lacaze-Masmonteil, 2016).

Reproductive autonomy is a crucial aspect of prenatal screening in Canada and refers to the right of an individual to decide and control their own reproductive decisions (Haidar et al., 2018). Some providers in this study struggled with withholding information about fetal sex based on this reproductive right. Orr-Ferdinand (2021) conducted an anonymous online survey in 2020 consisting of open-ended questions to learn about U.S. genetic counsellors' experiences of counselling patients who intended to use NIPT towards non-medical sex selection. These counsellors also emphasized the importance of patient autonomy when considering NIPT for this purpose (Orr-Ferdinand, 2021). Proponents of procreative liberty also argue that sex selection is a practice of reproductive autonomy as an individual has the right to choose the sex of the fetus to fulfill an individual's social and familial needs (Puri & Nachtigall, 2010; Robertson, 2003; Seavilleklein & Sherwin, 2007; Wertz & Fletcher, 1998).

Based on this tension, one participant stated they felt "lucky" that they do not practice in a geographical area in Canada where they would have to face patients interested in sex selection. Another participant reportedly deals with this discomfort by withholding information during pre-test counselling that NIPT can detect fetal sex. Similarly, in a survey of obstetric physicians from the United States, not all respondents discussed fetal sex detection with their patients (19% never/rarely and 15% sometimes) (Farrell et al., 2016). In contrast, none of the genetic counsellors from the Orr-Ferdinand (2021) interview study denied patients access to fetal sex information. This difference could represent a growing comfort in providers discussing NIPT for sex selection from 2016 to 2020. This distinction could also be due to variations in how healthcare professionals handle these conversations. Genetic counsellors from the Orr-Ferdinand (2021) study reportedly compartmentalize their conflicting personal values to prioritize a patient's reproductive autonomy. Strategies like these may be essential to discuss with prenatal care providers to reduce stress and increase preparedness for discussing NIPT for non-medical sex selection.

Prenatal care providers' discomfort with using NIPT for non-medical fetal sexing can also create a divide in communication between these healthcare professionals and their patients. Studies have shown that some patients using NIPT for non-medical sex determination often do not share their intentions with medical professionals caring for them (Bennett & Whiting, 2018; Bowman-Smart et al., 2020; Crabbe et al., 2019). As many providers in the current study were concerned about using NIPT to screen for fetal sex for non-medical reasons, pregnant individuals may withhold this motivation from their clinician based on fear of being judged for their decision to use NIPT for this purpose.

Some providers also felt uncomfortable with the idea of offering NIPT for screening for SCAs and microdeletion syndromes. Three participants in this study described this scenario as opening up a can of worms. This phrase emphasizes the ethical complexity involved when considering these expanded indications for NIPT. For example, beneficence is the ethical practice of using professional judgment and evidence to assess the benefits of performing a genetic test against the potential harm it could cause their patients (Beauchamp & Childress, 2001; Meulen, 2005). In line with this ethical principle, participants considered the potential benefits and harms of implementing NIPT for SCAs and microdeletions in current and future contexts.

Participants struggled with the prospect of offering NIPT to use for expanded conditions based on the lack of perceived benefits to testing. The Society for Maternal-Fetal Medicine (SMFM), the American College of Obstetricians and Gynaecologists (ACOG), and the American College of Medical Genetics and Genomics (ACMG) organized a workshop in 2017 for members from several professional organizations and commercial laboratories to discuss the goals of prenatal genetic testing (Norton & Wapner, 2018). From this discussion, participants expressed that genetic screening and testing should improve perinatal outcomes for patients and their families (Dukhovny & Norton, 2018). Participants of this current study may feel that there is not enough information about conditions such as SCAs and microdeletions that would change the overall clinical outcome for these patients. Guidelines reinforce the use of NIPT for clinically significant conditions only. International Society of Prenatal Diagnosis states that: "...[NIPT]

should be limited to clinically significant disorders with a well-defined severe phenotype” (Benn et al., 2013, p.730). In addition, ACMG recommends informing all pregnant individuals of the availability of the expanded use of NIPT to screen for “clinically relevant” chromosome abnormalities (Gregg et al., 2016, p.6).

Providers questioned the clinical usefulness of screening for conditions with unclear phenotypes. The concern for providers seemed to be that testing would bring up more questions than answers perceived as pertinent to screening. Likewise, researchers have raised caution that the drive for microdeletion screening is due to feasibility and genotype rather than clinical need (Hashiloni-Dolev et al., 2019; Di Renzo et al., 2019).

In contrast, a few providers expressed optimism about using NIPT to gain more information about the fetus in the future; this was also a goal shared by other prenatal care providers when asked their opinions regarding the expansion of NIPT to include microdeletions (Gammon et al., 2016; Kim et al., 2018). A more recent survey of European prenatal care providers indicated that, although the current use of expanded panels is relatively low, there is a strong interest in the future use of expanded panels for select microdeletions (such as 22q11.2, Prader Willi-Angelman, Cri du Chat, Wolf-Hirschhorn, and 1p36), followed by whole autosome aneuploidy and subchromosomal copy number changes at the resolution of standard karyotyping (≥ 7 Mb) (Benachi et al., 2019).

The perceived potential for expanding NIPT use could be due to a belief that the severity of these syndromes justifies screening. For example, although microdeletion syndromes can have variable phenotypes, they can also result in physical and intellectual impairments that could be more severe than traditional aneuploidies (Wapner et al., 2015; Chitty et al., 2018). Provider interest in obtaining additional information about the fetus could result from the ever-evolving prenatal and postnatal interventions steering towards NIPT being beneficial for these conditions (Dukhovny & Norton, 2018; National Research Council, 2001; Di Renzo et al., 2019; Handleman & Harris, 2005). Therefore, the prenatal screening and testing focus could change from screening for potentially untreatable disorders for information purposes only or possible pregnancy termination to

identifying conditions within fetuses that would benefit from an early diagnosis (Dukhovny & Norton, 2018).

Some participants struggled with gatekeeping what other disorders should be screened for beyond traditional aneuploidies, partly due to their belief in reproductive autonomy. Disability activists argue against the assumption that the presence of a disability, in the context of a chromosomal anomaly, is automatically considered severe harm a child or potential child (Owen et al., 2020). From this ethical perspective, the concept of clinical significance for patients can be broader and highly context-dependent compared to what medical professionals may believe is clinically useful and actionable (Jamal et al., 2017). Consequently, using NIPT to screen for expanded conditions is a legitimate exercise of reproductive choice. Many individuals may also want to know as much as they can about the fetus (Riedijk et al., 2014; van der Steen et al., 2015) regardless of their risk status (Hochner et al., 2020). These desires could include the need to know about conditions beyond common aneuploidies (van der Steen et al., 2018), such as fetal sex, conditions with uncertain implications or late-onset conditions (Benn & Cuckle, 2014; Farrimond & Kelly, 2013). There are concerns that the action of health services qualifying choice to “serious disorders” does not adequately reflect the diverse reproductive choices that individuals may wish to make if given the opportunity (Dondorp et al., 2015; de Jong & de Wert, 2015; Stapleton, 2017; Munthe, 2015).

Clinical guidelines and expert groups also emphasize patient autonomy in decision-making. For example, ACMG states: “patient preferences for information should play a pivotal role in guiding the use of [NIPT] in prenatal care” (Gregg et al., 2016, p.3). Therefore, as this technology is available, and patients become aware of this as an option in prenatal testing, denying individuals available testing is difficult to justify ethically (Chitty et al., 2018; Geeter, 2015). Indeed, omitting information about SCAs and microdeletions in a pre-test counselling session could be considered paternalistic and a way to restrict patient autonomy (McGillivray et al., 2012). In line with this belief, other healthcare professionals have reported offering NIPT for microdeletions and SCAs to give patients autonomy of choice (Yang et al., 2020; Flynn, 2018).

Notwithstanding, the concept of reproductive autonomy addresses only the individuals' choice and disregards the social, economic, and organizational context in making screening decisions. In analyzing the concept of reproductive autonomy for NIPT through a social lens, participants may have also been cautious about using NIPT for expanded reasons through the lens of a public screening program. Other experts have noted that a publicly funded prenatal screening program promoting complete reproductive autonomy is impractical due to resource constraints (Munthe, 2015; Donley et al., 2012; Schmitz et al., 2009; Harper & Clarke, 1997; de Jong & de Wert, 2015; Wilkinson, 2015).

Providers were also worried about NIPT stumbling into “scary” territory and wondered what the limits to this testing should be from a societal perspective. It is important to consider the wider societal inequalities and injustices when developing guidelines, policies, and regulations pertaining to NIPT (Shakespeare et al., 2017). For example, experts are concerned that the potential for non-medical sex selection promotes gender discrimination and gender essentialism (Browne, 2017; Chapman & Benn, 2013; King, 2012; Seavilleklein & Sherwin, 2007; World Health Organization, 2011). Disability activists state that prenatal screening such as NIPT may imply a discriminatory message to people living with specific diseases (Dondorp et al., 2015; Shuster, 2007; The German Ethics Council, 2013; Wertz et al., 2003; International Bioethics Committee, 2015). They caution how the expansion of NIPT can reinforce the medical model that disability itself, not societal discrimination against people with disabilities, is the problem to be solved (Owen et al., 2020).

Still viewing screening through a social lens, participants were concerned that NIPT screening could lead down a “slippery slope” towards the quest for a “perfect child” with society practicing eugenics and aiming for “designer” children (Newson, 2008; Chachkin, 2007; Ma et al., 2013). The powerful slippery slope metaphor conjures the visual of a slow descent, and participants described the feelings of sliding downwards towards using NIPT for additional conditions as a “complicated” and “loaded” process. The slippery slope argument towards new technology plays an essential role in medical law and ethics (de Jong et al., 2010). This argument presents the position that if all groups involved allow one seemingly harmless act or process to occur, this creates an opportunity to slide

down a dangerous path towards a disastrous outcome (Walton, 2015). As NIPT has the potential to detect many different conditions, disability activists argue it has an acute potential of being eugenic (Glover, 2008; Parens & Asch, 2000). Similarly, healthcare professionals in Quebec, interviewed to explore their perceptions and views regarding issues raised by NIPT, raised concerns that this technology could be used for eugenic purposes (Haidar et al., 2020). Eugenics in this context refers to techniques and policies that allow for the reduction of children born with “undesired” attributes while promoting the reproduction of people with “desired” attributes (Thomas & Rothman, 2016). Opponents of non-medical sex selection contend that sex selection is the start of this slippery slope, which could open the door for NIPT being used for other non-medical reasons (Chapman & Benn, 2013; Dondorp et al., 2013; Yu, 2015; Alexander et al., 2015). As NIPT has the potential to detect many different conditions, disability activists argue it has an acute potential of being eugenic (Glover, 2008; Parens & Asch, 2000). Similar to the fear of discussing NIPT for sex selection, prenatal care providers in our and previously published studies raised the concern of eugenic practices with NIPT technology in particular (Bianchi et al., 2015; Bryant et al., 2006; Lewis et al., 2012a), and are afraid of navigating an ever-expanding test menu of conditions. A discomfort with the future of expanded screening options for NIPT highlights the need for additional regulations and support for providers who continue to play a more prominent role in pre-test counselling for these morally complex topics.

Prenatal care providers in our study also struggled with gatekeeping who should be offered NIPT. Counsellors from Orr-Ferdinand’s (2021) study valued the ethical principle of justice and did not want to act as a gatekeeper of NIPT and wanted to treat all patients in the same way regardless of their motivations for testing (Orr-Ferdinand, 2021). The principle of justice in the context of prenatal screening relates to equal access to prenatal screening for all pregnant individuals (Kater-Kuipers, de Beaufort, Galjaard, et al., 2018). It is perhaps due to this belief that many participants in this study, along with other providers, emphasize the importance of all individuals having access to NIPT and are willing to offer this test to low-risk individuals (Horsting et al., 2014; Musci et al., 2013; Hui et al., 2015; Benn et al., 2014; Silcock et al., 2015; Tamminga et al., 2015; Weingarten, 2016; Ahmed et al., 2017; Martin et al., 2018; Kim et al., 2018; Ngan, 2018;

Di Gioacchino et al., 2019; Suskin et al., 2016; Ngan et al., 2017; Haymon et al., 2014). Participants in this study believed that private pay is a way to provide access while still maintaining a practical public funding model. Likewise, many genetic counsellors (65%) decided that discussing private pay options within a publicly funded healthcare system was ethical, based on patient autonomy (Di Gioacchino et al., 2019).

Some prenatal care providers in this study discuss NIPT with all individuals, with the caveat that some may not be eligible for public funding. This practice is contrary to many guidelines relevant in 2016 which did not recommend NIPT as a first-tier test in average-risk pregnancies due to the lack of performance data available for this population (Langlois et al., 2013; Wilson et al., 2013; ACOG-SMFM, 2015). However, around the time of these interviews, studies had emerged which reported high sensitivity and specificity for NIPT in the general population (Song et al., 2013; Pergament et al., 2014; Dan et al., 2012; Nicolaidis et al., 2012; Bianchi et al., 2014; Norton et al., 2015; Bianchi et al., 2012; Dar et al., 2014; Zhang et al., 2015). Unlike other professional statements, the American College of Medical Geneticists and ISPD did not limit NIPTs use to individuals at increased risk for aneuploidy (Gregg et al., 2013). ISPD's position statement released in 2015 stated that NIPT should be offered as a primary test to all pregnant individuals. They noted that individuals "...perceive risk differently, [and] may prefer particular approaches or may choose to finance their testing personally. Patient requests for testing that falls outside recommendations should not be the sole basis for the denial of testing" (Benn et al., 2015, p.732). Providers in this study may have been aware of these studies, and felt comfortable discussing NIPT with all individuals based on the individual's own interest in testing.

Marketing materials at the time may have also influenced providers to offer NIPT to a wider target population. Vanstone, Yacoub, Winsor, et al. (2015) used inductive qualitative content analysis to examine how NIPT is constructed using informational documents, including professional statements and manufacturer information for providers and laypeople. A major finding from this study was that while many professional statements at the time described NIPT for use in a high-risk population only, manufacturer information described a much wider target population. This information

included ambiguous or vague statements that allude to NIPT being used for any pregnant or any pregnant individual who may be interested (Vanstone, Yacoub, Winsor, et al., 2015). NIPT's potential worldwide net market worth has been measured in billions of dollars (Marketers Media, 2022; Fortune Business Insights, 2021; Renub Research, 2022). This value creates a considerable incentive to frame the clinical use of this testing as beneficial to the broadest cohort of users possible (Murdoch et al., 2017). As a result, companies advertise NIPT as a first-tier screen for all pregnant women in order to increase the market size (Heger, 2014).

Participants in this study may have offered NIPT to all individuals based on the growing evidence that the testing can be applied to low-risk individuals and to uphold ethical principles of reproductive autonomy and justice, despite policy recommendations at the time. They may have also been influenced by manufacturer messaging, which promoted the use of NIPT for a wider target population. This practice highlights the gap in practice and policy that can occur due to a rapidly evolving technology and the importance of remaining current with ongoing changes to NIPT. Eventually, other clinical guidelines were updated after these interviews, which now recommend offering NIPT to all pregnant individuals, regardless of risk status (Audibert et al., 2017; Gregg et al., 2016; ACOG-SMFM, 2020). For example, SOGC-CCMG updated practice guidelines released in 2017 recommend that pre-test counselling should include offering all individuals NIPT where available, “with the understanding that it may not be provincially funded” (Audibert et al., 2017, p.806).

A similar path seems to be occurring for offering expanded panels for NIPT. Although guidelines currently do not recommend routine NIPT screening for fetal microdeletions (Gregg et al., 2016; ACOG-SMFM, 2020; Audibert et al., 2017), some providers in this study believe that patients should have access to these screening options based on its availability. Clinically relevant microdeletions and duplications occur in greater than 1% of all pregnancies regardless of a person’s aneuploidy risk (Nussbaum et al., 2007). Therefore, some experts suggest that all individuals should be offered expanded testing (Wapner et al., 2015; Wapner et al., 2012). Manufacturer information also promotes using these expanded panels for a wider target population, based on the fact that

“...microdeletions occur in pregnancies at the same rate for mothers of any age” (Natera, 2021a, p. 3). Although professional position statements currently do not recommend routine NIPT screening for expanded panels, providers may feel the need to uphold reproductive autonomy and justice principles and offer expanded screening to a wider target population. Therefore, professional position statements should provide guidance on how to counsel for expanded screening, given its current availability and use.

Unfortunately, not all individuals can pay for NIPT privately, and therefore equity of access becomes a significant concern (Hui et al., 2015; Benn & Chapman, 2016; Bellai-Dussault et al., 2020; Rink & Kuller, 2018). Participants were troubled that not everyone who wants testing has access to it due to costs. Equity of access has been a concern for other providers in Quebec (Haidar et al., 2020), the United States (Allyse et al., 2015) and other countries (Yi et al., 2015; Ngan et al., 2017; Kater-Kuipers, Bunnik, De Beaufort, et al., 2018; Filoche et al., 2017). Patients from Ontario have suggested additional government funding to alleviate these inequalities (Vanstone et al., 2018; Vanstone, Yacoub, Giacomini, et al., 2015; Haidar et al., 2018). However, some patients acknowledge that using additional public funds for NIPT could send a message that the government encourages testing uptake. In turn, funding may hinder patient autonomy and make individuals feel that participation is expected (Haidar et al., 2018; van Schendel et al., 2017; Farrell, Mercer, Agatista, et al., 2014). In addition, several scientific societies and health technology assessments have also argued against NIPT as a first-tier test due to a lack of unbiased and clear evidence that first-tier NIPT would be a good use of health care funding (UK National Screening Committee, 2015; Canadian Agency for Drugs and Technologies in Health, 2014). For example, Health Quality Ontario assessed the cost-effectiveness of NIPT as a first-tier test in an average-risk population. The authors concluded that NIPT was not yet financially viable as a publicly funded first-tier test for the average-risk population, as it would lead to a substantial increase to the Ontario Healthcare budget of \$35 million per year in 2017 Canadian dollars (Health Quality Ontario, 2019a). Lastly, public funding is not financially feasible to cover all expanded options. One participant noted the moral conflict with some individuals having access to expanded panels through private pay, while others cannot afford this option. This dilemma may become more pronounced as options for NIPT expand, and providers will

have to decide whether they are comfortable discussing private-pay options with all patients.

Pregnant individuals largely prefer their information about NIPT comes from clinician counselling (Agatisa et al., 2015; Farrell, Agatisa & Nutter, 2014; Lewis et al., 2013; Lau et al., 2016; Agatisa, Mercer, Mitchum, et al., 2018; Farrell, Agatisa, Mercer, et al., 2015). However, participants from this study were concerned that other prenatal care providers are not spending enough time to appropriately counsel patients on NIPT, resulting in patients making uninformed decisions about testing. Prenatal care providers have expressed similar concerns in Hong Kong, Pakistan, and the Netherlands (Ngan et al., 2017; Ahmed et al., 2017; Kater-Kuipers, Bunnik, De Beaufort, et al., 2018). For example, 90% of Hong Kong obstetricians and midwives indicated that they were “somewhat” or “extremely” concerned about the lack of pre-test counselling that occurs for NIPT (Ngan, 2018). Assessment surveys and qualitative interviews with patients confirm that the content of initial discussions about NIPT may not be sufficient to meet their reported information and decision-making needs (Piechan et al., 2016; Constantine et al., 2014; Lewis et al., 2016b; Farrell, Agatisa & Nutter, 2014; Lewis et al., 2013; Agatisa et al., 2015; Farrell, Agatisa, Mercer, et al., 2015; Lau et al., 2016). There is a reported lack of communication from providers to patients about the benefits, limitations, and follow-up during the pre-test counselling process (Piechan et al., 2016; Spelten et al., 2015; Samura, 2020; Martin et al., 2015).

After receiving referrals from the community, providers from this current study describe encountering frustrated patients who were improperly counselled and, as a result, erroneously believed that NIPT is a diagnostic test. These accounts correspond to other reports regarding patients who have not been counselled adequately about NIPT by their prenatal healthcare providers. For example, panelists from patient advocacy groups reported that their organizations often receive panicked messages from patients with NIPT screen positive results that they understood as definitive from their providers (Meredith et al., 2016). Notably, our findings highlight providers’ concerns that family physicians specifically do not spend enough time discussing NIPT with their patients. This was even discussed by midwives and the nurse practitioner who were interviewed

for this current study. Family physicians in this study confirmed the challenges of prioritizing information in an otherwise busy prenatal visit. Patients have also reportedly been disappointed by family physicians' incomplete and inconsistent information (Vanstone et al., 2018; Lewis et al., 2012a). This concern is increasingly relevant based on the surge in family physicians in Ontario who have been offering NIPT to patients since 2016 (Dragojlovic et al., 2021; Burgess et al., 2020).

A lack of adequate pre-test counselling for NIPT becomes a burgeoning concern with the expansion and complexity of available screening options. For example, the Panorama™ baseline NIPT panel has no opt-out option for sex chromosome abnormalities and triploidy (Natera, 2021a). Therefore, patients must receive the proper counselling to understand the possibility of all results. Other test options include the baseline NIPT panel and screening for 22q11.2 deletion syndrome or the entire microdeletion extended panel. The first conversation with their prenatal care provider about prenatal testing may involve navigating these options. Consequently, with the variety of testing now available, it is crucial that appropriate pre-test counselling occurs to ensure patients are informed about the benefits and limitations to each before deciding to undergo testing.

5.1.2 Difficulties Experienced with Pre-test Counselling

Participants emphasized how challenging it was to fit in pre-test counselling for NIPT and prenatal testing in a busy prenatal session. Professional societies recommend discussing aneuploidy screening and diagnostic testing with all pregnant individuals as early as possible (ACOG-SMFM, 2020, Audibert et al., 2017; Benn et al., 2015; Chitayat et al., 2017). In addition, prenatal genetic screening is often offered to all patients at the first prenatal visit (Colicchia et al., 2016; Farrell et al., 2016). However, participants in this current study consider these initial visits information heavy. Early pregnancy visits usually include detailed physical assessments and in-depth discussions surrounding a patient's medical history (Best Start, 2020; Heathy Families BC, 2012). Genetic counsellors in the U.K. expressed concerns that other prenatal care providers cannot provide adequate counselling within the context of this already overstretched service (Alexander et al., 2015). Notably, primary care providers who engage in generalist practice in this current study, found pre-test counselling for NIPT challenging based on

the small part in their overall practice it played and the little time available to cover a large amount of information. In a recent survey of primary care providers from the United States, only 20% said they had sufficient time in their practices to counsel patients about genetic risk for disease (McCauley et al., 2017). One midwife in this present study noted that family physicians' time might also be limited given the large volume of patients they may see. Indeed, a recent survey reported that primary care physicians in Canada saw a median of 100 patients per week in 2019 (Canadian Institute for Health Information, 2020). Therefore, competing priorities in an otherwise busy prenatal session can impede prenatal care providers' ability to engage patients in decision-making about NIPT.

Other providers have identified the time constraints of a clinical encounter as a barrier for informed decision-making for NIPT and other prenatal testing options (Minkoff & Berkowitz, 2014; Lewis et al., 2013; Gammon et al., 2018; Gammon et al., 2016; Ngan, 2018; Burgess et al., 2020; Filoche et al., 2017; Farrell et al., 2016; Benachi et al., 2019; Alexander et al., 2015; Suskin et al., 2016). Pregnant individuals agree that the time available for consultation is not sufficient for thorough counselling (Lewis et al., 2013), and patients call for more information about NIPT from clinicians (Lewis et al., 2016b; Farrell, Mercer, Agatasa, et al., 2014; Lewis et al., 2013; Agatasa et al., 2015; Farrell, Agatasa, Mercer, et al., 2015; Lau et al., 2016). Individuals who had undertaken NIPT in Hong Kong noted in interviews that they often had various questions and concerns that went unaddressed due to the short appointment time with their provider (Lau et al., 2016).

Professional societies state that pre-test counselling should be performed in a manner "which allows patients sufficient time to understand information and make informed decisions regarding testing..." (American College of Obstetricians and Gynecologists, 2017, p.1). Obstetricians and Gynaecologists from Australia and New Zealand have indicated that 15 minutes is an appropriate length of time for pre-test counselling (Filoche et al., 2017). In reality, the time spent on pre-test counselling is far less. In a survey of South Korean obstetricians (n=203) regarding attitudes and practices of prenatal screening and NIPT, two-thirds of respondents spent between 1 to 5 minutes on prenatal

counselling for fetal aneuploidy (Kim et al., 2018). In addition, providers may not be covering all recommended counselling points. A qualitative study by Colicchia et al., 2016 analyzed transcripts and audio recordings of 210 obstetricians' first prenatal visits and found that only 1.5% of these providers covered all ACOG-recommended points for prenatal screening during the first prenatal visit (American College of Obstetricians and Gynecologists, 2007) and these sessions lasted less than 2 minutes (Colicchia et al., 2016). These results confirm prenatal care providers' challenges with prioritizing NIPT counselling, among other topics, within the limited time allotted for an early prenatal visit.

Despite the importance of this initial conversation, some prenatal care providers note how it can be difficult to make patients receptive to having this discussion. This challenge may be in part due to what Mishler (1984) describes as communication between two distinct worlds, including the biomedical world of physicians and the “life-world” of patients (Hunt et al., 2005, p.303). These differences in perspectives have been described as a “different language” (p. 303) being spoken between clinicians and patients by Hunt and colleagues (2005). As part of their everyday clinical work, prenatal care providers are primarily concerned about identifying and preventing health issues (Kleinman, 1980; Cohen et al., 1994). In contrast, patients exist in a world where health and illness are highly context-specific and rooted within their personal life histories, as well as their social and environmental situations (Hunt & Arar, 2001). Participants in this study, along with bioethicists, note that prenatal screening is often introduced within the context of the first prenatal visit while patients may still be adjusting to the news of a pregnancy (Allyse et al., 2013). During this time, individuals and their partners may also be experiencing feelings of joy, happiness, and pleasurable future expectations about their pregnancy and anticipated child (Kleinveld, 2008; Lou et al., 2017). Primary care providers recognize that a patient’s primary focus might be the overall protection and nurturance of their pregnancy.

Based on these competing priorities, it is not surprising that participants struggle to discuss prenatal screening during one of the first prenatal visits. Providers noted how screening creates the possibility that something could be wrong with the fetus and,

therefore, may be an unwelcome serious conversation during this time in pregnancy. Similarly, when discussing screening, some women have noted that they declined screening because they “did not think about it at all” (Bakkeren et al., 2020, p. 115) or did not want to think about what to do with a possible abnormal test result (García et al., 2008).

This study provides insight into the challenges prenatal care providers face with initiating the prenatal screening conversation while juggling various tenets of prenatal care within the same prenatal visit. Participants describe their initial discussion about a patient’s pregnancy as a conversation that shifts into biomedical knowledge and evaluation, which can devalue a woman’s “embodied knowledge” (Lou et al., 2017, p. 1321) and experience of pregnancy (Remennick, 2006). A patient’s overall reception of NIPT and how this technology has the potential to alter the broader patient experience of pregnancy is an area of research that has not received a lot of attention (Alexander et al., 2015). The need to discuss screening early in pregnancy with patients, especially NIPT, adds further complexity to this initial prenatal visit. Currently, professional society documents focus on NIPT counselling alone, giving very little guidance on approaching this conversation in the broader context of a prenatal screening visit.

Based on the previously discussed time constraints and competing priorities, providers were cautious about sharing too much information during pre-test counselling about the incidental findings that can occur with NIPT. Although providers believed it was unethical to withhold incidental findings from patients after testing, they did not discuss the possibility of these results in their pre-test counselling. Providers may have felt that this information fell beyond the scope of a routine prenatal session and could overwhelm patients. Guidelines available at the time of these interviews were variable in how they discussed incidental findings for NIPT. Some guidelines only mentioned that incidental findings could occur with this testing (ACOG-SMFM, 2015; Gregg et al., 2013). However, others directly stated that pre-test counselling for NIPT should include the possibility of unexpected findings (Benn et al., 2015; Sachs et al., 2015). Since these interviews, other guidelines have been updated to discuss the importance of pre-test counselling for incidental findings (Audibert et al., 2017). For example, ACMG states:

“Although it is not the purpose of [NIPT] to identify clinically relevant maternal genomic information, patients and providers should be aware of the potential for inadvertent discovery of such information...” (Gregg et al., 2016, p.7).

Information overload is an identified risk of pre-test counselling, where individuals can become burdened by the amount of information and choices offered (Bunnik et al., 2013). Indeed, when clinicians present too much information in too short of a time, patients can feel overwhelmed (Farrell, Agatisa & Nutter, 2014; Lewis et al., 2014; Barr & Skirton, 2013; Piechan et al., 2016; Agatisa, Mercer, Mitchum, et al., 2018), which can confuse and overload the patient and ultimately hinder the decision-making process (Chervenak & McCullough, 2014; Dondorp et al., 2016; Stapleton, 2017; Farrell, Agatisa & Nutter, 2014). Orta (2016) specifically designed a survey for members of the NSGC to investigate Genetic Counsellors' clinical practice surrounding incidental findings for NIPT. Half of the counsellors (56%) indicated that they do not always include the possibility for incidental findings in their pre-test counselling as this information further complicated pre-test counselling (Orta, 2016). Information overload in patients is a significant challenge to address in pre-test counselling, especially as NIPT screening expands and exacerbates the risk of overwhelming patients with information (Bedei et al., 2021).

Participants also experience difficulties managing patient expectations for prenatal screening and struggle to find ways to have patients fully understand the scope and limitations of screening tests in general. Patients may have unrealistically high expectations about what a prenatal screening test can tell them based on the increasing medicalization of pregnancy. The medicalization of pregnancy is the phenomenon of ever-expanding medical management and surveillance, and how pregnant individuals engage and depend on these medical technologies to manage their pregnancy (Inhorn, 2007; Lupton, 1999; Davis-Floyd, 2004). In response to this medicalized perspective, Rothman (1993) notes that prenatal surveillance technologies can influence an individual's experiences of pregnancy and create a “tentative pregnancy.” In response, an individual may feel less inclined to bond with their future child until they have an assurance that the fetus is “healthy” (Asch & Wasserman, 2005; Rothman, 1993;

Richardson & Ormond, 2018; Tymstra, 1991; Lippman, 1991; Williams et al., 2005; Chiang et al., 2007). This detachment is a psychological defense mechanism that can also help patients cope better if they eventually choose to terminate the pregnancy (Vanstone et al., 2018; Vanstone, Yacoub, Giacomini, et al., 2015; Lewis et al., 2012b). Providers in this study discussed how some patients expect a screening test to ensure that their fetus is “healthy.” As a result, the choice to undergo a screening test may be one to seek reassurance (den Berg et al., 2005; Götzmann et al., 2002; O’Connor et al., 2003) which can create unrealistic expectations about the scope of a screening test (Palomaki et al., 2017).

Although this delayed attachment to pregnancy or “tentative” pregnancy is not a new experience, participants discussed how NIPT enhances this phenomenon due to a lack of visual acknowledgement of pregnancy. For example, one participant noted how the decision to terminate a pregnancy earlier would be emotionally easier for patients based on the fewer ultrasounds involved compared to other screening and diagnostic testing methods. Depending on how NIPT is implemented, some pregnant individuals will have NIPT as their first prenatal genetic screen in their pregnancy. Accordingly, they may no longer be offered the first-trimester ultrasound included as part of multiple marker screening. In addition, the early timing of NIPT could also mean results before the detailed anatomical second trimester ultrasound. For some pregnant individuals, ultrasound plays an important part in bonding with their future child (Floyd et al., 2016). Participants also mentioned that as NIPT is performed early, termination can occur before the individual is visibly pregnant. Studies have found that pregnant women will withhold the pregnancy announcement (Öhman et al., 2006) as if they’re not pregnant (Aune & Möller, 2012) in situations where the fetus's health could be in question based on biomedical information. The timing of NIPT allows patients to have reassurance or consider additional follow-up testing before they must announce their pregnancy publicly.

With expanded screening available, NIPT may place the initial conversation of prenatal screening in a highly medicalized context by providing opportunities for more complex screening than traditional serum screening early in pregnancy. This context may lead

individuals to believe that they must choose the most comprehensive panel available to ensure that their fetus is “healthy.” For these reasons, prenatal care providers may encounter more patients with unrealistic expectations about NIPT as panels continue to expand. These expectations are a difficult underlying belief that must be addressed by prenatal care providers within the confines of an already busy pre-test counselling session.

These high prospects for NIPT can be especially problematic when counselling patients who may be unprepared in the event of an unfavourable outcome (Öhman et al., 2006). and the cognitive bias that leads people to believe that more desirable events, such as a “healthy” pregnancy, are more likely to occur (Chiang et al., 2007; Ajzen, 1996; Rose et al., 2016; Seavilleklein, 2009). ACOG and SMFM recommendations state that providers should counsel patients that a negative test result does not prevent an unaffected pregnancy (ACOG-SMFM, 2020). However, commercial labs use positive taglines such as: “For your baby’s health and your peace of mind” (Roche, 2021) and “Get peace of mind about the health of your baby earlier” (Panorama, 2021) to advertise NIPT. This vague positive messaging, as noted by Vanstone et al. (2015), describes a broader use for NIPT and emphasizes reassurance. This is in contrast to professional society documents, which describe a narrow use to NIPT as a screen for various conditions to decide whether or not to proceed with invasive diagnostic testing (Vanstone, Yacoub, Winsor, et al., 2015).

Participants in this study, experts, and other healthcare professionals are concerned that the understanding that NIPT is diagnostic is an incorrect belief shared widely by both patients and healthcare professionals (Mozersky et al., 2017; Long & Goldblatt, 2014; Advani et al., 2017; Stoll, 2013a; Stoll, 2013b; Stoll, 2014; Stoll & Lindh, 2015; Evans et al., 2016; Hui et al., 2015; Haidar et al., 2020). In addition, participants in the current study noted that their colleagues might not have time to make sure patients understand that NIPT is a screening test and is not diagnostic. In a survey of general obstetrics-gynecology professionals by Farrell et al. (2016), a few respondents reported that they “never/rarely” (4%) or only “sometimes” (11%) discuss the differences between diagnostic and screening tests. Updated guidelines from SOGC-CCMG published in 2017

emphasize that individuals and their health care providers “need to fully understand that cfDNA screening is not a substitute for invasive diagnostic testing” (Audibert et al., 2017, p.810). This misconception can prevent pregnant individuals from making informed decisions about NIPT due to confusion between diagnostic and screening tests.

Qualitative interviews before and after 2016 revealed that patients have misperceptions about the differences between a prenatal screen and diagnostic test (Floyd et al., 2016; Long et al., 2018). Studies have reported individuals terminating pregnancies based on a positive NIPT result without further verification through diagnostic testing (Dar et al., 2014; Dobson et al., 2016; Ramdaney et al., 2018). It was unclear what directions they received from their healthcare providers. As discussed previously, patients can be heavily influenced by a referring physician's counselling, especially those with a strong, trusting relationship with this provider (Bensend et al., 2014). Therefore, dispelling the misperception that NIPT is diagnostic may be a major barrier to counselling for prenatal care providers if another healthcare professional is also misinformed or has not taken the time to address the difference between a screening and diagnostic test.

One reason for the misperception that NIPT is diagnostic may be in part due to how prenatal care providers compare NIPT to other prenatal screening and diagnostic testing methods. For example, many participants in this study cite that NIPT has increased accuracy compared to other screening tests and that it's non-invasive compared to diagnostic tests like CVS. This comparison could lead to confusion as patients may erroneously believe this test is diagnostic, especially if the provider does not spend enough time educating the patient on this critical distinction.

A patient's impression that NIPT is diagnostic could also be due to the description of the test. As seen in other disciplines, labels that contextualize available options can affect and even manipulate a person's decision-making process (Dolan et al., 2017; Ho et al., 2012; Morris et al., 2010). Both PanoramaTM and HarmonyTM have labelled their maternal plasma cfDNA screening test “NIPT” (Harmony, 2021; Natera, 2021a), and educational materials specific to Ontario also refer to this testing by the same name (PSO, 2020). Joint SOGC-CCMG clinical practice guidelines acknowledge that this testing is “widely

referred to as NIPT,” but the preferred nomenclature is maternal plasma cfDNA screening (Audibert et al., 2017, p.810). Other guidelines also describe this procedure as cell-free fetal DNA screening (ACOG-SMFM, 2020; Salomon et al., 2014). To further emphasize that this method is not diagnostic, the American College of Medical Genetics and Genomics recommends the acronym NIPS, with the “S” representing “screening” (Gregg et al., 2016). Beyond the naming convention itself, Vanstone, Yacoub, Winsor, et al. (2015) note how many vendor documents, for both patients and providers, can have additional ambiguous or vague wording such as “detect,” “evaluate,” or “assess,” which can imply that the use of NIPT is for diagnostic purposes (Vanstone, Yacoub, Winsor, et al., 2015). Fisher et al. (2020) found that colloquial and industry-derived terms acted as sources of decision-making support by providing contextual information about screening options. The authors concluded that consumer-driven terms create the potential for patient attachment to industry-driven labels, which in turn could impact a patient’s decision-making in a clinical setting (Fisher et al., 2020). The impact on naming conventions is not well studied. Still, findings by Fisher et al. (2020) emphasize the need for non-biased education materials for both patients and providers that use the preferred terminology for NIPT to clarify expectations.

In addition, manufacturers marketing materials provided to both patients and providers are subject to bias and misleading language. For example, NIPT has been advertised by manufacturers as an assay that will provide “definite, informative results.” (Illumina, 2014, p. 5) (Resta, 2014; Stoll, 2013a; Stoll, 2013b; Stoll, 2014; Lewis et al., 2015). This confusing language may lead patients into thinking NIPT is diagnostic (Murdoch et al., 2017); which is especially concerning as patients have reported seeking information about this testing from these sources (Yi et al., 2013; Floyd et al., 2016; Lewis et al., 2016a; Daley et al., 2017; van Schendel, Van El, Pajkrt et al., 2017; Lau et al., 2016).

Patients’ and providers’ poor understanding of validation measures may also contribute to the misconception that NIPT is diagnostic. Participants mentioned that screening tests’ performance data such as false-positive and false-negative rates are difficult for patients to comprehend. These mathematical concepts underlying screening tests are not ones that most people encounter during their everyday lives, and this has caused confusion for both

patients and providers (Advani et al., 2017). For example, patients have misrepresentations around the accuracy of NIPT compared with that of invasive diagnostic tests (Floyd et al., 2016; Vanstone, Yacoub, Giacomini, et al., 2015; Vanstone et al., 2018). Accordingly, patients have reported a greater need for additional, more trustworthy information about the sensitivity and specificity of NIPT (Lewis et al., 2016b; Kibel & Vanstone, 2017; Floyd et al., 2016; Piechan et al., 2016; Farrell, Agatisa, Mercer, et al., 2015), and the implications of false-positive or false-negative results (Farrell, Agatisa & Nutter, 2014; Floyd et al., 2016; Farrell, Agatisa, Mercer, et al., 2015). Participants in this study did not say they have difficulties comprehending performance metrics for NIPT; however, healthcare providers in Lebanon and Quebec showed concerns regarding providers' lack of knowledge about NIPT's performance measures, such as its sensitivity and specificity (Haidar et al., 2020).

Many providers in this current study do not differentiate between the detection rates for aneuploidies beyond trisomy 21, and very few mentioned any additional validation measures to their patients. This practice occurred despite guidelines in 2016 stressing the importance of discussing the potential for PPV and/or false-positive results during pre-test counselling (ACOG-SMFM, 2015; Langlois et al., 2013; Wilson et al., 2013). Without discussing these additional performance metrics, some patients may be led to believe that NIPT is diagnostic. The European Society of Human Genetics and the American Society of Human Genetics released a position document in 2015 stressing that “although 10 times better than the PPV of current first-trimester screening in a similar population... [these values are] still far below the near 100% required for a diagnosis of Trisomy 21” (Dondorp et al., 2015, p.1439).

The performance data for different conditions can also become overlooked, combined, and confused with other metrics, impairing reliable genetic counselling for low-risk populations and the various conditions that NIPT can screen for (Di Renzo et al., 2019; Rose et al., 2016; Dondorp et al., 2015; Kliff & Bhatia, 2022). Updated guidelines such as SOGC-CCMG and ACMG discuss how these different performance values are essential for healthcare providers and patients to discuss in order to enable more accurate and informative counselling (Audibert et al., 2017; Gregg et al., 2016). They state that

laboratories should provide visible and clearly stated detection rates, specificities, positive predictive values, and negative predictive values for each condition being screened in pretest marketing materials to support patients and providers in making decisions. Despite these recommendations, these specific performance metrics are not always present in marketing materials; PanoramaTM, for example, provides the sensitivity and false-positive rate only for trisomy 21 screening in marketing materials (LifeLabs, 2018). Confusion with performance metrics and misleading messaging may “blur the line” between screening and diagnostic testing (Rose et al., 2016, p.10). There is a clear need for further education of physicians regarding NIPT's technical capabilities and limitations. Furthermore, consistent guidelines should be developed to guarantee that tests are validated and robust and that knowledgeable professionals provide appropriate pre-test counselling.

Clinicians in this current study did not discuss differences in performance measures with expanded panel testing in 2016 as they may not have been aware of this data at the time. However, some genetic counsellors from the U.S. emphasize that prenatal care providers are still not informed about these specifics and emphasize the importance of providing this education (Kliff & Bhatia, 2022; Agatisa, Mercer, Coleridge, et al., 2018). Pregnant individuals have also said they would like more detailed information about the performance measures of NIPT. Additional information includes the sensitivity and specificity of NIPT (Lewis et al., 2016b; Kibel & Vanstone, 2017; Floyd et al., 2016; Piechan et al., 2016; Daley et al., 2017; Farrell, Agatisa, Mercer, et al., 2015) and the implications of a false-positive or false-negative result (Farrell, Agatisa & Nutter, 2014; Floyd et al., 2016; Farrell, Agatisa, Mercer, et al., 2015).

The confusing performance measurements of NIPT are exacerbated by the microdeletion syndromes available for testing (Kliff & Bhatia, 2022). Expanded screening provides a risk assessment about numerous conditions that conventional prenatal screening has not previously assessed, with associated metrics for each (Suskin et al., 2016; Palomaki et al., 2017). Due to the low incidence in the general population, the PPVs for the five microdeletions currently offered are low, and the risk of false positives is high (Bianchi et al., 2014; Meck et al., 2015; Vora & O'Brien, 2014). For example, NateraTM recently

released a new study on the performance of NIPT screening for 22q11.2 and reported a PPV of 52.6% (n=18,043) (Dar et al., 2022). Consequently, this will increase the number of invasive procedures performed to verify results, which screening tests like NIPT are designed to avoid (Audibert et al., 2017; Dondorp et al., 2015).

In addition, there is concern that commercial laboratories have proprietary approaches to obtaining these validation measures, and this data is often hard to find or is not provided at all (Skrzypek & Hui, 2017; Shaw et al., 2020; Ye et al., 2021; Harmony, 2019; Kliff & Bhatia, 2022). HarmonyTM, for example, currently does not give a detection and false-positive rate for 22q11.2. Instead, a report states that, “limited numbers of 22q11.2 cases have been evaluated to date” (Harmony, 2019, p.8). Patients were recently interviewed for a New York Times article investigating the performance of microdeletion panels for NIPT. These individuals wished they had been informed about these false-positive rates for microdeletion syndrome before agreeing to test (Kliff & Bhatia, 2022). Indeed, patients have noted anxiety and uncertainty related to confusion surrounding the accuracy, false-positive, and false-negative rates of prenatal testing (Lewis et al., 2016a; Li et al., 2017; Yi et al., 2013; Farrell, Agatisa & Nutter, 2014; Mozersky, 2015; Floyd et al., 2016; Farrell, Agatisa, Mercer, et al., 2015; Vanstone, Yacoub, Giacomini, et al., 2015). Others were concerned about how they would cope with the potential outcomes associated with false-positive and false-negative results of NIPT (Kibel & Vanstone, 2017; Li et al., 2017; Lewis et al., 2013). In addition, systematic reviews suggest expanded panels have higher false-positive rates than those reported by the manufacturers (Badeau et al., 2017; Varela-Lema et al., 2018; Iwarsson et al., 2017; Taylor-Phillips et al., 2016). Other authors suggest that the PPV and NPV rates in marketing materials, and in some cases, test reports, are inflated as well (Stoll & Lindh, 2015). It is therefore important that unbiased sources such as Prenatal Screening Ontario update their website to provide some information on what is known about the performance measures for microdeletions (PSO, 2019b).

Providers in this study also noted how difficult it would be to counsel for conditions beyond traditional aneuploidies as they can have variable phenotypes. This variability also introduces a level of uncertainty to their counselling that they were uncomfortable

providing. Certainly, SCAs may have a generally mild phenotype, while others are asymptomatic and never diagnosed (Health Quality Ontario, 2019a; Geeter, 2015; Benn, 2016; Viuff et al., 2015). Similarly, the microdeletions currently available for NIPT screening present phenotypic variability with very little information available for assessing their clinical significance (Armour et al., 2018; Agatista, Mercer, Coleridge, et al., 2018; Dukhovny & Norton, 2018; Benn, 2016; Gammon et al., 2016; Health Quality Ontario, 2019a; Samura, 2020). Providers felt the additional uncertainty that comes with these options only further complicated a patient's decision-making process, and pre-test counselling challenges for these expanded disorders would be multiplied exponentially as screening options grow. Previous studies have indicated how difficult it is to engage patients in decision-making without a clear understanding of the condition itself (Agatista et al., 2015; van Schendel et al., 2014; Gregg et al., 2016; Geeter, 2015). It is also challenging to discuss these conditions concisely and in a way that is accessible to patients (Han et al., 2017; Skinner et al., 2016). Therefore, these expanded options for NIPT screening have several challenges that require extensive pre-test counselling (Bedei et al., 2021). Guidelines acknowledge these counselling challenges before and after these interviews (Salomon et al., 2017; Dondorp et al., 2015; Gregg et al., 2016), including SOGC-CCMG's updated guidelines, which states that "screening for microdeletions involves complex issues of pre-test...counselling that is currently unresolved" (Audibert et al., 2017, p. 812).

The concept of uncertainty is not new to prenatal genetics (Hogan, 2016). Newson et al. (2016) introduced the idea of genomic uncertainty, which they define as "...information...obtained from genomic testing that is imperfect or unknown, leading to uncertainty in clinical diagnosis or management" (p.3). Experiences of genomic uncertainty may create stress, a reduced sense of coherence, and loss of control (Newson et al., 2016). In addition, the individuals hope for a "healthy" fetus, and this added uncertainty may "cast a shadow on [an individual's] ... emotional experience around the pregnancy" (Di Renzo et al., 2019, p.4). In addition, introducing greater chances for uncertainty was likely concerning to these prenatal care providers as genetic testing is meant to reduce this uncertainty (Sankar et al., 2006). Uncertainty is prevalent in genomic medicine but is often framed negatively; it is usually desired as something that

needs to be avoided or eradicated. Individuals can see these uncertainties as a burden as they now face complex decision-making (Crawford et al., 2013).

Participants noted that this uncertainty is akin to that experienced with prenatal microarray testing. As prenatal microarrays look at chromosomal abnormalities at a higher resolution than traditional karyotype analysis, microarray technology can also detect microdeletions (Lefebvre et al., 2016). Some centers offer a microarray test to all individuals undergoing invasive testing (Armour et al., 2018). Providers felt that lessons learned with counselling for prenatal microarray testing could perhaps guide how to counsel for uncertainty when discussing expanding NIPT's use.

Newson et al. (2016) suggest healthcare providers directly acknowledge uncertainty during pre-test discussions when considering complex genomic testing. Instead of framing genetic testing to eliminate uncertainty, providers should help patients cope with the inevitable uncertainty of genetic testing. The authors argue that this involves complex pre-test counselling, where providers discuss uncertainty in a structured and supportive way, while ensuring that uncertainty becomes constructively incorporated into the decision-making process (Newson et al., 2016). The ACMG recognizes as well that the ever-evolving technology of NIPT should include pre-test counselling that explores the patient's ability to accept uncertainty concerning possible screening outcomes (Gregg et al., 2016). To tackle complex concepts in NIPT counselling, such as uncertainty, prenatal care providers must engage in a genetic counselling model that promotes psychosocial support (Ferrier et al., 2013). For example, the "counselling model" of genetic counselling emphasizes the support of patients on an emotional and personal level while still providing education (Kessler, 1997). Ideal counselling consists of an appropriately trained professional who understands genetics and provides psychosocial support (Sequeiros & Ka, 2008).

To counterbalance the complexity of pre-test counselling for conditions with variable phenotypes, one clinician in this study mentioned the need for two different tiers of counselling: those individuals who paid privately versus those who undergo public screening. Despite the increasing complexity of counselling expected of prenatal care

providers, clinicians are reimbursed for offering and counselling on NIPT at the same rate as counselling for other prenatal screening tests (Burgess et al., 2020). In addition, prenatal care providers may feel that private counselling could offer the additional time and expertise required to counsel on expanded testing, compared to what they could provide within the confines of their prenatal visit. In response to the growing need for genetic counselling in general, commercial laboratories employ increasing numbers of genetic counsellors (Stoll et al., 2017). More specifically, privatized genetic counselling support has been made available in Canada for select genetic tests after 2016 (Genolife, 2021; LifeLabs, 2021). However, private laboratories' patient education materials and counselling may not necessarily be neutral, as the company may profit from a patient's decision to undergo testing (Stoll et al., 2017; O'Brien & Dugoff, 2018; Vanstone, Yacoub, Winsor, et al., 2015). Although societies like the NSGC have published a code of ethics that states genetic counsellors must acknowledge and disclose any conflict of interest (NSGC, 2021), further regulation is required for this process. The discussion of a two-tier system for NIPT illustrates a need for policy determining best practices within the Canadian healthcare system and for the need to discuss private pay testing with patients. This statement also highlights the prenatal care provider's desire for a more overt definition of their role as a prenatal counsellor compared to a genetic specialist, especially as the options for private pay expand.

5.1.3 Engaging Patients in Decision-making

As the provider who often introduces prenatal screening to their patients, participants discussed the importance of this initial conversation in order to understand their patients' values and beliefs and set general screening goals. Providers begin this discussion by identifying if prenatal testing options will support the patient's values and belief systems. This preliminary discussion in genetic counselling is known as contracting (Veach et al., 2018). Contracting is the "...two-way communication process between the genetic counsellor and the patient/client, which aims to clarify both parties' expectations and goals for the session" (Accreditation Council for Genetic Counselling, 2019, p.8). According to prenatal counselling guidelines, this is a fundamental process to undergo in genetic counselling (Gregg et al., 2016; Wilson et al., 2013; ACOG-SMFM, 2020) and

informed decision-making “rests on the practice of contracting with patients” (Case et al., 2007, p.655). Our findings revealed how prenatal care providers utilized contracting as an essential first step in the decision-making process for NIPT.

Participants described their role in NIPT pre-test counselling as communicating adequate information about the test to facilitate informed decision-making and choice. Effective communication of relevant information is essential for pre-test counselling and informed decision-making (Ferrier et al., 2013). Relevant information in this context, according to our results, were the indications for NIPT screening, as well as its advantages and limitations compared to other prenatal screening and diagnostic options. This information is analogous to what other providers self-reportedly discuss with their patients and what is recommended as key discussion points by professional societies and expert groups (Audibert et al., 2017; Chitayat et al., 2017; Devers et al., 2013; Salomon et al., 2014; ACOG, 2017; Wilson et al., 2013; Gregg et al., 2016; Sachs et al., 2015; Tognetto et al., 2019; Rink & Kuller, 2018; ACOG-SMFM, 2020).

Many participants did not counsel on expanded options for NIPT, despite these options being available for private pay. Some providers did not discuss these options with patients because they were unaware they existed. In contrast, others may have chosen to omit this information based on their struggle to perceive the clinical usefulness of screening for these conditions and the sparse validation data available. These two motives were also listed among the reasons genetic counsellors do not offer expanded testing at all in their practice (Flynn, 2018). In addition, these reasons are why guidelines and expert groups do not recommend NIPT as a first-tier screening test for these conditions (Gregg et al., 2016; ACOG-SMFM, 2020; Audibert et al., 2017). Providers may have also been uncomfortable discussing the uncertainty of these disorders with patients. Guidelines acknowledge these counselling challenges (Salomon et al., 2017; Dondorp et al., 2015), including SOGC-CCMG, which states that “screening for microdeletions involves complex issues of pre-test...counselling that is currently unresolved” (Audibert et al., 2017, p. 812). Rather than withholding this information from patients, additional support in this area could provide prenatal care providers with the skills to participate in

more complex pre-test counselling conversations about expanded screening options for NIPT.

5.2 Support Required

Primary care providers have raised concerns that further genetic responsibilities will be given to them without sufficient support (Harding et al., 2019). In addition to the implicit discussion surrounding participants' need for more guidance and education, participants in this study expressly spoke about the support they require as they take on a larger role in prenatal counselling for NIPT. There is also an overall need for bolstering education and dissemination efforts and updating guidelines and regulations to accommodate the expanding options of NIPT. This support will ensure prenatal care providers can deliver adequate counselling in an otherwise busy prenatal session.

5.2.1 Need for Regulations and Directives

Providers indicated they felt pressure from the industry to adopt NIPT quickly in a practice setting. Industry involvement of this technology has rapidly led to intense competition between companies for patents, markets and commercial exploitation of NIPT (Löwy, 2020). Much of the commercialization and innovation of this testing has occurred in the United States, with Canada experiencing intense pressures of this testing as a result (Agarwal et al., 2013). Consequently, participants from this study expressed the need for stricter regulations for ordering NIPT to ensure access for all pregnant individuals is appropriate and equitable. Some worry that NIPT is not cost-effective in how it's currently being used. There is empirical evidence that providers are inappropriately using public funding for NIPT in Ontario. Bellai-Dessault et al. (2020) reported in the descriptive cohort study of all pregnant individuals who received NIPT screening in Ontario between January 2016 to December 2017, that 2.9% of all publicly funded NIPT tests (N= 11,166) were administered to pregnant individuals who were not eligible for funding between January 2016 to December 2017. These individuals had discrepancies between the clinical indication and the data entered into the BORN registry. For example, of the patients who received funding for the indication of "increased nuchal translucency measurement," 17.9% of these individuals did not meet

this criterion. The authors postulated that misuse of screening resulted from a lack of awareness of funding guidelines, especially in the first month of public funding for NIPT screening in Ontario. A clinician from the current study observed other colleagues purposefully taking advantage of public funding as a means for access to low-risk patients who may not be able to afford to test. Although funding criteria for Ontario were eventually codified in 2018 and circulated more widely, providers may still purposefully misuse public funding criteria to provide patients access to testing. Therefore, it is essential to develop strategies to monitor and ensure the appropriate utilization of publicly funded testing of NIPT.

A significant finding from this current study was that participants strongly expressed a need for guidelines and regulations to be updated to correspond with the current testing practices. In 2016, guidelines by some expert groups such as SOGC were outdated and had not yet provided any information about expanded testing (Langlois et al., 2013; Gregg et al., 2013). Other guidelines available in 2016, as well as current recommendations, do not recommend routine screening for fetal microdeletions (ACOG-SMFM, 2015, 2020; Audibert et al., 2017). However, screening for SCAs is available through basic NIPT panels and microdeletions as a self-pay option in Ontario (Harmony, 2021; Natera, 2021a). Of all the pregnant individuals who underwent NIPT between January 2016 to December 2017 in Ontario (N=23,845), 33% chose private pay (Bellai-Dussault et al., 2020). A recent study of Canadian professionals, including geneticists, genetic counsellors, and nurses, reported NIPT as the second most frequent private pay genetic test discussed (Di Gioacchino et al., 2019). More specifically, there is evidence that many individuals are ordering expanded testing, with NateraTM reporting over 400,000 NIPT screening tests for the 22q11.2 microdeletion in 2020 (Natera, 2021b).

Despite the possibility of individuals choosing to pay for screening for sex selection and expanded panels using NIPT, very little guidance still exists for pre-test counselling for SCAs and microdeletions. Providers in this study discussed their discomfort with dealing with counselling situations where they discussed topics like sex selection. Ultimately this distress can be positively associated with burnout and negatively associated with job satisfaction (Bernhardt et al., 2009; Bernhardt et al., 2010; Johnstone et al., 2016). Other

clinicians have noted the intensive industry-driven marketing aimed at the consumer, which remains ahead of established clinical practice guidelines (Rink & Kuller, 2018). Additional attention should be placed on addressing the effects of clinician well-being as this counselling becomes more complex. Providing this support will help address the possible occupational distress and burnout that these prenatal care providers may be experiencing, which has also been reported in prenatal genetic counsellors (Benoit et al., 2007; Bernhardt et al., 2009; Figley, 2002; Johnstone et al., 2016).

Some professional position statements and guidelines provide conceptual guidance on using NIPT for non-medical fetal sexing. However, not all resources have been clear or consistent before and after this study's interviews were completed. For example, some guidelines have stated that NIPT should not be performed if the indication is only for sex identification (ACOG-SMFM, 2015) and others have encouraged providers to deter patients from screening for these purposes (Gregg et al., 2016). The most recent joint SOGC-CCMG guideline for NIPT directly addresses the ethical conflicts prenatal care providers feel towards using this testing for non-medical reasons, such as fetal sexing, stating that it is not indicated "...even with patient autonomy considerations" (Audibert et al., 2017, p. 813). In contrast, a position statement from the Board of the International Society for Prenatal Diagnosis (ISPD) in 2015 states that individuals should have the option to choose sex chromosome analysis for NIPT (Benn et al., 2015). ACOG's latest clinical management guidelines for obstetrician-gynaecologists in 2020 does not explicitly address the use of NIPT for this purpose and only notes that "...if fetal sex determination is elected, the risk of maternal and fetal sex chromosome aneuploidy should be discussed as a potential finding" (ACOG-SMFM, 2020, p.e56).

The lack of agreement among these resources makes it difficult for real-life applications. Certified nurse-midwives from the U.S. noted in the qualitative portion of a survey that a significant challenge in counselling for NIPT, in general, was the absence of consistent professional guidelines (Weingarten, 2016). In addition, these guidelines do not directly address how to counsel patients on sex determination or sex selection. Genetic counsellors have explained that their discomfort with handling counselling surrounding non-medical sex selection is due to a lack of training and practical guidance (Orr-

Ferdinand, 2021; Burke, 1992). Therefore, prenatal care providers in this study might feel uncomfortable with counselling for non-medical indications based on a lack of tools to navigate this morally sensitive topic. Guidelines require updating to reflect the possibility of this testing and provide more standardized guidance on counselling patients interested in paying for these expanded options.

Many providers emphasized how important it was to regulate what conditions NIPT can be used to screen, including distinguishing between those that should be publicly and privately available. This is especially important as companies push to screen for more conditions, with the eventual goal of mapping the entire fetal genome (Lefkowitz et al., 2016; Hui & Chiu, 2016; Rojahn, 2013). In Ontario, clinicians are reimbursed for offering and counselling about NIPT at the same rate as counselling for other prenatal screening technologies (Vanstone, Yacoub, Giacomini, et al., 2015; MOH, 2021). However, additional counselling is more complex and takes longer for microdeletions and SCAs (Health Quality Ontario, 2019a). Therefore, participants in this study were concerned about spending additional public healthcare resources on counselling patients for expanded panels that are privately paid for. Ongoing regulation on how this counselling is reimbursed is crucial as the expansion of this technology is moving at an unprecedented pace (Swaney et al., 2016; Murdoch et al., 2017; Health Quality Ontario, 2019a; Benn & Chapman, 2016; Agatista, Mercer, Coleridge, et al., 2018).

In this study, prenatal care providers, genetic counsellors and other healthcare professionals believe that clinical utility and validity are essential measures of whether a condition is appropriate to screen for using NIPT (Alexander et al., 2015; Vora & Wapner, 2018). Several systematic reviews and meta-analyses have been conducted to investigate these NIPT measures in common aneuploidies and SCAs. However, most have focused on the high-risk population (Gil et al., 2017; Mersy et al., 2013; Mackie et al., 2017; Yang et al., 2015; Jin et al., 2017). Only a few reviews exist for the average-risk or general population, with even less including SCAs (Badeau et al., 2017; Varela-Lema et al., 2018; Iwarsson et al., 2017; Taylor-Phillips et al., 2016). Badeau et al., 2017 note that there is a “paucity of data” (p. 2) on the accuracy of NIPT as a first-tier aneuploidy screening test in a population of low-risk individuals. In reviewing the

accuracy of NIPT across studies, Health Quality Ontario reported a lower sensitivity and specificity for NIPT compared to that which was reported by manufacturers. The authors speculate that this could have been because most of these studies focused on the high-risk population, which has a higher test sensitivity for trisomies 21, 18 and 13 (Health Quality Ontario, 2019a).

NIPT screening for microdeletion syndromes have not undergone large-scale studies, and sparse test performance information is available (Health Quality Ontario, 2019a; Bedei et al., 2021). Due to the rarity of these syndromes, the determination of sensitivity and specificity is difficult to obtain based on the large numbers of patients that would need to be involved in clinical validation studies (Health Quality Ontario, 2019a). Therefore, additional published data is required to firmly establish performance metrics for NIPT in the low-risk population and for expanded conditions. Ongoing discussions surrounding clinical utility and unbiased large-scale validation studies should continue to be performed on expanded panels in both low and high-risk populations in order to inform regulations on what conditions NIPT should screen for.

As commercial laboratories are conducting many of these large-scale tests and validating this technology (Norton et al., 2015; Dan et al., 2012; Chen et al., 2011; Chiu et al., 2008), there is significant risk of bias in research outcomes. This bias includes a likelihood that benefits of testing are exaggerated, and their potential harms are downplayed (Omenn et al., 2012; Roseman et al., 2011; Lumbreras et al., 2009; Bell et al., 2006; Petersen & Krisjansen, 2015; Fugh-Berman, 2013; Tsilidis et al., 2013; Lexchin, 2012; Stamatakis et al., 2013). As much of the research is done in private laboratories, some suggest a lack of independent monitoring and evaluation. This oversight can lead to bias or proficiency issues (Takoudes & Hamar, 2015). For example, two meta-analyses on the performance of NIPT noted that many published studies had low-quality methodologies. Many studies were labelled at high-risk for bias as they used case-control studies or did not explicitly state how their samples were selected (Gil et al., 2015; Gil et al., 2019). Similarly, many of the test accuracy studies reviewed for the Health Technology Assessment of NIPT in Ontario were identified as having a substantial risk of bias due to the lack of clarity in the method of patient enrolment

(Health Quality Ontario, 2019a). In addition, the independent confirmation of test performance and utility can be hindered by a manufacturer's ownership of a patent, which can restrict independent access to technologies (Thumm, 2004). Independent confirmation of test performance is essential, especially as NIPT screens for the number of conditions expand.

Prenatal care providers discussed their feelings of commercial pressures in the NIPT industry and the fear that introducing screening for additional conditions could lead down a slippery slope. Currently, no validation thresholds exist before a certain condition can be marketed and released for clinical use for NIPT screening. Creating these regulations could reduce current pressures on prenatal care providers, who struggle with understanding this performance data, and support them in the subsequent gatekeeping they must face with these expanded conditions.

Providers in this current study desired more transparency in creating policies and guidelines. They also thought that they should be directly involved with policy development. This issue is crucial to address, as prenatal care providers were not directly involved with NIPT's public health policies in 2014. As these providers are central in public testing and take on a more prominent role in pre-test counselling, providers in this study believed it is crucial to involve them in policies directly impacting their practice. U.K. genetic counsellors in the Alexander et al. (2015) study strongly believed that professionals trained in this test should have some influence on how the test is offered and used. Prenatal care providers involved in policy creation is consistent with the "bottom-up" philosophy of engagement, which involves reviewing and developing recommendations by those expected to apply them. It starts by analyzing what is necessary for policy implementation with those closest to the problems (Elmore, 1980; Sabatier, 1986). After this study was conducted, the provincial prenatal screening program "Prenatal Screening Ontario" launched in 2018 has created various committees and working groups which depend on experts' and advisors' input to certify all elements of a robust screening program implementation (PSO, 2020). As the expansion of NIPT continues, it is imperative to keep prenatal care providers informed and engaged within these working groups.

Participants also thought it was important to have standardized guidelines surrounding information and counselling on NIPT. Other clinicians have expressed a desire for more trustworthy and definitive information and evidence about this testing (Horsting et al., 2014; Gammon et al., 2016; Filoche et al., 2017; Alexander et al., 2015; Suskin et al., 2016). The media's portrayal of NIPT has been framed mostly by industry and therefore the perception of this testing is predominately positive (Kamenova et al., 2016).

However, recently, the New York Times published an article titled "When They Warn of Rare Disorders, These Prenatal Tests are Usually Wrong" (Kliff & Bhatia, 2022). This article questions the performance measures of NIPT for microdeletion syndromes and acknowledges that these companies are biased in their messaging. Articles like this one, although criticized for its inflammatory messaging (Matloff, 2022), emphasizes the need for standardized information that often is seen between advertised test capabilities, professional recommendations, and actual clinical use (Gammon et al., 2016; Kloza et al., 2015; Haymon et al., 2014).

Educational resources are still heavily created and disseminated by the companies that sell NIPT (Vanstone, Yacoub, Winsor, et al., 2015; Kamenova et al., 2016; Panorama, 2021; Natera, 2021a). However, some educational resources, including webinars, modules and courses, have been developed by independent third parties since this study ended (ACOG, 2021; Perinatal Quality Foundation, 2022; Genetics Education Canada, 2020). Still, after these interviews were conducted, O'Brien & Dugoff (2018) noted a high level of variability reported in presenting informational materials for NIPT, both within and across commercial laboratories. Indeed, Ontario providers still voiced a need for standardized information from an unbiased, trustworthy source in 2018 (Burgess et al., 2020).

5.2.2 Education and Dissemination of Information

Participants noted that the dissemination of information surrounding the overall process of NIPT was suboptimal when it was first rolled out. Publicly funded screening for NIPT in Ontario was introduced in 2014, with no province-wide education or training strategy for providers (Bellai-Dussault et al., 2020). The original policy surrounding public funding was not written or publicized and instead was exclusively shared through word

of mouth (Burgess et al., 2020). At the time of interviews in 2016, these policies were distributed more widely. Commercialization of this test through Ontario-based commercial laboratories also increased awareness of these tests by this time. Providers mentioned that they learned about NIPT through various methods, including conferences, meetings, information through their genetics department, continuing medical education, the Ministry of Health, companies offering the test, specialty organizations such as the SOGC and word of mouth from other professionals.

Despite a broader distribution of information since its implementation in Ontario, participants in this study still report a lack of knowledge with NIPT. Many clinicians report low knowledge and confidence in NIPT (Horsting et al., 2014; Gammon et al., 2016; Filoche et al., 2017; Alexander et al., 2015; Suskin et al., 2016). A greater need for education in NIPT has even been identified for genetic counsellors. In 2019, a special interest group for NSGC conducted a survey to assess genetic counsellors' current genomic technologies knowledge. Even for those counsellors who received their degree in more recent years (2000-2015) (n=171), some (40%) said that they required "some" or "significant" amount of additional training in NIPT in order for them to perform their practice adequately (Hagman et al., 2020).

In addition, specialist providers (e.g., obstetricians, maternal-fetal medicine specialists) in this current study felt that family physicians' knowledge of NIPT was inadequate, considering their involvement in the NIPT's pre-test counselling process. Beyond self-reporting, recent studies have measured a lack of knowledge and understanding of NIPT in obstetricians from countries such as the United States and New Zealand (Brewer et al., 2017; Filoche et al., 2017; Mayes et al., 2016). In addition, some patients have reported that their clinician did not have enough knowledge about NIPT to provide counselling (Kibel & Vanstone, 2017; Floyd et al., 2016; Lau et al., 2016; van Schendel, Kater-Kuipers, van Vliet-Lachotzki, et al., 2017). In 2018, prenatal care providers still self-perceived a strong need for more NIPT education in Ontario, based on qualitative interviews conducted by Burgess et al., 2020. Providers have also discussed a lack of knowledge of the different companies and labs that offer versions of NIPT in Ontario (Burgess et al., 2020). This knowledge deficit creates a barrier to counselling and can

severely impair a provider's ability to engage their patients in informed decision-making for NIPT.

Importantly, prenatal care providers in this study conveyed that it is challenging to keep up to date about expanded panels available for NIPT and potential incidental findings. For example, many participants were unaware of maternal genomic information that testing could identify and many also did not know that several companies offer the option to screen for microdeletions. This lack of knowledge is representative of the educational delays that prenatal care providers experience with implementing new technology into their practice setting. Since 2016, expert groups such as SOGC-JOGC have included information in their guidelines about the possibility of incidental findings including performance metrics of the microdeletions offered (Gregg et al., 2016; Audibert et al., 2017). However, surveys still report gaps in knowledge for providers regarding the availability of NIPT testing for microdeletion syndromes (Brewer et al., 2017; Filoche et al., 2017; Mayes et al., 2016; Swaney et al., 2016).

Knowledge translation is the dynamic process of bridging the gap between generated knowledge and practice (Straus et al., 2009; Davis et al., 2003; Landry et al., 2006). Knowledge translation strategies extend beyond creating more information and focus on "how" this information is disseminated to participants in practice. Unfortunately, translating knowledge into clinical practice takes time (Morris et al., 2011) and is one of the most challenging problems in health care (Khoury et al., 2007). For example, studies have demonstrated a continued lack of knowledge and confidence in genomic medicine from prenatal care providers, despite high-quality genomics references and education materials available (Feero et al., 2016). The process of knowledge translation needs to be an active, tailored, and targeted distribution of education and training (Chapman et al., 2020). Even if much-needed updates to professional society's guidelines and policies are developed, there are challenges to inform health providers of these items. One participant mentioned that it is helpful when guidelines and policies provide information on accessing the most up-to-date NIPT information. Prenatal care providers in this study also stated that they preferred either in-person or electronic formats for ongoing NIPT education. These informational sources have been mentioned more recently as a way

prenatal care providers would like to be informed of any updates to this screening (Benachi et al., 2019; Filoche et al., 2017; Burgess et al., 2020).

One clinician provided Cancer Care Ontario (CCO) as a specific example of an organization that successfully disseminates information and updates to guidelines. CCO has a strategy to foster community by publishing a regular newsletter to keep members updated on learning opportunities and general information in cancer guideline development (Browman, 2012). CCO represents a programmatic approach that focuses on knowledge translation; this same approach is necessary when providing ongoing education of prenatal care providers performing NIPT counselling. In August 2019, Prenatal Screening Ontario launched its new website, which provides information for pregnant individuals, families, and healthcare providers (<https://prenatalscreeningontario.ca>). Part of PSO's mandate is to "provide education supports, information, and transparency needed for health care providers and pregnant individuals and their families to make informed decisions" (PSO, 2020). This website has information that addresses the possibility of unexpected fetal or maternal results and some information about expanded testing for NIPT (PSO, 2020). However, with the ongoing expansion of NIPT, it is vital to review and augment PSO's information about the expanded testing available. These updates include providing easy to access education regarding the different performance metrics of this testing to prenatal care providers.

Another significant finding of this study was that prenatal care providers specifically addressed the need for better distribution of information for family physicians. Indeed, these primary care providers may be challenged by rapidly changing information in this genomic era of prenatal testing (Huang et al., 2018). Previous research indicates that primary care providers, including family physicians, mentioned that they do not know where to find information about genetics or available genetic tests relevant to their practice (Carroll et al., 2019; Carroll, Makuwaza, Manca, et al., 2016; Haga et al., 2011; Manolio, 2017; Sebastian, 2020). It is clear from this study that family physicians specifically require dissemination strategies for new information regarding NIPT that are accessible to meet their needs as general practitioners. Some participants discussed the importance of providing accessible education through in-person outreach programs for

primary care providers or electronic forms of communication. They emphasized that this information must be accessible to all prenatal care providers who are unwilling or unable to attend in-person conferences. Indeed, these strategies could be essential for busy family physicians (Alexander et al., 2015; Adams et al., 2015) in isolated settings with little access to genetic professionals (McCauley et al., 2017).

5.2.3 Importance of Genetics Professionals

A lack of comfort with pre-test counselling patients for NIPT may explain why some participants referred patients to genetics when NIPT first became available. It may also be why some family physicians in this study said they still referred their patients to genetics for pre-test counselling. Professional societies recommend that if a patient requests further information about conditions before the screening, it is ideal to refer them to a qualified provider for a more detailed discussion (Benn et al., 2015; Allen et al., 2017; Bensend et al., 2014). The ACOG also encourages healthcare providers to refer patients to a more specialized provider, such as a genetic counsellor, if they do not have the "... necessary knowledge or expertise in genetics to counsel a patient appropriately" (ACOG, 2017, p. 693). Indeed, other physicians have noted that feelings of unpreparedness would discourage them from engaging in any genomic medicine, and instead, would refer to a genetic counsellor (Christensen et al., 2016).

However, the strategy of referring to genetics becomes problematic if there are not enough specialists to handle an increasing caseload (O'Brien & Dugoff, 2018; Burgess et al., 2020). By 2018, Ontario specialists have largely rejected referrals for cases that primary care physicians could otherwise manage (Burgess et al., 2020). These gaps in education and awareness emphasize how important it is that prenatal care providers become knowledgeable and comfortable in NIPT counselling, especially as they take on more counselling responsibilities in their prenatal role.

Prenatal care providers identify genetic professionals as valuable sources of information and support for implementing NIPT in their practices. Overall, prenatal care providers who have incorporated genetics in practice emphasized the importance of genetic professionals (Qureshi et al., 2004; Hamilton et al., 2014; Carroll, Makuwaza, Manca, et

al., 2016). Participants mentioned the positive impact of having genetic departments physically close to where they practice; “hallway consults” were helpful to be kept informed and up-to-date. Closer relationships may naturally exist between prenatal care providers and genetics specialists who work in close proximity (Carroll, Makuwaza, Manca, et al., 2016). Midwives with direct access to genetic counsellors described them as a helpful resource (Dettwyler et al., 2019). Building relationships between NHGPs and genetics specialists is critical. The links that naturally exist with other specialists do not necessarily occur with genetics, as not every hospital has a genetics department (Carroll, Makuwaza, Manca, et al., 2016).

Genetic counsellors must establish and maintain interdisciplinary professional relationships and assist prenatal care providers in improving patient care (Ferrier et al., 2013; Accreditation Council for Genetic Counselling, 2019). Agatisa, Mercer, Coleridge, et al. (2018) conducted interviews in 2016 with 25 prenatal genetic counsellors in the U.S. to understand their experience with the continued expansion of NIPT screening. Counsellors felt a professional obligation to educate obstetricians about prenatal genetic tests (Agatisa, Mercer, Coleridge, et al., 2018). Although this support has shown to be essential to prenatal care providers, further investigations are required regarding the exact responsibilities that genetics professionals and their respective societies have in assuring prenatal care providers have adequate knowledge and support for this testing in the future.

Importantly, collaboration between genetic centers and the primary care community make genetic medicine services more accessible. Strategies such as provider-to-provider telegenetic consultation have been suggested to pair genetics providers with non-genetic professionals (Raspa et al., 2021). In a survey conducted in 2011-2012 by Carroll et al. (2019), many physicians in Ontario (88.8%, n=347) noted that contact information to a genetics clinic, such as telephone/fax or email, would be useful to achieve this connection. PSO launched a toll-free prenatal screening information line in 2018 where a certified genetic counsellor is available 8 am-4 pm Monday to Friday to answer questions from patients, providers and other stakeholders like lab personnel (BORN Ontario, 2020).

These services must be made known to those isolated providers in the community and the genetics services should initiate these connections.

5.3 Conclusion

This grounded theory provides a unique perspective of prenatal care providers in Ontario and their experience with pre-test counselling for NIPT. These providers play an increasingly prominent role in NIPT pre-test counselling and continue to face complex counselling conversations with their patients. However, there are very striking practical, educational and ethical challenges between current NIPT panel options and prenatal care providers' comfort with pre-test counselling for these possibilities. The consequences of these challenges ultimately affect how prenatal care providers engage patients in decision-making for NIPT. Ongoing support for these providers is essential to ensure that patients receive adequate counselling as NIPT options expand (Sahlin et al., 2016; Piechan et al., 2016).

Chapter 6

6 Conclusion

Prenatal care providers play an essential role in offering NIPT to pregnant individuals. This dissertation generated a theoretical model, ‘prenatal care providers’ involvement with pre-test counselling for NIPT in Ontario,’ explaining how prenatal care providers in Ontario have implemented NIPT into their prenatal screening practices. Participants discussed the additional responsibilities they have in providing pre-test counselling for NIPT. Providers discussed how they struggle to prioritize pre-test counselling for NIPT in their current practice. They also felt underprepared and uncomfortable using NIPT for indications other than traditional aneuploidies.

These ethical considerations and difficulties experienced during counselling informed what additional support prenatal care providers require. They emphasized the need for ongoing development of regulations and guidelines and the importance of ensuring these were disseminated efficiently and effectively in the future. Genetics professionals were highlighted as valuable sources of information regarding education and learning about any updates to genetic technology.

6.1 Implications for Prenatal Care Providers: An Increase in Genetics in Practice

This study revealed what it means for prenatal care providers to be providers of frontline genetic services. These providers were no longer referring to genetic specialists and counsellors when an individual was interested in NIPT. Instead, participants in this study discussed taking on the additional responsibilities in providing pre-test counselling for NIPT based on the limited genetic counsellors available. By 2018, Burgess et al. (2020) indicated that most community-based clinicians in Ontario who were interviewed provided pre-test counselling instead of referring to genetic services.

Participants noted that the quality of pre-test counselling patients about NIPT was challenged by time constraints and prioritizing what is covered at each prenatal visit. Clinicians in this current study struggled with prioritizing pre-test counselling for this test during a busy prenatal visit early in pregnancy and were worried that other prenatal care providers were not spending enough time to appropriately counsel patients on this screening option. Notably, family physicians who engage in generalist practice find NIPT counselling challenging to accommodate within an otherwise hectic prenatal appointment. This concern contributed to why some providers did not discuss NIPT's incidental findings with patients and explains some of their hesitations in discussing expanded testing. Further investigations are warranted into how prenatal care providers can incorporate complex information about NIPT into the consent process given the time restrictions of their practice (Piechan et al., 2016).

In addition, participants stated that the introduction of NIPT augmented difficulties with establishing realistic expectations about prenatal screening and the scope and limitations of this testing. Participants discussed how difficult it was to address these misconceptions, given the poor understanding of concepts such as sensitivity and specificity in prenatal screening. The findings provide insight into the challenges providers may face with discussing a technology that further medicalizes pregnancy and is advertised as a test that will reassure a healthy pregnancy.

As a result of various tensions of offering testing for non-medical indications including fetal sexing and conditions with variable phenotypes, such as SCAs and microdeletion syndromes, some participants did not discuss screening for these indications during the pre-test counselling process. These indications introduced ethical concerns into providers' prenatal counselling and made them question the clinical usefulness of offering NIPT for these additional indications. These concerns for counselling on complex issues, and differences in values, can contribute to the variation observed by prenatal care providers in how professionals choose to provide counselling (Arora et al., 2017).

6.2 Implications for Policy and Guideline Development

Commercial pressures have rapidly pushed NIPT towards broader applications (Murdoch et al., 2017); however, providers in this study questioned the boundaries of NIPT use. As screening has evolved throughout the years, providers have reflected on the goals of prenatal screening and how these tests impact perinatal outcomes (Dukhovny & Norton, 2018). This study emphasized how the future scope of prenatal screening and NIPT should involve the perspectives of various stakeholders, such as prenatal care providers, as guidelines and policies towards expanded testing for NIPT are updated. Indeed, Prenatal Screening Ontario has developed various committees and working groups to facilitate stakeholder input and advice on operational areas of prenatal screening in Ontario, including an advisory committee, genetics expert and education working groups (PSO, 2020). These groups are interdisciplinary and include family medicine representatives, ensuring a “bottom-up” engagement model for policy implementation. Similarly, a health technology assessment of NIPT was performed in Ontario in 2017 to evaluate the clinical benefits and harms, monetary value, budgetary impact, and patient preferences related to NIPT in the average-risk population. This evaluation was conducted by Health Quality Ontario and included a multidisciplinary team including prenatal care providers who are active in the prenatal screening community. These assessments and working groups should continue to include prenatal care providers to help inform the use of NIPT in the future, including the expansion of this testing.

The ethical considerations discussed by participants emphasized the need to enforce current regulations to ensure the appropriate utilization of this publicly funded test in Ontario. These considerations also correspond with the importance of policy enforcement and the creation of new regulations regarding how NIPT is utilized publicly and privately. They discussed the ethically complex topic of offering expanded testing panels through private pay. Prenatal care providers are reimbursed for offering and counselling NIPT at the same rate as counselling for other prenatal screening technology (Vanstone, Yacoub, Giacomini, et al., 2015; MOH, 2021). From a provider’s perspective, there was concern that the counselling required for these additional options would burden them with additional pre-test counselling that they may not have the resources or confidence to

provide. Currently, no policies separate the type of counselling prenatal care providers should be responsible for compared to genetic professionals. There is a definite need for policies to clarify the scope of prenatal care providers' counselling as NIPT options expand. In addition, with privatized counselling support currently available in Canada (Genolife, 2021; LifeLabs, 2021), stricter regulations should be enforced to ensure these companies provide unbiased education materials and counselling. Regulations on this issue will lead to consistency in patients' care (Boycott et al., 2015; Toews & Caulfield, 2014).

Participants raised concerns regarding equal access to NIPT, including the discrepancy in testing availability and affordability across Canada. Indeed, provincial, and territorial policies regarding the implementation and public coverage of NIPT are diverse and evolving. In addition to Ontario, NIPT is publicly funded for pregnant individuals who meet certain requirements in British Columbia, Manitoba, Nova Scotia, Nunavut, Prince Edward Island, Yukon and Quebec (Ryan, 2018; Impact Ethics, 2019; Hayeems et al., 2015). Eligibility for public funding in these regions varies widely. For example, pregnant individuals are eligible for publicly funded NIPT in Nova Scotia if they either had a previous pregnancy affected with trisomy 13, 18 or 21 or are found to be at an increased risk for trisomy 21 based results of maternal serum screening (Reproductive Care Program of Nova Scotia, 2022; IWK Health Centre, 2022). The criteria in Quebec are similar to Nova Scotia's criteria, except public funding is also provided to individuals who will be 40 years or older at the time of delivery (Gouvernement du Québec, 2022). Access to public funding in these areas are more restrictive than Ontario, which provides funding for more indications including sex chromosome determination in individuals at risk of a sex-limited disorder (Dynacare, 2020c; PSO, 2021a). In contrast, an individual can have NIPT funded in the Yukon for indications that are not available to individuals in Ontario. This includes public funding for NIPT if an individual is 35 years or older at the time of delivery, if the pregnancy is a result of IVF (with intracytoplasmic sperm injection) or if the pregnant person is HIV positive (Dynacare, 2017; Heft, 2019). Further investigation is required to see what prenatal care providers from differing regions in Canada feel about barriers to access of public funded NIPT based on these disparities.

In addition, participants from this study expressed the need for stricter regulations for ordering NIPT in Ontario to ensure access for all pregnant individuals is appropriate and equitable. Some provinces have instituted regulations to control how publicly funded NIPT is ordered. In Manitoba, results of a positive maternal serum screen must be attached to the NIPT requisition in order for this test to be publicly funded (Dynacare, 2020e). In British Columbia, patients are required to give an authorization code as proof of indication for funded NIPT which is provided by a prenatal biochemistry lab or medical genetics (Provincial Health Services Authority, 2022). It is worth investigating whether regulations like these could be adopted by MOH to monitor and ensure the appropriate utilization of public funded testing in Ontario.

In certain regions in Canada, patients need to pay for the test out of pocket or through private insurance, which may create major issues of equity of access and justice for providers and patients. For example, Birko et al. (2019) reported the results of three large-scale Canadian surveys which investigated stakeholders' perceptions and attitudes towards NIPT. The study included 184 healthcare professionals, a majority which practiced in regions where public funding for NIPT was not available at the time (Birko et al., 2019). These professionals reported that a "lack of coverage of the test" was the number one barrier to clinical implementation. Although SOGC-CCMG recommends offering NIPT as a possible screening option to all individuals in Canada (Audibert et al., 2017), 50% of professionals in the study by Birko et al. (2019) agreed that NIPT's coverage would influence their decision to offer NIPT to a specific patient. Such issues may be abated by public funding for NIPT, however additional studies are required to investigate stakeholders' preference regarding the implementation and coverage of this testing through a public funding model.

Additionally, providers in this current study attributed initial difficulties with pre-test counselling for NIPT due to suboptimal education of public funding guidelines in 2014. Other provinces and territories wishing to implement a public funding model for NIPT can learn from these experiences and invest in resources to disseminate information about public funding guidelines to the appropriate stakeholders.

Participants raised the concern that other prenatal care providers have variable quality in their ability to effectively provide counselling for NIPT, and called for updated guidelines to support providers with these difficulties. Although there are various expert policy statements and guidelines regarding the use of NIPT, they are diverse in their pre-test counselling recommendations. Sachs et al. (2015) released a standardized framework that included recommended pre-test counselling points for providers offering NIPT. However, providers need an updated pre-test counselling framework that is more representative of the current NIPT climate in Ontario. This framework can address the difficulties providers experience with pre-test counselling, including the challenge of communicating this information after patients have been exposed to advertising materials. Therefore, pre-test counselling points could highlight the importance of pre-test counselling patients on the difference between screening and diagnosis testing and specifying what NIPT does and doesn't screen for. Emphasis could include how NIPT does not screen for single-gene disorders, open neural tube defects or late pregnancy complications or replace routine fetal anatomic screening by ultrasound. Importantly, providers should emphasize that a negative NIPT result does not ensure a "healthy" baby, even if expanded screening is performed. In addition, this framework could touch on pre-test counselling for a low-risk population and the differences in PPV for the different aneuploidies in this population. This framework could also discuss pre-test counselling points for microdeletions, including lower PPVs and the uncertainty associated with these syndromes. Standardized guidance could give providers a clear direction for what essential points to address in their pre-test counselling. Standardization could also prevent prenatal care providers from overloading patients with information during pre-test counselling, which was another concern raised by prenatal care providers in this study.

Other healthcare providers have suggested that professional societies could work together to publish joint consensus statements about best practices rather than conflicting ones (Vora & Wapner, 2018). These consensus statements include guidelines surrounding the use of NIPT for non-medical fetal sexing (Orr-Ferdinand, 2021). More specifically, the Ethics Committee of the American Society for Reproductive Medicine encouraged clinics to create written policies regarding whether, and under what circumstances, nonmedical sex selection will be available (Ethics Committee of the American Society for

Reproductive Medicine, 2015). Additional practical guidance in this area could lessen the emotional distress that prenatal care providers experience when pre-test counselling for NIPT includes this ethically and morally sensitive topic.

Prenatal care providers also discussed standardizing the education and training of NIPT for pre-test counselling for this technology. Standardization includes creating unbiased education sources to prevent ongoing education of NIPT from being shaped by commercial pressures alone (Agarwal et al., 2013). In addition, minimum standards, or requirements for certification specific to genetic counselling for NIPT, separate from overarching training requirements, could ensure that prenatal care providers can provide higher quality counselling to patients (O'Brien & Dugoff, 2018; Piechan et al., 2016; Gammon et al., 2016; Murdoch et al., 2017). These requirements are critical if NIPT continues to be offered to a broader, larger population of individuals.

Participants also need additional counselling guidelines for NIPT and its expanding options as these providers are increasingly entrenched in the pre-test counselling process. For example, providers were uncomfortable counselling about indications beyond common aneuploidies due to ethical concerns and the complexity of pre-test counselling involved. Current guidelines, such as SOGC-CCMG and ACMG acknowledge the complexity of counselling required for these expanded testing options and do not recommend offering screening for these indications to low-risk individuals at this present time (Audibert et al., 2017; Gregg et al., 2016); however, these expanded panels are available privately through Ontario laboratories. Therefore, this study revealed a gap in what prenatal care providers are comfortable discussing and what is currently offered. With more patients becoming aware of these options (Burgess et al., 2020), prenatal care providers may have to provide pre-test counselling for these expanded screening possibilities. Therefore, guidelines on providing pre-testing counselling for indications beyond the traditional aneuploidies are required (Farrell et al., 2016).

Participants mentioned that screening tests' validation measures are difficult for patients to comprehend, and NIPT is often thought of as a diagnostic test. Confusion with these metrics leads to patient uncertainty, stress, and anxiety (Lewis et al., 2016a; Li et al.,

2017; Yi et al., 2013; Farrell, Agatista & Nutter, 2014; Mozersky, 2015; Floyd et al., 2016; Farrell, Agatista, Mercer, et al., 2015; Vanstone, Yacoub, Giacomini, et al., 2015). This confusion is further muddled by the fact that laboratories in Ontario have validation measures for NIPT that are misleading, hard to find, or not present (Mercer et al., 2014; Health Quality Ontario, 2019a). These counselling considerations coincide with the necessary creation of new policies to regulate what performance data each commercial lab offering NIPT should make available. Optimally, data such as sensitivity, specificity, PPVs, and cut-off levels, including expected false-negative and false-positive rates, should be accessible to prenatal care providers. Ensuring these metrics are present could clarify misconceptions surrounding NIPT's performance for those aneuploidies beyond trisomy 21.

Lastly, NSGC professional practice guidelines state that pre-test counselling for NIPT should be performed by "qualified providers" (Devers et al., 2013, p. 291). However, it is unclear what constitutes a "qualified" provider and what education, background and credentials are required to provide adequate pre-test counselling for NIPT (Liehr, 2021). For example, although midwives are independent prenatal clinicians in Ontario who provide care for low-risk pregnant individuals, provincial policies prevent them from ordering NIPT. Instead, they are required to refer their patients to a physician for counselling and follow-up (PSO, 2021a). This process has been described as frustrating for both types of clinicians, as it creates an unnecessary time and cost burden within the time-sensitive practice of prenatal testing (Burgess et al., 2020). It is important to investigate why midwives are excluded from offering NIPT given their involvement in pregnancy and informed choice conversations. Overall, it is crucial to explore what constitutes a provider qualified to perform pre-test counselling for NIPT and what additional standardized activities or requirements may be necessary beyond their facility level of education and training (O'Brien & Dugoff, 2018). Core competencies in genetics for health professionals in medicine have been developed (Skirton et al., 2010; Korf et al., 2014); however, this is not specific to Ontario prenatal care providers or NIPT. Creating standards and requirements will be essential as the complexity of counselling increases and NIPT counselling is performed by additional healthcare providers such as nurses or medical assistants (Farrell et al., 2016).

6.3 Implications for Dissemination of Information and Education

When publicly funded screening for NIPT was introduced in Ontario, there was no priority to providing education or training for health providers (Bellai-Dussault et al., 2020). This study identified the existing gaps in knowledge and confidence that prenatal care providers hold in pre-test counselling for NIPT as well as their lack of awareness of updates to this rapidly expanding test. Canadian health care providers still expressed these concerns in qualitative studies conducted in 2018 and 2020, with a perceived need for greater education and awareness among clinicians (Burgess et al., 2020; Haidar et al., 2020).

Ongoing dissemination of updates to NIPT was a crucial proactive strategy identified by prenatal care providers in this study. With such a rapidly developing test, providers were concerned that they would encounter the same educational delays they experienced with implementing this technology. Importantly, there is still an identified need for NIPT educational materials by providers in Canada (Burgess et al., 2020; Haidar et al., 2020), despite the development of educational resources that occurred after this study took place (Perinatal Quality Foundation, 2022; Genetics Education Canada, 2020). Although genetic resources exist, prenatal care providers lack the awareness and time to find, identify and use them (Carroll, Grad, Allanson, et al., 2016; Haga et al., 2011). There should be a streamlined process to distribute educational materials about NIPT and NIPT developments to all prenatal care providers delivering pre-test counselling (Ngan, 2018). In this study, providers suggested in-person and electronic educational strategies. It is recommended to implement these educational resources as an effective way to access up-to-date medical information (Agius & Bagnall, 1998; Ruiz et al., 2006). In the past, the outcomes of online interventions in genetics have been shown to improve knowledge, confidence, and skills and can indicate when to appropriately refer to genetic professionals (Bell et al., 2015; Carroll, Grad, Allanson, et al., 2016; Paneque et al., 2017; Telner et al., 2017). In addition, PCPs exist in large numbers, and therefore

targeted, effective education can affect thousands of providers and, consequently, affect patients (Dougherty et al., 2016).

Importantly, prenatal care providers highlight family physicians as a group with a concerning divide between education, awareness, and practice. Updating isolated prenatal care providers in the community is considered especially important as they may not have the luxury of having a genetics department nearby. As per the suggestions of prenatal care providers in this study, outreach programs could inform family physicians of any updates to policies or guidelines. Outreach could include in-person or electronic workshops and educational materials created by third-party genetic specialists (Paneque et al., 2016).

6.4 Opportunity for Different Models of Genetic Counselling and Service Delivery

This study underlines how the continued expansion and extension of NIPTs use necessitates new approaches and techniques to pre-test counselling (Agatisa, Mercer, Coleridge, et al., 2018). For example, as NIPT expands into the average-risk population, more providers are faced with the difficult task of providing NIPT counselling to every individual considering prenatal screening (Parham et al., 2017). Respondents in this study were concerned about the lack of time spent educating patients about the complexities of this test in a prenatal session. This concern is rooted in the assumption that, if given more time, patients could receive sufficient information to allow for informed consent (Gabriel & Diskin, 2018). This belief aligns with the “teaching” approach to genetic counselling practice. Initially described by Kessler in 1997, the primary purpose of the teaching model in genetic counselling is to communicate information to patients. This thinking is abstracted in the informed consent literature as the “conduit/container” model, or “professional monologue,” where information transfers from one person to the other (Kessler, 1997). However, more information shared by a provider is not always equivalent to more information understood and integrated by a patient (Gabriel & Diskin, 2018). Informed consent and reproductive autonomy may not be enhanced when more information is given, and an excessive amount of medical-technical information could

overload patients and hinder reproductive autonomy (Dondorp et al., 2016; Gabriel & Diskin, 2018). Indeed, participants from this current study were also concerned about overloading patients with information during NIPT's pre-test counselling session.

In contrast, other counselling models have been proposed that do not solely focus on the knowledge component of pre-test counselling. For example, Kessler (1997) also described the “counselling” model as another primary professional approach to genetic counselling practice. This framework is grounded in psychology and based on the belief that individuals seek genetic counselling not only for information but also for alleviating psychological distress, promoting autonomy, and gaining a greater sense of control of a situation. This model emphasizes the support of patients on an emotional and personal level while still providing education (Kessler, 1997). The counselling model is associated with increased knowledge retention, reduced anxiety, and higher satisfaction with decision-related outcomes as compared to teaching-based models (Roter et al., 2006; Dijkstra et al., 2013).

Despite this, prenatal care providers and genetic counsellors often use the teaching model in modern practice for pre-test counselling (Lerner et al., 2014; Meiser et al., 2008; Roter et al., 2006; Martin et al., 2014; Walser et al., 2017). Many professional practice guidelines available in 2016 and onward emphasize objective information in pre-test counselling (Audibert et al., 2017). For example, a main point of pretest counselling in ACOG’s clinical management guidelines is that it should be done “...in a clear, objective, and non-directive fashion, which allows patients sufficient time to understand information and make informed decisions regarding testing...” (ACOG-SMFM, 2020, p.e56).

In contrast, the emphasis in pre-test genetic counselling should involve clinicians addressing the psychological nuances that prenatal care providers in this study have acknowledged. For example, participants discussed how NIPT screening for additional conditions such as SCAs and microdeletions introduces new levels of uncertainty in their pre-test counselling process that they may be uncomfortable counselling on. Indeed, after these interviews were conducted, ACMG’s policy statement addressed how the ever-

evolving technology of NIPT should include pre-test counselling which explores the patient's ability to accept uncertainty concerning possible screening outcomes (Gregg et al., 2016). To tackle complex concepts such as uncertainty, prenatal care providers must engage in a genetic counselling model that promotes psychosocial support (Ferrier et al., 2013). Therefore, future guidelines, education, and prenatal care provider training should incorporate and emphasize psychological counselling into the pre-test communication process for NIPT.

The teaching model may also be used by prenatal care providers based on time constraints and the high volume of patients (Brunger & Lippman, 1995). Further investigations and strategies are required as to how prenatal care providers can incorporate this complex information within a time-limited visit (Piechan et al., 2016). Educating patients about NIPT through alternative techniques including telemedicine, educational pamphlets, videos, or decision aids are all options that may facilitate the information provision part of the pre-test counselling session while allowing more time for psychosocial support (Gammon et al., 2016; Metcalfe, 2018; Gammon et al., 2018; Kim et al., 2018; Raspa et al., 2021). These additional educational methods have shown to be equivalent to, or better than, in-person genetic counselling in promoting knowledge and achieving long-term comfort with choices made (Glazier et al., 1997; Hilgart et al., 2012; Kuppermann et al., 2014; Yee et al., 2014). Another option includes group information sessions about NIPT, coupled with abbreviated counselling. An alternative counselling model such as this one has been shown to have significant positive effects on patients' knowledge of NIPT and other prenatal testing options and their decisional confidence and sense of preparation (Gammon et al., 2018). These alternative service delivery models and counselling aids could reduce the burden of prenatal care providers delivering information and allow them to integrate psychosocial aspects in their counselling. In addition, these delivery models could standardize counselling and add a quality control component, which some providers have concerns about regarding NIPT counselling. Developing educational tools and decision support tools to enhance a patient's understanding is critical for ongoing research and work by professional societies (O'Brien & Dugoff, 2018).

6.5 Responsibilities of Genetic Professionals and Professional Societies

This study confirms that genetic services and genetic counsellors play an essential role in providing education and support to prenatal care providers. With genetics becoming increasingly prominent in primary care providers' practice (Joseph, 2018; Patch & Middleton, 2018; Battista et al., 2011), genetic services need to take on a more supportive role for these professionals during the pre-test counselling process. For example, participants noted the importance of having interdisciplinary professional relationships with genetic departments and genetic counsellors for this support. Genetic counsellors must continue to maintain interdisciplinary professional relationships and assist prenatal care providers in improving patient care (Carroll et al., 2019; Agatisa, Mercer, Coleridge, et al., 2018).

In addition, interdisciplinary medical education can improve learning outcomes and increase the confidence and comfort of prenatal care providers who provide NIPT counselling (Dougherty et al., 2016). Focusing on interprofessional education and collaboration may also help address the lack of transparency prenatal care providers felt with genetics policy development. Practical options include developing interprofessional coursework for prenatal care providers and genetic counsellors, joint panel presentations at conferences, completion of observational rotations, offering continuing education, teamwork training, and interdisciplinary rounds (Mann et al., 2014; Oxenford et al., 2017; Cernat et al., 2019). It is also crucial to investigate what role educational and certifying organizations, such as the Canadian Association of Genetic counsellors, play in supporting these additional education and training initiatives (Gabriel & Diskin, 2018).

6.6 Future Directions and Research

More research is required regarding the effect of providing NIPT pre-test counselling to patients at such an early time in their pregnancy. Little is known about the added stress and anxiety that NIPT may place on patients who are still adjusting to the news of a pregnancy. The patient's overall reception of NIPT and how this affects their broader

pregnancy experience is an area of research that has not been widely explored (Alexander et al., 2015). Future research could include exploring the specific experiences of both patients and providers who have discussed NIPT at the first prenatal visit. Examining how NIPT relates to the medicalization of pregnancy could provide insight into how NIPT shapes an individual's early experience of pregnancy. An in-depth understanding of individuals' pre-natal counselling experiences could, in turn, inform pre-test counselling for providers who must discuss screening at such an early time in pregnancy.

Further research is also needed to explore prenatal care providers' experience with pre-test counselling for the ever-expanding screening options available for NIPT. This area of research is crucial to study in a timely fashion as NIPT screening is expanding rapidly. For example, laboratories in Ontario are now offering screening for more microdeletions and aneuploidies than previously available when this study was conducted in 2016 (Dynacare, 2020b). In addition, many expect that NIPT for single-gene disorders and whole-genome sequencing will eventually be introduced into clinical practice (Shaw et al., 2020). With this expanded testing comes a broader range of possible outcomes that requires more complex pre-test counselling (Dondorp et al., 2015). Future research should explore how these ever-expanding options will impact prenatal care providers' practice, such as the complexity of the required counselling or their perspectives of offering to screen for these additional conditions. This research should also explore providers' and patient perspectives on the ethical concerns associated with the ongoing expansion of NIPT, including on informed consent, reproductive autonomy, and equity of access to testing for an increasingly larger panel of conditions. In addition, more research is necessary to explore what educational resources are essential for pre-test counselling for this range of conditions (Botkin et al., 2015; Richardson & Ormond, 2018).

Importantly, this research has implications for other areas where non-genetic professionals are involved with genomics in medicine in both the public and private sectors. For example, oncology-based/rapid genetic testing is a process where genetic testing is offered to a patient by their breast cancer specialist rather than a genetic specialist, which is meant to provide a more streamlined and efficient experience for the patient. This practice, otherwise known as "mainstreaming," is clinically useful when the

impact of the genetic test result has treatment implications (Beard et al., 2021). Mainstreaming is an emerging area of practice in Ontario that has just been initiated in September 2021 as part of Cancer Care Ontario's initiative to provide equitable access to hereditary cancer services across the province (Cancer Care Ontario, 2021). This method allows cancer patients to access genetic testing at one of their routine cancer clinic appointments, eliminating the need to be first referred to a genetic counsellor. However, very little is known about how oncologists experience mainstreaming and their challenges when providing pre-test cancer genetic counselling within an otherwise routine oncology appointment.

Direct-to-consumer testing (DTC) is a genetic test that is more directly accessible to consumers than those offered through existing health services. With DTC, the consumer pays the company directly, and it is possible to order testing without the involvement of a health professional (Eng & Sharp, 2010). However, many companies now require a referral from the consumer's healthcare provider (Borry et al., 2010). This requirement means non-genetic providers should know how to advise on these additional genetic tests that may offer testing for many conditions. For example, Myriad genetics[®] offers a carrier screening test that examines over 100 genes associated with severe and prevalent inherited conditions (Myriad, 2021). However, healthcare providers report low awareness and experience with DTC (Bernhardt et al., 2012; Ram et al., 2012; Goldsmith et al., 2012; Powell et al., 2012a; Powell et al., 2012b). In addition, primary care providers from Ontario and Alberta have described direct-to-consumer testing as "scary" territory they do not know much about (Carroll, Makuwaza, Manca, et al., 2016, p. 629). Very little is known about the effect of having these tests available for consumers and the consequential challenges that this may cause prenatal care providers in their practice. Comparing the results of this current study to future studies in the contexts of non-genetic specialists offering genetic testing may illuminate common challenges and support required for prenatal care providers who are offering genetic testing in their practice.

Pharmacogenetics (PGx) is the study of interactions between genetic factors and drug response. PGx testing can help predict therapeutic response and minimize adverse events by detecting variants in genes that influence drug response (Spear et al., 2001; Lee et al.,

2014). This type of genetic testing is expected to define the future of medical and pharmaceutical practice in terms of prescriptions, treatment and management of patients (Green et al., 2010). Health Canada has approved the placement of PGx biomarker information on labels of over 100 drugs (PharmGKB, 2018). Primary care providers, including physicians and pharmacists, will play an essential role in offering PGx during routine clinical care (Obeng et al., 2018). However, there has been a slow uptake of PGx testing in clinics (Singh, 2007). Reasons for this slow uptake mirror that of NIPT and other emerging healthcare technologies, including unfamiliarity of health care providers with PGx, time constraints, absence of clear clinical guidelines, inconclusive clinical utility and other ethical considerations (Drozda & Pacanowski, 2017; Hall, 2003; Rothstein, 2003). Therefore, it is important to understand the perceptions of primary care providers and pharmacists on the implementation of PGx testing in clinical practice. Therefore, additional research is required to understand the limitations faced by these providers and further define their role in the implementation of PGx testing to support these non-genetic specialists who offer genetic testing.

Future research should also involve the evaluation of educational interventions for NIPT. Since 2016, third-party resources on NIPT have become available for patients and providers, such as the information found on Prenatal Screening Ontario's website (<https://prenatalscreeningontario.ca>). After exploring the various information needs of prenatal care providers in this study, further steps should be taken to evaluate the effectiveness of these resources, including measuring knowledge outcomes for prenatal care providers. Similarly, alternative techniques of providing NIPT education to patients, such as telemedicine, pamphlets or decision aids, should be evaluated for their effectiveness compared to in-person genetic counselling in terms of knowledge and long-term comfort with choices made.

6.7 Strengths and Limitations

6.7.1 Study Limitations

There are limitations to this study needing mention. To begin, all participants were self-selected volunteers and so perhaps more interested than average in research or about the topic of NIPT. Participants who would volunteer for this research may be experiencing more extreme barriers to counselling than other prenatal care providers who provide prenatal counselling. The study findings and interpretation must be considered within the context of the research design and methodology. The results represent Ontario providers in an urban setting. Therefore, they do not reflect the more extensive experiences and attitudes of a wider group of prenatal care providers. However, by using in-depth interviews of the participants, I was able to get a thorough understanding of these prenatal care providers' experiences with NIPT. The experiences of prenatal care providers interviewed for this study may have changed since these interviews were conducted in 2016. However, additional literature was sourced for this analysis which explored the experiences of prenatal care providers after 2016, including Ontario providers (Burgess et al., 2020). Further analysis of this new data confirmed the model generated from this study was still relevant and emphasized that prenatal care providers still required additional support to provide adequate pre-test counselling for NIPT.

Another potential limitation of this study is based on the process of coding, which can remove context and narrative flow and thus fragment results (Coffey & Atkinson, 1996). I attempted to limit this by writing field notes and memoing throughout the entire data collection phase. Memos are written records of a researcher's thinking during the entirety of the research process and they allowed me to become actively engaged in the material, develop ideas, fine-tune subsequent data gathering and engage in critical reflexivity (Charmaz, 2014). Lastly, some of the interviews were conducted by telephone, which can lead to less interaction between the interviewer and participant compared to face-to-face interviews (Shuy, 2002; Trochim and Donnelly, 2007; Weiss, 1994). Consequently, there may be a lack of rapport and loss of the natural conversation, which makes participants feel less comfortable during an interview (Shuy, 2002). For interviews conducted over

the phone, I tried to engage in small talk before the recording occurred in order to build this rapport (Glogowska et al., 2011). In addition, participants may be reluctant to elaborate on their responses over the phone, which compromises the richness and quality of the collected information (Hermanowicz, 2002). I practiced intensive interview techniques as per Charmaz (2014), which included asking the participant to elaborate, clarify, or give examples of responses (Charmaz source). In addition, the interview script communicated the purpose of the study and emphasized the importance of the participant contribution, which also promotes an in-depth telephone interview (Glogowska et al., 2011; Musselwhite et al., 2007; Smith, 2005). Another disadvantage of conducting phone interviews was the inability to observe or respond to visual cues during conversation (Nagy et al., 2010). However, I recorded any vocal cues as field notes such as pauses and inflections in speech to provide additional contextual information.

6.7.2 Strengths of Study

While there has been some research on genetic professionals' experience with counselling on NIPT, an exploration of how NIPT has affected counselling for prenatal care providers is lacking. Therefore, qualitative inquiry effectively discovered and documented aspects of the prenatal care providers' experience with pre-test counselling for NIPT, which may be unknown or unexpected. The use of constructivist grounded theory helped provide a clear and nuanced picture of the experience of pre-test counselling for prenatal care providers. The creation of this model identified what challenges and concerns these providers experience in their practice and informed the practical support required as they take on a more prominent role in pre-test counselling for NIPT. In addition, this is one of the few studies which probes how these providers feel about using NIPT for indications beyond traditional aneuploidies.

In addition, this research has overarching use in other areas of medicine where non-genetic professionals are becoming increasingly entrenched with offering genetic testing. Like NIPT, DTC genetic testing, including pharmacogenetics, is heavily commercialized (Borry et al., 2010). Additional research studies could utilize methodologies and methods

from this current study to explore the experiences of non-genetic professionals, such as oncologists, pharmacists and physicians, and their increasing role in providing pre-test counselling for genetic tests. Understanding how these non-genetic specialists navigate this pre-test counselling within their practice could identify barriers and subsequently inform what further support is required for these clinicians to provide the highest quality of care possible. Support could include improvements to practice guidelines and can inform policies in order to clarify how these genetic tests should be used in practice.

6.8 Conclusion

The model “Prenatal care providers’ involvement with pre-test counselling for NIPT in Ontario” explains what is involved in these providers' pre-test counselling process, including important challenges that NIPT places on the clinical infrastructures of prenatal care providers. These burdens contribute to a significant risk that individuals will not make informed decisions surrounding NIPT. Prenatal care providers, especially family physicians, who are taking on a more prominent role in NIPT’s pre-test counselling process, need better guidance and support to provide quality pre-test counselling. Support is important to ensure that NIPT will be used effectively and ethically as testing increases into a more extensive and diverse set of genetic variants and uses among the low-risk obstetric population. This research suggests that NIPT’s implementation and ongoing expansion within prenatal care providers' clinical practice is complex and dynamic. Recognizing the needs of these providers is essential to ensure quality counselling for patients undergoing decision-making for NIPT. In addition, to ensure the continuous ethical implementation of this prenatal screening and avoid a downslide towards eugenics, it is important to include prenatal care providers in discussions surrounding the expansion of this testing.

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Appendices

Appendix A: Ministry of Health Criteria

<p>CATEGORY I Can be ordered by any physician or nurse practitioner For investigation of trisomy 21, 18 or 13 ONLY</p>
<p>Any of the following:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Maternal multiple marker screening result positive for aneuploidy <input type="checkbox"/> Individual of advanced maternal age, defined as ≥ 40 years of age at expected time of delivery. In the context of <i>in vitro</i> fertilization, the maternal age is guided by the age at egg retrieval (whether own or donor egg) <input type="checkbox"/> Ongoing twin pregnancy (both twins must demonstrate fetal activity by ultrasound) <input type="checkbox"/> Nuchal translucency (NT) ≥ 3.5mm <input type="checkbox"/> Previous pregnancy or child with trisomy 21, 18 or 13
<p>CATEGORY II Funding for these indications must be submitted by a genetics or maternal fetal medicine (MFM) specialist</p>
<p>Risk indicators:</p> <p>A)</p> <ul style="list-style-type: none"> <input type="checkbox"/> Fetal congenital anomalies identified on ultrasound, which are suggestive of trisomy 21, 18 or 13 <p>OR</p> <p>B)</p> <ul style="list-style-type: none"> <input type="checkbox"/> Risk of aneuploidy for trisomy 21, 18 or 13 is greater than that of a positive maternal multiple marker screen. <ul style="list-style-type: none"> • Individuals < 40 years of age at expected date of delivery must have at least one other risk factor • Risk of aneuploidy can be calculated by including any combination of risk indicators including soft markers*, biochemistry, maternal age, etc. <p>OR</p> <p>C)</p> <ul style="list-style-type: none"> <input type="checkbox"/> NIPT for sex chromosome determination (at least one of the following): <ul style="list-style-type: none"> <input type="checkbox"/> Risk of a sex-limited disorder <input type="checkbox"/> Ultrasound findings suggestive of a sex chromosome aneuploidy <input type="checkbox"/> Ultrasound findings suggestive of a disorder of sex determination (DSD)

Note. Ministry of Health Criteria for eligibility (Dynacare, 2020c; PSO, 2021a)

*Soft markers include absent nasal bone, choroid plexus cysts, clinodactyly, cystic hygroma, hyperechogenic bowel, hypoplastic nasal bone, increased nuchal fold/edema, increased nuchal translucency, intracardiac echogenic focus/foci, short femur, short humerus, ventriculomegaly.

Appendix B: Email Script-Clinicians

Dear [Name],

I'm involved with a qualitative research study and I wonder if you might consider participating in an interview or focus group. The study is looking for health care provider opinions of non-invasive prenatal testing (NIPT) to potentially inform future policy decisions about public funding of NIPT. The interview or focus group will last approximately one hour, and can be scheduled at a time and location of your choosing. The interview will be audio-recorded with your permission and transcribed for analysis.

If you are willing to participate or would like more information, please contact our research assistant Leichelle Little or the Local Principal Investigators, Drs. Barbra de Vrijer and Marilyn Evans at [email omitted from published thesis]. I've also attached our official letter of information about the study.

Thank you for considering this request.

Sincerely, [Research Team Member Name]

on behalf of Barbra de Vrijer, MD, Dept Obstetrics & Gynaecology, Schulich School of Medicine & Dentistry, Western University, [email omitted from published thesis]
(Local Principal Investigator)

Marilyn Evans, RN, PhD, Associate Professor, Arthur Labatt Family School of Nursing, Western University (Local Principal Investigator)

Meredith Vanstone, PhD, Assistant Professor, Department of Clinical Epidemiology and Biostatistics, McMaster University, [contact information omitted from published thesis] (Principal Investigator)

Appendix C: Letter of Information and Consent



LETTER OF INFORMATION AND CONSENT - CLINICIANS/PROFESSIONALS

Study Title: Women's and Clinician's Experiences of Non-Invasive Prenatal Testing

Local Principal Investigators:

Barbra de Vrijer, MD, Dept Obstetrics & Gynaecology, Schulich School of Medicine & Dentistry, Western University, nipt@uwo.ca

Marilyn Evans, RN, PhD, Associate Professor, Arthur Labatt Family School of Nursing, Western University

Principal Investigator:

Meredith Vanstone, PhD Clinical Epidemiology & Biostatistics, McMaster University

Co-Investigators

Jeff Nisker, MD, PhD, Obstetrics & Gynaecology, Western University

Mita Giacomini, PhD, Clinical Epidemiology & Biostatistics, McMaster University

Lisa Schwartz, PhD, Clinical Epidemiology & Biostatistics, McMaster University

Sarah McDonald, MD, Department of Obstetrics & Gynaecology, McMaster University

Sponsor Information

Canadian Institutes of Health Research

Introduction

You are being invited to participate in a research study because you are a health care provider or professional involved in the provision of prenatal care. NIPT is a category of tests that can analyze fetal DNA by using a sample of the mother's blood. They are known by many different commercial names, such as Verifi, Harmony or Panorma, and others.

Background

NIPT is a new type of prenatal test that is becoming widely available through private companies. Very recently, it has become covered by the Ontario provincial health insurance plan (OHIP) for some indications. Because until recently it was only available privately, there are very few rules or guidelines about how or when the test should be done, which health care providers should be involved, or what information or counseling should be provided to women who are wondering whether or not they want to do this test. We don't know how women are finding out about NIPT, what type of information they consider when deciding whether or not to do the test, if they are able and willing to pay for this test privately, or what type of support from health care providers they would like access to in relation to this test. It's also unknown when NIPT might be optimally offered, and as the clinical science and evidence around NIPT advances, the time that NIPT should be offered and the patient population to whom it should be offered may change. We are also unaware of how NIPT might integrate within current clinical practice, and what information health care providers wish for in order to feel comfortable counseling about NIPT.

Purpose

This study seeks to learn how NIPT is being used in Canada, and what women and health care providers think about this test. This study will produce information that is important for policy-makers in Ontario and other jurisdictions to consider as they decide to expand or reduce the public funding of NIPT.

Up to 120 people will participate in this study at this institution.

Study Procedure

If you volunteer to participate in this study, we will ask you to choose EITHER a one-on-one interview or a focus group with other prenatal health care providers. The content of the interview and focus group will be similar. A researcher will ask you about your thoughts, opinions, and experiences with NIPT. We are interested in your thoughts about how NIPT currently is used in your clinical practice and your insights on how that might (should) change. We will also discuss your own information requirements for counseling about NIPT to your patients. The interview/focus group will be audio-recorded with your permission and transcribed for analysis.

We expect that one interview or focus group will be enough time to talk about your experiences with NIPT, but when we are listening to your interview later, we might have some follow-up questions. At the end of your first interview, we will ask you if it's ok to contact you again with our follow-up questions. If this is ok, we might contact you (by phone or e-mail, your choice) with a few additional questions after the interview.

Voluntary Participation

Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now and then change your mind later. You may leave the study at any time without affecting your care. You may refuse to answer any question you do not want to answer, or not answer an interview question by saying "pass".

Withdrawal from Study

You may withdraw from this study at any time and this will in no way affect the quality of care you receive. You have the option of removing your data from the study, by notifying the interviewer during the interview, or by contacting the Principal Investigator with the date and time of your interview. The investigator may withdraw you from this research if circumstances arise which warrant doing so.

Risks

There are no physical risks or discomforts to this study, it consists only of an interview or focus group. If you choose a focus group session, you may experience social discomfort if your opinions or practices about NIPT differ from those of your colleagues.

Benefits

We cannot promise any personal benefits to you from your participation in this study. However, the information you share with us may be used by policy-makers in the future when deciding whether or not (and under what circumstances) to fund NIPT. The information you provide about your current experiences with NIPT may help to inform the way NIPT is implemented in the future.

Confidentiality

Your data will not be shared with anyone except with your consent or as required by law. Your personal information will only be kept until your data collection is complete (to facilitate contacting you for follow-up questions if needed). After we are finished collecting data from you, we will destroy any record of your personal information (e.g. name, e-mail address, phone number). While in the process of data collection, we will protect your confidentiality by removing your personal information (e.g. name, e-mail address, phone number) from the data and replacing that information with a code number. A list linking the number with your name will be kept in a secure place, separate from your file, in a locked research office.

For the purposes of ensuring the proper monitoring of the research study, it is possible that a member of the University of Western Ontario Health Sciences Research Ethics Board may look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study followed proper laws and guidelines

The audio-recordings of the interviews will be transcribed (typed) by a professional transcription company. The audio-recordings, without any identifying information attached, will be transferred to that company by uploading them to a password protected secure server. If you choose to state identifying information on the audio-recording (we will not ask you for identifying information, but sometimes when people are talking they accidentally say the name of their family doctor, or their own first name), the transcription company will have access to that information. Any identifying information on the audio-recording will be removed when the interview is transcribed (typed). Audio-tapes will only be listened to by members of the research team and they will be destroyed after 10 years. If you wish to review the audio-tape of your interview, you are welcome to do this. Please contact the Local Principal Investigator, Barbra de Vrijer. If your data collection has ceased when you contact us to review your audio-tape, we will require the date and time of your interview in order to identify which tape is yours. We will need this information because after data collection for an individual is finished, we will have removed your name from our records and the date and time of your interview will be the only way to identify your tape.

Costs

If you agree to take part, you will receive a \$40 honorarium in the form of a gift card. If you are not able to complete your whole interview, you will still receive this same amount.

Rights as a Participant (in the event of a study related injury)

You do not waive any legal right by signing this consent form

Questions About the Study

If you require any further information regarding this study or your participation in the study, you may contact our Research Assistant, Leichelle Little & Contact information omitted from published thesis

If you have any questions about your rights as a research participant or the conduct of this study, you may contact Dr. David Hill, Scientific Director, Lawson Health Research Institute & Contact information omitted from published thesis

CONSENT

Study Title: Women's and Clinician's Experiences of Non-Invasive Prenatal Testing

Local Co-Principal Investigators:

Barbra de Vrijer, MD, Dept Obstetrics & Gynaecology, Schulich School of Medicine & Dentistry, Western University, Contact information omitted from published thesis

Marilyn Evans, RN, PhD, Associate Professor, Arthur Labatt Family School of Nursing, Western University

Principal Investigator:

Meredith Vanstone, PhD Clinical Epidemiology & Biostatistics, McMaster University

I have read the Letter of Information, have had the nature of the study explained to me, and I agree to participate. All questions have been answered to my satisfaction.

I give permission for the interview to be audio-recorded.

Participant's Name (please print): _____

Participant's Signature: _____

Date: _____

Person Obtaining Informed Consent (please print): _____

Signature: _____

Date: _____

Appendix D: Interview Guide-Clinicians

The purpose of this study is to examine how NIPT is currently being used in Ontario, and how the practice of prenatal testing might have changed since the introduction of public funding for NIPT in early 2014. We have conducted interviews with women who've had personal experiences with this technology and we are now speaking with prenatal care providers about the ways in which it is used in their practices, and how their practices have changed in response to this new technology.

1. To start, could you tell me a bit about your prenatal care practice. For instance, what kind of practitioner are you, do you generally see low or high-risk women, what kind of settings do you work in?
2. How do you typically encounter NIPT in clinical practice?
 - How frequently do you encounter NIPT?
 - Tell me about any difficulties that you may have faced since implementing this new test?
 - By the time you discuss NIPT with a patient, what point are they at in the decision-making process [testing pathway]?
3. Let's pretend for a moment that I'm a woman to whom you are offering NIPT. Please explain this technology to me in the language you would use with women.
 - How do you explain the limitations of this technology? Confidence in test accuracy?
 - How do you explain the relationship to other prenatal tests?
 - What resources on NIPT do you provide to your patients?

4. What has influenced the way that you use and offer NIPT?
 - How confident and comfortable are you with this source of information? Is it easy to find information about this technology?
 - What is the preferred way in which you would like to be informed about changes to NIPT?
 - With all the other things you must keep up to date on, where does this fit in?
 - How informed do you think prenatal care providers in the community are informed about this test? How much information would be reasonable to expect them to have?

5. In addition to fetal sex, NIPT results may screen for sex chromosome aneuploidies such as Turner syndrome (monosomy X) or Klinefelter syndrome (XXY). There is a wide variety in the severity and expression of features among individuals with the same sex chromosome aneuploidy, and many individuals may go undiagnosed in the general population. What are your thoughts on the utility of this application to your current clinical practice?
 - Were you aware that these results were possible with NIPT?
 - What are your thoughts about offering testing for fetal sex chromosome aneuploidy to everyone who obtains NIPT? What are you concerned about?
 - How comfortable are you explaining the results of this test to your patients?

6. In rare cases, NIPT may also raise suspicion for unexpected secondary chromosomal abnormalities for fetal or maternal conditions that were not initially targeted by NIPT. Reported incidental findings have included maternal

chromosome differences, such as sex chromosome aneuploidies, maternal cancers (imbalances in the number of copies of chromosomes have flagged the presence of a tumour), and also fetal or placental chromosome differences such as placental mosaicism and smaller duplications/deletions to fetal DNA other than the aneuploidies for which the test is being performed.

- Were you aware of these secondary findings that were possible with NIPT?
- What are your thoughts on utility of this application to your current clinical practice?
- How comfortable are you explaining the potential for these results to your patients?
- How should secondary findings be handled in pre-test counselling? Do you have any concerns about discussing these potential findings with your patients?
- Using the same language you would with a patient, how do you discuss the potential for secondary findings?

7. In addition to testing for trisomy 21, 18 and 13 and sex chromosomes, NIPT is currently being offered with an expanded panel that includes testing for two aneuploidies associated with nonviable pregnancies (trisomy 16 and 22) as well as rare microdeletion/microduplication syndromes (22q11 deletion syndrome [DiGeorge syndrome], cri-du-chat [5p minus], Prader Willi/Angelman syndrome and 1p36 deletion syndrome). These syndromes may result in physical and/or intellectual impairments that can be more severe than whole chromosome abnormalities. A clinically relevant microdeletion/microduplication occurs in 1% of all pregnancies, and is independent of maternal age.

Is this application of NIPT part of your clinical practice? Tell me about how you work with the expanded panel testing.

- Were you aware of the additional testing available with NIPT?
 - What are your thoughts about offering an NIPT screen which tests for a larger number of microdeletion/microduplication syndromes?
 - Who do you think should be offered this expanded testing? - Do you have any concerns about offering this expanded testing?
 - What are you concerned about?
 - How likely are you to discuss this expanded testing with a patient? If not likely, is someone else having this conversation?
 - What are your thoughts on utility of this application to your current clinical practice?
 - How comfortable are you explaining potential microdeletion NIPT results to your patients?
 - Using the same language you would with a patient, how do you discuss the potential results of this additional panel?
8. We've been discussing expanded testing options for NIPT. The number of conditions NIPT can be used to detect will likely continue to expand, including detecting the presence of monogenic disorders, such as cystic fibrosis, Huntington's disease and achondroplasia, allowing for recognition of these conditions in a fetus early in pregnancy. Some people are concerned that expanding this test to screen for additional genetic abnormalities may cause uncertainty for some women, potentially inundating them with too much information and unquantifiable risks. However, others recognize the woman's

right to know this personal health information about her pregnancy, and worry about who is restricting access to this information. {Additional information: monogenetic disorders are caused by mutations in a specific gene}. We are interested in understanding your opinion about policy and regulation which could guide the future use of NIPT.

What is your opinion?

- What guidance would you offer to policy-makers tasked with deciding these limits?
- If there should be limits, what type of people should be involved in making this type of policy? What issues should they consider?
- Do you have a different opinion on the conditions that should be included in NIPT testing, if the patient pays out of pocket vs. if the test is publicly funded?

9. What excites you about this technology? What good might it do?

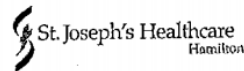
10. What worries you about this technology? What harm might it do?

11. Is there anything else you think we should know about your thoughts or opinions about this technology?

Appendix E: Example of how Subcategory “Difficulties Experienced with Counselling” was Generated

Category	Subcategory	Initial Code (Gerund)	Supporting Quote
Counselling Considerations	Difficulties experienced with counselling	Facing Difficulties with educating patients about prenatal testing in general	<p>“I think the whole idea of false-positives, false-negatives...for the average person out there who has not really heard those terms before, I think that’s more difficult than most people think to actually get around. And the idea of a screening versus a diagnostic test, I think not all people understand the difference.”</p> <p>[FP: 016]</p>

Appendix F: Original Research Ethics Approval and Amendment Approval Notice



Hamilton Integrated Research Ethics Board (HIREB)

293 Wellington St. N., Suite 102, Hamilton, ON L8L 8E7
Telephone: 905-521-2100, Ext. 42013
Fax: 905-577-8378

February 10, 2014

PROJECT NUMBER: 14-056

PROJECT TITLE: Women and Clinicians' Experiences with Non-Invasive Prenatal Testing

PRINCIPAL INVESTIGATOR: Meredith Vanstone

This will acknowledge receipt of your letter dated January 31, 2014 which enclosed revised copies of the Information/Consent Forms, Recruitment Posters and Ad, Outstanding Signature and the Application Form for the above-named study. These issues were raised by the Hamilton Integrated Research Ethics Board at their meeting held on January 21, 2014. Based on this additional information, we wish to advise your study has been given *final* approval from the full HIREB.

The following documents have been approved on both ethical and scientific grounds:

- The submission
- Information/Consent Form – Women version 2 dated January 31, 2014
- Information/Consent Form – Clinicians version 2 dated January 31, 2014
- Consent to Contact Future Participation in Research version 1 dated January 17, 2014
- Poster Ad for Women version 2 dated January 31, 2014
- Poster Ad for Clinicians version 2 dated February 10, 2014
- Online Ad for Women version 2 dated January 31, 2014
- Cover Letter for Mail (Women) version 1 dated December 31, 2013
- Email Script for Women version 1 dated December 31, 2013
- Email Script for Clinicians version 1 dated December 31, 2013
- Phone Script for Women version 1 dated December 31, 2013
- Focus Group Guide for Clinicians version 1 dated December 31, 2013
- Interview Guide for Clinicians version 1 dated December 31, 2013
- Interview Guide for Women version 1 dated December 31, 2013

Please note attached you will find the Information/Consent Forms and Poster Ads with the HIREB approval affixed; all consent forms/posters used in this study must be copies of the attached materials..

The Hamilton Integrated Research Ethics Board operates in compliance with and is constituted in accordance with the requirements of: The Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans; The International Conference on Harmonization of Good Clinical Practices; Part C Division 5 of the Food and Drug Regulations of Health Canada, and the provisions of the Ontario Personal Health Information Protection Act 2004 and its applicable Regulations; for studies conducted at St. Joseph's Hospital, HIREB complies with the health ethics guide of the Catholic Alliance of Canada

Meredith Vanstone
14-056

We are pleased to issue final approval for the above-named study for a period of 12 months from the date of the HIREB meeting on January 21, 2014. Continuation beyond that date will require further review and renewal of HIREB approval. Any changes or revisions to the original submission must be submitted on an HIREB amendment form for review and approval by the Hamilton Integrated Research Ethics Board.

PLEASE QUOTE THE ABOVE-REFERENCE PROJECT NUMBER ON
ALL FUTURE CORRESPONDENCE

Sincerely,

Signature omitted from published thesis

Suzette Salama, PhD.
Chair, Hamilton Integrated Research Ethics Board

**Western University Health Science Research Ethics Board
HSREB Amendment Approval Notice**

Principal Investigator: Dr. Barbra de Vrijer
Department & Institution: Schulich School of Medicine and Dentistry/Obstetrics & Gynaecology, Western University

Review Type: Full Board
HSREB File Number: 106393
Study Title: Women and Clinicians' Experiences of Non-Invasive Prenatal Testing
Sponsor: Canadian Institutes of Health Research

HSREB Amendment Approval Date: February 19, 2016
HSREB Expiry Date: October 01, 2016

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Other	Letter of Attestation	2015/12/17
Revised Western University Protocol	Protocol-PDF	2016/01/20
Revised Letter of Information & Consent	Consent-women-PDF	2015/12/18
Revised Letter of Information & Consent	Consent-clinicians-PDF	2015/12/18
Other	Email-clinicians-PDF	2015/12/18
Other	Email-women-PDF	2015/12/18
Advertisement	Poster-clinicians-PDF	2015/12/18
Advertisement	Poster-women-PDF	2015/12/18
Other	Version: Jan 20, 2016-pdf	2016/01/20

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the amendment to the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number

Signature omitted from published thesis

Ethics Officer, on behalf of Dr. Marcelo Kremenchtzky, HSREB Vice Chair

Ethics Officer to Contact for Further Information: Erika Basile ___ Katelyn Harris ___ Nicole Kaniki ___ Grace Kelly ___ Vikki Tran ___

This is an official document. Please retain the original in your files

Curriculum Vitae

Name: Leichelle Little

**Post-secondary
Education and
Degrees:** University of Waterloo
Waterloo, Ontario, Canada
2004-2009 B.Sc.

Sarah Lawrence College
Bronxville, New York, U.S.A.
2009-2011 M.S.

The University of Western Ontario
London, Ontario, Canada
2012-2022 Ph.D.

**Related Work
Experience** Laboratory Genetic Counsellor
CHEO Diagnostic Laboratory
2016-Present

Teaching Assistant Training Program Coordinator
The Centre for Teaching and Learning, The University of Western
Ontario
2012-2016

Research Genetic Counsellor
School of Communication Sciences and Disorders
2012-2014

Publications:

Burgess, R., Cernat, A., **Little, L.**, & Vanstone, M. (2020). Implementing Publicly Funded Noninvasive Prenatal Testing for Fetal Aneuploidy in Ontario, Canada: Clinician Experiences With a Disruptive Technology. *Qualitative Health Research*, 1049732320945303.

Little, L., & Vanstone, M. (2016) Women's Misconceptions about Non-invasive Prenatal Testing: A qualitative secondary analysis (Abstract Program, Oral Presentation). Society of Obstetricians and Gynaecologists: Annual Clinical and Scientific Conference. Vancouver, BC, June