Impact of provincially-funded non-invasive prenatal testing on the utilization of invasive diagnostic testing in British Columbia

by

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Abstract

Introduction: Non-invasive prenatal testing (NIPT) is an accurate and safe screening test for detection of Down syndrome, trisomy 18, and trisomy 13, which can be used to reduce the need for invasive diagnostic testing in high-risk women. In November 2015, British Columba (BC) introduced publicly-funded NIPT as a contingent screening test for women at an increased risk of having a trisomic pregnancy. The objective of this research was to quantify the extent to which the introduction of publicly-funded NIPT influenced the utilization of invasive diagnostic testing in BC.

Methods: We used linked population-based provincial prenatal biochemistry and cytogenetic laboratories data maintained by the BC Prenatal Genetic Screening Program and Perinatal Services BC. Our study population included all known singleton pregnancies in BC between April 1, 2011 and April 30, 2017 with a positive result from provincially-funded serum integrated prenatal screen (SIPS), integrated prenatal screen (IPS), and quad marker screen (Quad). We divided this timeframe into three periods: period 1 with no NIPT (April 1, 2011-January 31, 2013), period 2 with self-pay NIPT only (February 1, 2013-October 31, 2015), and period 3 with publicly-funded NIPT (November 1, 2015-April 30, 2017). We performed an interrupted time series analysis using log-binomial regression to evaluate the change in use of invasive diagnostic testing after the introduction of self-pay NIPT and publicly-funded NIPT. Models were adjusted for maternal age and self-reported maternal race.

Results: Among the 8,649 pregnancies included in the study, the estimated rate of invasive diagnostic testing decreased by 12.7% (95% CI: 0.79 to 0.97) when self-pay NIPT was

introduced. With the introduction of publicly-funded NIPT, the estimated rate of invasive

diagnostic testing decreased by 47.8% (95% CI: 0.40 to 0.68). The estimated trend of decrease in

the rate of invasive diagnostic testing utilization was 1.7% per month (95% CI: 0.98 to 0.99)

within the second period with self-pay NIPT.

Conclusions: The introduction of publicly-funded NIPT was associated with a significant

decrease in the number of invasive diagnostic tests performed in BC among singleton

pregnancies screened positive with provincially-funded SIPS, IPS, and Quad. Future cost-

consequences studies including detailed healthcare costs would be valuable.

Lay Summary

Non-invasive prenatal testing (NIPT) is a relatively new blood test for detecting certain birth defects, such as Down syndrome. NIPT is considered as an accurate and safe contingent screening test that can be used to reduce the need of sampling tissue from the womb in high-risk women. In November 2015, British Columba (BC) introduced publicly-funded NIPT for women with an increased risk of having a pregnancy with certain genetic disorders. The objective of this research was to examine the impact of publicly-funded NIPT on the use of invasive diagnostic testing in BC. The results from this research can be used as evidence for providing publicly-funded NIPT in other Canadian provinces or similar healthcare system. Our findings also have implications on several aspects of obstetrical practice that will require further investigation. Future studies incorporating the actual healthcare costs should be conducted to fully understand the impact of publicly-funded NIPT in BC.

Preface

The work presented in this thesis was conducted and written by me with support and infrastructure provided by Perinatal Services BC. I was responsible for data management, statistical analysis, interpretation, and thesis writing. The thesis was completed with assistance from my thesis committee, which included Drs. Jennifer Hutcheon, Jason Sutherland, and Sylvie Langlois, and my director from Perinatal Services BC, Ms. Amy Hobbs. The committee members and my director provided feedback to improve clarity of the content. Chapter 3 of this thesis will be submitted for publication after my oral defense. This study was approved by the University of British Columbia Children's and Women's Research Ethics Board (H17-01959).

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List of Abbreviations

AFP   Alpha-fetoprotein

BC   British Columbia

CVS   Chorionic villus sampling

FTS   First trimester screening

hCG   Human chorionic gonadotropin

IPS   Integrated prenatal screen

NIPT   Non-invasive prenatal testing

NT   Nuchal translucency

PAPP-A   Pregnancy-associated plasma protein A

Quad   Quad marker screen

SIPS   Serum integrated prenatal screen

SOGC   Society of Obstetrics and Gynaecology Canada

uE3   Unconjugated estriol

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Dedication

To my grandpa（爺爺）

1   Introduction

Congenital anomalies include structural or functional birth defects that occur during intrauterine growth and can be identified prenatally, at birth, or later in infancy.(1) The cause of congenital anomalies includes factors related to genetics, socioeconomic status and demographic, environment, and maternal nutrition; however, the specific cause cannot be identified for approximately 50% of all anomalies.(1) In Canada, approximately 1 in 25 babies born is diagnosed with at least one congenital anomaly each year.(2) In British Columbia (BC), roughly 1 in 17 births had any confirmed or suspected congenital anomalies.(3)

Chromosomal anomalies are a type of congenital anomalies in which there is an abnormal number of chromosomes (e.g., a trisomy) or a structural abnormality in one or more of the chromosomes. In 2014, the Canadian rate of Down syndrome, trisomy 18, and trisomy 13 were 16.3 per 10,000 births, 2.57 per 10,000 births, 1.2 per 10,000 births, respectively.(4) In 2015/16, the BC rate of confirmed or suspected chromosomal anomalies, which included Down syndrome, trisomy 18, or trisomy 13, was 21 per 10,000 births.(3) The risk of Down syndrome, trisomy 18, and open neural tube defects based on maternal age are shown in Table 1.(5) Screening tests including blood samples and ultrasound indicate the probability of a fetus having a chromosomal anomaly, and diagnostic tests through invasive procedures can be used for confirmatory purposes. The results of the tests will be used for informed decision-making of a woman's pregnancy, termination, or delivery. It is a woman's choice on whether to have prenatal genetic screening and/or invasive diagnostic procedures. Some women choose not to have prenatal genetic screening because of the desire to continue the pregnancy not matter what the result is, while other women would like to have prenatal genetic screening for better management of the

pregnancy and preparation for the birth even when they wish to continue the pregnancy regardless of the result.

Table 1. Risk of Down syndrome, trisomy 18, and open neural tube defects based on maternal age.

Maternal age	Risk of Down syndrome	Risk of trisomy 18	Risk of open neural tube defects
25	1 in 2,500	1 in 25,000	1 in 1,000 irrespective of maternal age
30	1 in 840	1 in 8,400	
35	1 in 356	1 in 3,560	
40	1 in 94	1 in 940	

Perinatal Services BC, a provincial agency that provides leadership, support, and coordination for the strategic planning of perinatal services in BC(6), manages the BC Prenatal Genetic Screening Program. The BC Prenatal Genetic Screening Program was established in 2009 and it offers provincially-funded prenatal genetic screening tests, such as serum integrated prenatal screen (SIPS), integrated prenatal screen (IPS), and quad marker screen (Quad), to estimate the fetal risk of Down syndrome (also known as trisomy 21), trisomy 18, and open neural tube defects for women with Medical Service Plan coverage in BC. (7–9) The choice of screening tests offered is based on gestational age at the first prenatal visit, maternal age at delivery, pregnancy plurality, and maternal and/or family history.(9)

SIPS consists of two blood tests, the first one for measuring pregnancy-associated plasma protein A (PAPP-A) and the second one for measuring alpha-fetoprotein (AFP), unconjugated estriol (uE3), human chorionic gonadotropin (hCG), and Inhibin-A.(9) IPS involves the same blood tests as SIPS with the addition of nuchal translucency (NT) ultrasound, which measures the

width of the fluid-filled space at the back of the fetus's neck.(9,10) Quad only includes the

second blood test in SIPS/IPS and is used for women who missed their opportunity to get the

first blood test prior to 14 weeks of gestation.(9) First trimester screening (FTS), also known as

combined FTS or combined screening, consists of PAPP-A, free beta-hCG, and NT

ultrasound.(11) Since the BC Prenatal Genetic Screening Program does not offer provincially-

funded FTS, this screening test can be done between 11 and 14 weeks of gestation through

private clinics.(12) Based on the above mentioned screening tests, if a woman receives a

positive result for Down syndrome or trisomy 18, she is counseled by her healthcare provider as

to the options of non-invasive prenatal testing (NIPT) or invasive diagnostic testing, including

chorionic villus sampling (CVS) and amniocentesis.(9) Referral to genetic counselling for a

detailed ultrasound and possibly an invasive diagnostic test are made when a woman receives a

positive result for open neural tube defects.(9)

Prior to the introduction of NIPT, screening tests results from SIPS, IPS, Quad, or FTS were

used to determine whether invasive diagnostic testing should be offered to pregnant women.(9)

CVS takes a small sample of placental tissue and the procedure is done between the 11th and 13th

week of pregnancy.(13) Amniocentesis takes a small amount of amniotic fluid and the procedure

can be done after the 15th week of pregnancy.(14) CVS and amniocentesis are associated with a

risk of pregnancy loss between 1% and 2% and between 0.5% and 1%, respectively.(13,14)

NIPT is a relatively new blood test that isolates cell-free fetal DNA circulating in maternal

blood. Analyzing cell-free fetal DNA enables the detection of chromosomal abnormalities

without the use of CVS and amniocentesis.(15) There is no known risk of pregnancy loss with

NIPT.(15) Additionally, NIPT can be accessed at numerous medical laboratories, whereas CVS and amniocentesis require travelling to a tertiary care centre with maternal-fetal medicine subspecialists. Due to the high detection rate (greater than 99% for Down syndrome, approximately 97% for trisomy 18, and approximately 93% for trisomy 13) and low false positive rate (less than 0.1%), NIPT is considered as an accurate and safe contingent screening test that can be used to reduce the need for invasive diagnostic testing in women at an increased risk of Down syndrome, trisomy 18, or trisomy 13.(15) Nonetheless, genetic counselling and amniocentesis are recommended for women with a positive NIPT result.(16) Appendix A and B summarize the eligibility criteria, sample collection timeframes, sample type, detection rate, and false positive rate of provincially-funded SIPS, IPS, Quad, NIPT, CVS and amniocentesis based on the clinical guidelines provided by the BC Prenatal Genetic Screening Program.(9)

NIPT was first introduced in BC as a self-pay screening test in February 2013. Self-pay is defined as an out-of-pocket cost that may be reimbursed through patients' supplementary private insurers, who provide extended health benefits that are not already covered under the public health insurance available to all eligible residents of BC. Panorama NIPT is offered through LifeLabs Medical Laboratories at $550 with additional charge for screening of additional syndromes.(17) Harmony NIPT is offered through Dynacare Laboratories, hospital outpatient laboratories, fertility centres, maternity groups, and other private medical laboratories.(18) The cost of Harmony NIPT varies by suppliers; for example, Dynacare Laboratories charges $495 per test while some fertility centres charge $650 per test.(18) In November 2015, the BC Ministry of Health commenced publicly-funded NIPT for women with:

- a positive result from SIPS, IPS, or Quad

- a previous Down syndrome, trisomy 18, or trisomy 13 pregnancy, or

- a risk of Down syndrome greater than 1 in 300 based on screening results and ultrasound markers of aneuploidy; the ultrasound markers of aneuploidy are detected during the detailed ultrasound between 18 and 20 weeks of gestation.(19–22)

Elsewhere in Canada, the Ministry of Health and Long Term Care Ontario also provides publicly-funded NIPT to pregnant women who meet a similar set of eligibility criteria as BC's.(23)

NIPT is becoming a prevalent and desired genetic screening strategy for pregnant women because of its accuracy and safety. With its high cost of at least $495 per test, it is unclear how this new technology should be incorporated into publicly-funded healthcare systems such as Canada's. Many simulation studies have estimated the costs and benefits of implementing NIPT under different strategies including first-line NIPT for all pregnant women or contingent NIPT for women at an increased risk of having a trisomic pregnancy.(24,25,34–39,26–33) Studies from the United States, Australia, China, and the Netherlands have reported that the introduction of self-pay NIPT was associated with a decrease in the use of invasive diagnostic testing.(40,41,50,42–49) Since BC is one of the early Canadian provinces to incorporate publicly-funded NIPT into a population-based prenatal genetic screening program, it is important to examine the impact of such a program on the utilization of invasive diagnostic testing under real-world conditions. An understanding of how the introduction of publicly-funded NIPT affects resource utilization is critical for informing the implementation of this innovative technology in new jurisdictions and anticipating its costs and benefits.

The primary objective of this thesis was to evaluate the extent to which the introduction of publicly-funded NIPT in BC influenced the utilization of CVS and amniocentesis among pregnancies with a positive result from provincially-funded SIPS, IPS, and Quad. It was hypothesized that the number of CVS and amniocenteses conducted would be significantly reduced after the introduction of publicly-funded NIPT in November 2015. In order to extend our understanding of the effect of publicly-funded NIPT in BC, we also conducted an exploratory analysis estimating the direct public healthcare cost based on the number of invasive diagnostic tests and publicly-funded NIPT performed in the three different periods according to the availability of NIPT.

This thesis consists of four chapters. Chapter 2 is a literature review of the impact of NIPT on use of invasive diagnostic testing as well as studies estimating the cost-effectiveness of NIPT in different countries. Chapter 3 is a manuscript to be submitted for publication in a journal of interest; methods, results, and discussions of the impact of publicly-funded NIPT on the utilization of invasive diagnostic testing in BC are included in this chapter. Chapter 4 describes the results from our exploratory cost-consequences analysis.

2   Literature Review

2.1   Impact of NIPT on invasive diagnostic testing

Australia

Robson and Hui used publicly-available data on CVS and amniocenteses performed from 1994 to 2014 in Australia to examine trends in the use of invasive diagnostic procedures.(40) Following the date that coincided with introduction of NIPT, the number of CVS and amniocenteses dropped significantly by 37% and 51%, respectively.(40) However, the study did not have direct data on NIPT eligibility or uptake. Susman et al. applied data from Victoria, Australia to predict the detection of chromosomal abnormalities and the number of invasive diagnostic tests if NIPT was introduced as a first-line screening for all pregnant women.(41) Based on their simulations, the detection of Down syndrome would increase by 7% and the rate of invasive diagnostic testing would reduce by 84%.(41) The study also estimated that there was a 56% reduction in detection of other chromosomal abnormalities, such as trisomy 18 and trisomy 13.(41)

United States

The California Prenatal Screening Program offers sequential integrated screening (which is equivalent to IPS), SIPS, and Quad to all pregnant women at US$221.60 for the blood draws and with additional cost for NT ultrasound.(51) Free follow-up service including genetic counselling and invasive diagnostic testing at a State-approved Prenatal Diagnosis Center is provided to women who screened as high risk.(52) Women who are enrolled in Medi-Cal, a health insurance that offers free or low-cost coverage to eligible residents in California, are covered for prenatal genetic screening and NIPT.(42,53) Chetty et al. examined the impact of NIPT with 1,036

women having a positive prenatal genetic screening result in their single Prenatal Diagnosis Center.(42) The introduction of NIPT in March 2012 was associated with a statistically significant decrease in the use of invasive diagnostic testing from 47% to 39%.(42) This association remained unchanged after controlling for race, advanced maternal age, and insurance payer (public *vs.* private insurance).(42) With the availability of NIPT, there was a significant decrease in the likelihood of women declining further genetic testing from 53% of 21%.(42) The authors also identified that maternal age and insurance payer were not significant factors influencing the uptake of NIPT.(42)

Larion et al. investigated invasive diagnostic testing performed in a large academic referral center comprising three sites of the Eastern Virginia Medical School.(43) After introducing NIPT to high-risk women, the average number of CVS and amniocenteses conducted decreased significantly by 77% and 53% from the baseline of 5.7 and 25.9 tests per quarter, respectively.(43) The authors also examined the impact of FTS and NIPT on invasive diagnostic testing.(44) The average number of CVS and amniocenteses per month decreased significantly by 49% and 70% after the introduction of NIPT in March 2012, respectively.(44) The authors speculated that the changes were due to maternal preference of non-invasive procedures and provider preference of presenting early and efficient risk assessment.(44)

Wax et al. included a total of 2,510 women with singleton pregnancies from a single maternal-fetal medicine practice in Portland.(45) The use of CVS and amniocentesis after the introduction NIPT was 0.7 and 0.4 times the use of CVS and amniocentesis before the availability of NIPT, respectively.(45) At the Prenatal Diagnostic Unit at the University of North Carolina at Chapel

Hill, Beamon et al. observed that NIPT uptake increased steadily and the rate of amniocentesis decreased significantly among women with a high risk of having a Down syndrome pregnancy; however, the rate of CVS remained stable.(46) Friel et al. investigated women who were referred to the University of Texas Health Maternal-Fetal Medicine Clinics due to advanced maternal age or positive screening results. The introduction of NIPT did not affect the use of invasive diagnostic testing significantly for patients who received counselling at their first trimester; however, the opposite was true for patients between 14 and 22 weeks of gestation.(54)

Khalifeh et al. conducted a retrospective cohort study of 88,135 pregnancies at the four hospitals of the Main Line Health System in Pennsylvania to assess the impact of NIPT on the use of invasive diagnostic testing.(47) They found that the use of invasive diagnostic testing decreased from 2003 to 2013, and estimated that the introduction of NIPT resulted in a significant decrease in the use of invasive diagnostic testing by 64%.(47) Tiller et al. examined the impact of NIPT in women with an increased risk of fetal aneuploidy at four medical centers in the Kaiser Permanente Southern California system.(48) When comparing the prospective cohort to a matched historical cohort with 200 women in each group, the rate of invasive diagnostic testing performed significantly lowered from 29% to 11% after the implementation of NIPT.(48) Based on the questionnaire given to the prospective cohort of women, safety and accuracy were crucial factors in considering NIPT.(48) Platt et al. found variations in the implementation and uptake of NIPT based on patient demographics and preferences across six medical centers in California, Nevada, Minnesota, Virginia, and Connecticut.(55) Advanced maternal age was the most common indication for NIPT.(55) After the introduction of NIPT, yearly rate of amniocentesis

decreased in all six centers, while the yearly rate of CVS decreased in four centers and remained the same in the other two centers.(55)

China

Han et al. examined the uptake of NIPT of 5,694 women who screened positive for Down syndrome and were referred to a Chinese tertiary maternity site over a period of two years.(56) Among women with a local household registration, which allowed women to receive invasive diagnostic testing for free, the uptake of NIPT remained stable throughout the study period; among women without such status, the uptake of NIPT doubled when the price of NIPT decreased by half during the second year.(56) The authors concluded that financial cost was a major factor in women's decision-making process.(56) Li et al. investigated the change in the number of invasive diagnostic tests after the introduction of NIPT in the same Chinese tertiary maternity site.(57) Although the number of invasive diagnostic tests remained fairly similar after the introduction of NIPT, the number of invasive diagnostic tests required per trisomy case detected decreased from 57 to 26.(57)

Poon et al. compared the use of invasive diagnosis testing before and after the introduction of NIPT in a public hospital in Home Kong.(49) Prenatal genetic screening for Down syndrome and invasive diagnostic testing for women with a positive screening result were offered to pregnant women free of charge in public clinics, and NIPT was offered in private clinics.(49) After the introduction of NIPT in the private clinics, the uptake of NIPT increased from 16% in the first year to 27% in the second year.(49) The use of CVS and amniocentesis decreased from 52% to 45% and from 37% to 28%, respectively.(49) In the second year post-NIPT, the use of CVS

continued to decease but the use of amniocentesis increased by eight percentage points.(49) The authors also found being nulliparous was a significant factor in accepting NIPT and declining invasive diagnostic testing.(49)

Other countries

In the Netherlands, Oepkes et al. included 1,390 women with a singleton pregnancy choosing NIPT due to having an increased risk of carrying a Down syndrome, trisomy 18, or trisomy 13 fetus based on screening result or medical history.(50) This study was part of a nationwide implementation of NIPT.(50) Within the first five months between April and September 2014, the uptake of NIPT was approximately 86%, which lead to an estimated reduction of 62% for invasive diagnostic testing performed.(50) The study supported having NIPT as a contingent screening test for high-risk pregnancies under the Dutch national prenatal screening program.(50) However, the generalizability of these findings to Canada is questionable due to the uptake of prenatal genetic screening being less than 30% in the Netherlands.(50)

Manegold-Brauer et al. examine the use of invasive diagnostic testing before and after the introduction of self-pay NIPT with 2,271 singleton pregnancies that received FTS at a tertiary referral center in Germany.(58) The rate of invasive diagnostic testing was 11.6% and 11.3% before and after the introduction of NIPT, respectively; and the uptake of NIPT was only 3.7% of the study population.(58) The authors concluded that the introduction of NIPT was not associated with a decrease in the use of invasive diagnostic testing in their cohort.(58)

Methodological approaches for evaluating the impact of NIPT on invasive diagnostic testing

A pre-post study design was the most common methodology used to examine the impact of NIPT on the utilization of invasive diagnostic testing in the previously-reviewed studies. In a pre-post study design, the average rate of an outcome across a specific time period (e.g., pre-implementation of a new policy or program) is compared to the average outcome rate in another time period (e.g., post-implementation of a new policy or program). Because this approach assumes that rates are homogenous within each time period, it becomes challenging to distinguish changes attributable to the introduction of a new policy or program from other underlying temporal trends in the study outcome. For example, the design does not distinguish a steady, gradual decrease in the outcome within a time period from a pronounced, immediate drop at the time of a new policy or program introduction. An interrupted time series design is a more rigorous quasi-experimental design used when randomized controlled trials are impractical or infeasible.(59,60) It is methodologically superior to a pre-post study design because it controls for the underlying time trends.(59) Currently, no studies have used an interrupted time series design to examine the impact of NIPT on the utilization of invasive diagnostic testing.

2.2 Cost-effectiveness of NIPT based on decision-analytic models

Australia

In Australia, FTS has been publicly funded since 2003.(25) Ayres et al. simulated a cohort of 300,000 singleton pregnancies that matched the size of live births and the age of mothers in Australia.(24) The authors estimated the cost-effectiveness of the following strategies: FTS only, contingent NIPT for women screened as high-risk by FTS, first-line NIPT for women greater

than 35 or 40 years old, and replacing FTS with NIPT for all pregnant women.(24) The most cost-effective strategy was having first-line NIPT for women greater than 40 years old. This method increased detection of Down syndrome and decreased pregnancy losses related to invasive diagnostic testing at a much lower cost than first-line NIPT for all pregnant women.(24)

Maxwell et al. developed a decision-analytic model based on the same cohort of 300,000 screened pregnancies.(25) They examined the current practice with FTS only and contingent NIPT for women with an increased risk; high and intermediate risk was defined with different risk cut-offs ranging from 1 in 5 to 1 in 50 and from 1 in 300 to 1 in 2,500, respectively.(25) The authors concluded that contingent NIPT with high risk cut-offs at 1 in 10 or 1 or 20, or intermediate risk cut-offs at 1 in 1,000 or 1 in 1,500 improved the detection of Down syndrome, reduced procedure-related losses, and lowered cost per diagnosis than the current practice with FTS only.(25)

O'Leary et al. simulated the costs and benefits of having FTS only compared with having NIPT as a contingent screening for women who screened as high risk.(26) A decision model was established based on a cohort of 32,478 singleton pregnancies that completed FTS in Western Australia.(26) Implementation of NIPT as a contingent screening led to a reduction in the number of invasive diagnostic tests and hence, a decrease in the number of procedure-related losses; however, the cost would increase by almost 10% over a period of two years.(26)

Canada

Since 1993, Ontario has offered provincially-funded prenatal genetic screening for Down syndrome and the uptake rate of prenatal genetic screening was approximately 67%.(27) Okun et al. estimated the cost and performance of eight different scenarios, including the current screening practice without NIPT, replacing the current practice with first-line NIPT, and adding contingent NIPT on top of the current screening practice.(27) It was found that having contingent NIPT for women who screened positive improved overall screening performance, reduced the number of amniocenteses, and decreased the number of procedure-related losses.(27) Although they estimated that the total program cost would be increased, the cost per case of Down syndrome diagnosed would be decreased.(27)

Nshimyumukiza et al. conducted a decision-analytic model based on the characteristics of women in Quebec in 2014.(28) The authors compared the cost-effectiveness of 13 screening strategies, including six prenatal genetic screening tests recommended by Society of Obstetrics and Gynaecology Canada (SOGC), incorporating NIPT as a contingent screening for women screened as high risk based on the six SOGC recommended screening tests, and implementing NIPT as a first-line screening for all pregnant women.(28) The study estimated that having NIPT as a contingent screening decreased costs and reduced the number of invasive diagnostic tests by at least 79% in comparison to the currently recommended screening practices.(28) NIPT as a first-line screening for all pregnant women had the best detection but cost four to seven times more than other strategies.(28) Therefore, contingent NIPT for high-risk women defined by the conventional risk cut-offs was identified as the most cost-effectiveness option.(28)

United States

Benn et al. conducted an economic analysis to assess the value of replacing FTS with NIPT using a theoretical cohort of almost four million live births based on the annual number of births in the United States.(29) Such replacement increased detection of fetal aneuploidy and decreased the number of invasive diagnostic tests performed, which reduced the number of procedure-related losses.(29) The analysis indicated that NIPT, costing at a maximum US$744, could be provided universally without increasing cost to the healthcare system.(29) Fairbrother et al. used the same theoretical cohort of four million pregnant women to compare FTS and first-line NIPT in their decision-analytic model.(30) The study concluded that NIPT priced at US$453 or less per unit would be cost saving in comparison to FTS.(30)

Song et al. also created a decision-analytic model for a cohort of four million pregnant women in the United States. The study reported that it was more clinically effective and less costly to offer NIPT as first-line screening for women 35 years and older or with a medical history of increased risk, or offer NIPT as a contingent screening for women who screened positive through the conventional screening tests.(31) Implementation of this NIPT strategy would result in higher detection of Down syndrome and significant reduction in invasive diagnostic testing and procedure-related losses.(31) Evans et al. evaluated the cost-effectiveness of having a first-line NIPT for all pregnant women, a contingent NIPT for high-risk women identified through FTS, and a hybrid NIPT offered as first-line screening to women who were at least 35 years old and as a contingent screening to high-risk women less than 35 years old.(32) They found that contingent NIPT for women identified as high risk, especially with a risk cut-off of 1 in 1,000, resulted in the lowest cost of US$409 per women.(32)

Walker et al. simulated the cost-effectiveness of contingent NIPT and first-line NIPT from societal, government, and payer's economic perspectives.(33) They concluded that first-line NIPT was the best strategy from a societal perspective, which included immediate costs of screening, and direct and indirect life-time costs; contingent NIPT was the best strategy from a governmental perspective that included only immediate and direct costs.(33) Kaimal et al. not only compared the clinical outcomes and costs but also quality-adjusted life-years for the following strategies: IPS, contingent NIPT, first-line NIPT, concurrent system of having both IPS and NIPT, and invasive diagnostic testing only.(34) The authors concluded that the current screening practice of having IPS yielded the highest detection rate of chromosomal abnormalities, highest quality-adjusted life-years, and lowest costs; however, first-line NIPT became optimal when women approached 40 years of age.(34)

Other countries

Morris et al. examined the cost-effectiveness of NIPT being offered as either a first-line screening or a contingent screening under the publicly-funded National Health Service in the United Kingdom.(35) They identified that setting a risk cut-off at 1 in 150 and a maximum cost per contingent NIPT at £500 resulted in fewer pregnancy losses caused by invasive diagnostic testing.(35) Depending on the unit price of NIPT, it could led to cost neutral or even cost savings.(35) Chitty et al. developed a health economic model using both prospective cohort and national data to measure the costs and outcomes of having NIPT as a contingent screening with different risk-cut-offs at 1 in 150, 1 in 500, and 1 in 1,000.(36) Out of the 3,175 pregnant women who were offered NIPT in the eight participating maternity units across the United Kingdom, the

uptake rate of NIPT was 78.6%, 74.4%, and 80.3% for women with a risk of at least 1 in 1,000, at least 1 in 150, and between 1 in 150 and 1 in 1,000, respectively.(36) Contingent NIPT with a risk threshold of 1 in 150 improved screening performance, and decreased the number of invasive diagnostic testing and procedure-related losses with no significant effect on healthcare costs.(36)

In Belgium, the uptake of fully-reimbursed prenatal genetic screening was 80% (37,38) and 79% of these women received FTS.(38) Neyt et al. performed a cost-consequences analysis by comparing NIPT as a first-line screening or contingent screening for all singleton pregnancies in Belgium.(37) The authors concluded that reimbursing contingent NIPT at the current price of €460 significantly reduced procedure-related losses without increasing short-term costs.(37) They concluded that in the long term, first-line NIPT should be considered if price per NIPT could drop to €150.(37) Gyselaers et al. simulated the impact of contingent NIPT offered to women at an increased risk of 1 in 300 or 1 in 600.(38) Their model suggested that contingent NIPT offered at a risk cut-off of 1in 300 would reduce short-term cost by 11%, which could be used to improve Belgium's screening program.(38)

Beulen et al. conducted a cost-effectiveness analysis based on Dutch's healthcare system; they compared FTS only, NIPT as a contingent screening for pregnancies with a high risk for Down syndrome, and NIPT as a replacement of the current practice with FTS.(39) When NIPT was implemented as a contingent screening, the number of invasive diagnostic tests performed decreased, which reduced the average risk of procedure-related losses.(39) The authors also

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reported that having contingent NIPT resulted in the lowest cost per Down syndrome case diagnosed.(39)

Summary of findings from simulated cost-effectiveness studies

Out of the three studies from Australia, two studies identified contingent NIPT for women at an increased risk to be the most cost-effective strategy, while only one study concluded that first-line NIPT for women at advanced maternal age was the most cost-effective method. In Canada, contingent NIPT for women who screened positive with existing prenatal genetic screening tests was identified to be the most cost-effectiveness option when simulated using Ontario and Quebec data. Six cost-effectiveness studies were conducted in the United States and the results were mixed; some studies indicated that first-line NIPT would be either cost neutral or cost saving, some studies reported that first-line NIPT for women who were at least 35 years old or with an increased risk would be optimal, and other studies concluded that contingent NIPT for women with an increased risk would be a better option. Studies from the United Kingdom, Belgium, and the Netherlands also concluded that contingent NIPT would be the most cost-effectiveness strategy based on their simulations.

3   Impact of publicly-funded NIPT on invasive diagnostic testing in BC

3.1   Introduction

There are approximately 44,000 deliveries and 45,000 births in the Canadian province of British Columbia (BC) annually.(3) In 2015/16, roughly 60 per 1,000 births had any confirmed or suspected congenital anomalies, and 2.1 per 1,000 births had confirmed or suspected chromosomal anomalies, which included Down syndrome, trisomy 18, or trisomy 13.(3) In November 2015, BC Ministry of Health commenced publicly-funded non-invasive prenatal testing (NIPT) as a contingent screening for women who are at high risk of having a Down syndrome, trisomy 18, or trisomy 13 pregnancy.(19–21)

NIPT is a relatively new blood test that isolates and analyzes cell-free fetal DNA circulating in maternal blood to enable the detection of chromosomal abnormalities without the use of invasive diagnostic procedures such as chorionic villus sampling (CVS) or amniocentesis.(15) Unlike these invasive diagnostic tests, which have a risk of pregnancy loss between 0.5% and 2%,(13,14) there is no known risk of pregnancy loss with NIPT.(15) Although amniocentesis is the gold standard for detecting chromosomal abnormalities, NIPT detection rates for Down syndrome, trisomy 18, and trisomy 13 are greater than 99%, approximately 97%, and approximately 93%, respectively.(15) Due to the high detection rate and low false positive rate (less than 0.1%), NIPT is considered as an accurate and safe contingent screening test that can be used to reduce the need for invasive diagnostic testing in women at an increased risk of Down syndrome, trisomy 18, and trisomy 13.(15)

Despite its benefits, NIPT has a relatively high cost, from C$495 to C$650 per test in the private sector.(17,18) As a result, it is unclear how this new technology should best be incorporated into publicly-funded health care systems such as Canada's. Numerous studies have simulated the costs and benefits of having NIPT as a first-line screening for all pregnant women or as a contingent screening for women with an increased risk of having a trisomic pregnancy.(24,25,34–39,26–33) Studies from sites in the United States, Australia, China, and the Netherlands have reported that the introduction of self-pay NIPT was associated with a decrease in the use of invasive diagnostic testing.(40,41,50,42–49) However, the impact of incorporating publicly-funded NIPT into a population-based prenatal genetic screening program under real-world conditions has not been quantified. An understanding of how the introduction of publicly-funded NIPT affects resource utilization is critical for informing the implementation of this innovative technology in new jurisdictions. The objective of this research was to quantify the extent to which the introduction of publicly-funded NIPT influenced the utilization of CVS and amniocentesis in BC.

3.2 Methods

3.2.1 Introduction of NIPT

Perinatal Services BC, a provincial agency with oversight for the strategic planning of perinatal services in BC, manages the BC Prenatal Genetic Screening Program. The BC Prenatal Genetic Screening Program offers provincially-funded prenatal genetic screening tests, including serum integrated prenatal screen (SIPS), integrated prenatal screen (IPS), and quad marker screen (Quad), to estimate the fetal risk of Down syndrome, trisomy 18, and open neural tube defects for all women in BC with Medical Service Plan coverage.(8,9) The choice of screening tests

offered is based on gestational age at the first prenatal visit, maternal age at delivery, pregnancy plurality, and maternal and/or family history (detailed in Appendix A).(9)

In BC, NIPT was first introduced as a self-pay test in February 2013. Self-pay is defined as an out-of-pocket cost that may be reimbursed through patients' supplementary private insurers, who provide extended health benefits that are not already covered under the public health insurance available to all eligible residents of BC; women without supplementary insurance have to pay out-of-pocket in order to have NIPT performed. In November 2015, BC commenced publicly-funded NIPT as a contingent screening test for women with i) a positive SIPS, IPS, or Quad, ii) a previous Down syndrome, trisomy 18, or trisomy 13 pregnancy, or iii) a risk of Down syndrome greater than 1 in 300 based on prenatal genetic screening results and ultrasound markers of aneuploidy detected through a detailed ultrasound conducted between 18 and 20 weeks of gestation.(19–22)

3.2.2   Study population

Pregnancies were identified using linked population-based administrative and clinical datasets maintained by the BC Prenatal Genetic Screening Program and Perinatal Services BC. These datasets included screening results from the provincial prenatal biochemistry laboratory and diagnostic results from the provincial cytogenetic laboratories for all pregnant women who received provincially-funded prenatal genetic screening tests and invasive diagnostic tests, respectively. This study was approved by the University of British Columbia Children's and Women's Research Ethics Board (H17-01959).

Our study population was drawn from all known singleton pregnancies in BC between April 1, 2011 and April 30, 2017 with a positive result from provincially-funded SIPS, IPS, or Quad (i.e. who met the eligibility criteria for publicly-funded NIPT even if the pregnancy occurred prior to the introduction of NIPT). This group accounts for approximately 88% of all pregnancies that are eligible for publicly-funded NIPT in BC annually.(Langlois S. and MacFarlane J. Perinatal Services BC. Personal communication. 19th June 2017.) We excluded women eligible for publicly-funded NIPT through the second and third criteria outlined above due to the inability to identify these pregnancies through our data, such as lack of access to findings from detailed ultrasounds.

Based on the availability of NIPT, we divided our study duration into three periods: period 1 with no NIPT from April 1, 2011 to January 31, 2013, period 2 with self-pay NIPT only from February 1, 2013 to October 31, 2015, and period 3 with publicly-funded NIPT from November 1, 2015 to April 30, 2017. The uptake of self-pay NIPT in the second period was unknown due to lack of data on the use of private service, while the uptake of publicly-funded NIPT for women with a positive screening result was approximately 90% between November 1, 2016 and October 31, 2017 from an unpublished Perinatal Services BC report.(Langlois S. and MacFarlane J. Perinatal Services BC. Personal communication. 5th February 2018.)

3.2.3 Invasive diagnostic testing

Our primary outcome was the utilization of invasive diagnostic testing, which was defined as the use of either CVS or amniocentesis with a valid cytogenetic result. We calculated the rate of invasive diagnostic testing as the number of invasive diagnostic testing performed over the

number of pregnancies with a positive result from SIPS, IPS, or Quad. Appendix B provides further details including sample collection timeframes, detection rate, and false positive rate of CVS and amniocentesis based on the clinical guidelines provided by the BC Prenatal Genetic Screening Program.(9)

3.2.4 Statistical analysis

We performed an interrupted time series analysis using log-binomial regression(59–62) to isolate the effect of NIPT introduction on the use of invasive diagnostic testing. Two interventions were evaluated in the analysis: the introduction of self-pay NIPT in February 2013 and the introduction of publicly-funded NIPT in November 2015. The unit of time for the analysis was months, with a total of 73 months for the study period from April 1, 2011 to April 30, 2017. The model was adjusted for maternal age and maternal race. Maternal age in years at estimated delivery date was derived as the difference between the estimated delivery date and maternal date of birth. Self-reported maternal race included Black, Caucasian, East Asian, South Asian, First Nations, and Other. East Asian consisted of Japanese, Filipino, Chinese, Vietnamese, and Korean; South Asian comprised Indian, Pakistani, and Sri Lankan; and Other encompassed mixed, all else not mentioned, and records with missing information.

We estimated the level and slope change in the monthly rate of invasive diagnostic testing in our interrupted time series model using the following model specification:

$$\log Y_t = \beta_0 + \beta_1 time_t + \beta_2 intervention1_t + \beta_3 time\ after\ intervention1_t$$
$$+\beta_4 intervention2_t + \beta_5 time\ after\ intervention2_t$$
$$+\beta_6 maternal\ age\ at\ estimated\ delivery\ date + \beta_7 maternal\ race + \varepsilon_t$$

Where **Y** was the monthly rate of invasive diagnostic testing; **time** indicated the number of months from the beginning of the study; **intervention1** was an indicator variable for the time after *vs.* before the introduction of self-pay NIPT; **time after intervention1** counted the number of months after the introduction of self-pay NIPT; **intervention2** was an indicator variable for time after *vs.* before the introduction of publicly-funded NIPT; **time after intervention2** counted the number of months after the introduction of publicly-funded NIPT. The coefficient for **intervention2**, β_4, was the primary coefficient of interest as it estimated the extent to which the introduction of publicly-funded NIPT in BC impacted the rate of invasive diagnostic testing (i.e., the level change in use of invasive testing after *vs.* before introduction of publicly-funded NIPT, controlling for underlying time trends). We conducted several sensitivity analyses to verify model assumptions. First, we assessed linearity assumptions by adding a quadratic term and a restricted cubic spline for time.(63–65) We checked for autocorrelation in the model residuals over time using the Durbin-Watson statistic.(59) Finally, we examined the robustness of the model estimates for the intervention effects by specifying time lags of one and two months. Data analysis was conducted using SAS, Version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

3.3   Results

3.3.1   Study characteristics

There were 8,649 singleton pregnancies in BC with a positive result from SIPS, IPS, or Quad between April 1, 2011 and April 30, 2017. As shown in Table 2, mean maternal age was around 35 years old (SD: 5) for all three periods. Nearly half of the pregnancies were Caucasian; the second and third largest racial group was East Asian and South Asian, respectively. There was a

decrease of 1.2 and 1.9 percentage points from period 1 to 3 for Caucasian and East Asian

pregnancies, respectively; an increase of 1.3 percentage points from period 1 to 3 for Other

pregnancies; and an increase of 0.6 percentage points for all other racial groups.

Table 2. Maternal characteristics and utilization of invasive diagnostic testing among 8,649 singleton pregnancies in BC with a positive SIPS, IPS, or Quad result according to availability of NIPT, April 1, 2011 - April 30, 2017.

	Period 1 No NIPT (April 2011-Jan 2013) N (%) or Mean±SD	Period 2 Self-pay NIPT (Feb 2013-Oct 2015) N (%) or Mean±SD	Period 3 Publicly-funded NIPT (Nov 2015-April 2017) N (%) or Mean±SD
Total	2,573	3,943	2,133
Mean maternal age (years)	35.3±5	34.8±5	34.4±5
Maternal race			
Black	29 (1.1)	46 (1.2)	37 (1.7)
Caucasian	1,283 (49.9)	1,846 (46.8)	1,038 (48.7)
East Asian	708 (27.5)	1,083 (27.5)	545 (25.6)
South Asian	313 (12.2)	535 (13.6)	274 (12.8)
First Nations	64 (2.5)	90 (2.3)	66 (3.1)
Other	176 (6.8)	343 (8.7)	173 (8.1)
Invasive diagnostic testing done	1,424 (55.3)	1,279 (32.4)	218 (10.2)
CVS	19 (0.7)	18 (0.5)	6 (0.3)
Amniocentesis	1,405 (54.6)	1,261 (32.0)	212 (9.9)

3.3.2 Crude trends in utilization of invasive diagnostic testing

Table 2 and Figure 1 show the utilization rates of invasive diagnostic testing according to

different periods of NIPT availability. The rate of invasive diagnostic testing decreased from

55.3% in the first period with no NIPT to 10.2% in the third period with publicly-funded NIPT.

As shown in Figure 1, utilization of invasive diagnostic testing decreased steadily throughout the second period with self-pay NIPT, from 43.9% at the start of the period to 22.6% by the end of the period.
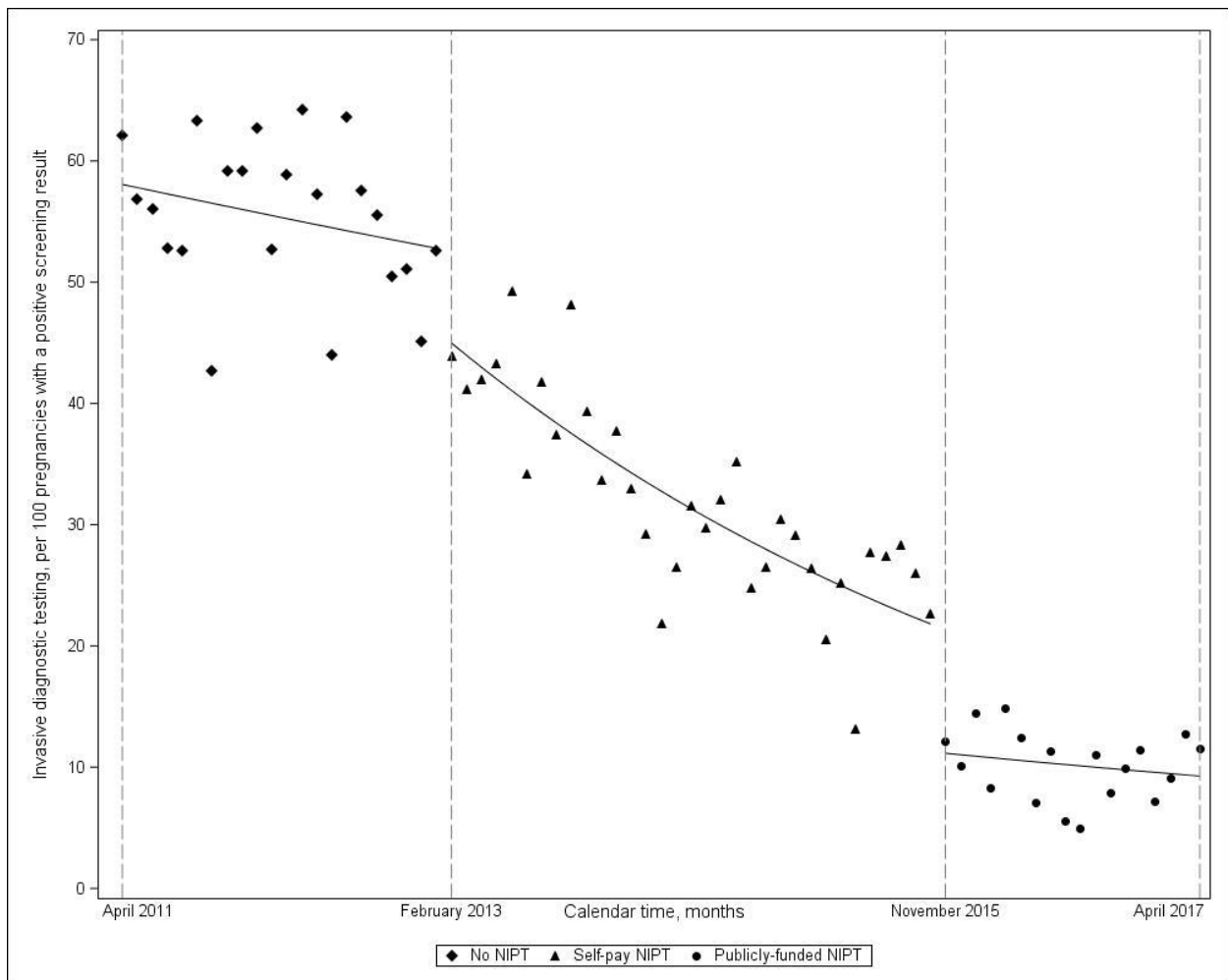

Figure 1. Estimated impact of introducing self-pay and publicly-funded NIPT on utilization of invasive diagnostic testing among singleton pregnancies with a positive SIPS, IPS, or Quad result in BC, April 1, 2011 - April 30, 2017. Diamonds, triangles, and circles indicate the observed monthly rate of invasive diagnostic testing. Lines indicate the smoothed

predicted monthly rate of invasive diagnostic testing from our unadjusted log-binomial interrupted time-series analysis.

3.3.3 Interrupted time-series analysis – introduction of self-pay NIPT

The Akaike information criterion of the linear, quadratic, and restricted cubic spline model was 9802.35, 9804.35, and 9800.76, respectively. Since the Akaike information criterion for the linear model and the restricted cubic spline model were fairly similar, we assumed that the trend of invasive diagnostic testing within each time period were linear in log-scale for the sake of parsimony.

Table 3 shows the crude and adjusted risk ratios from our time-series analysis. Adjustment for maternal age and race had little impact on model estimates. There were no significant changes in the rate of invasive diagnostic testing within the first period with no NIPT. The expected rate of invasive diagnostic testing based on the adjusted model was 52.3% in January 2013, the last month with no NIPT available, and 45.5% in February 2013, when self-pay NIPT was introduced. Our adjusted model estimated that the rate of invasive diagnostic testing decreased by 12.7% (95% CI: 0.79 to 0.97) at the time of the introduction of self-pay NIPT. The rate of invasive diagnostic testing utilization continued to decrease throughout the period with self-pay NIPT, with the trend of decrease estimated to be 1.7% per month (95% CI: 0.98 to 0.99) within the second period.

The Durbin-Watson statistic for the model adjusted for maternal age and race was 1.96 (p-value for positive autocorrelation: 0.03). Even though the p-value was statistically significant, we

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nevertheless assumed that there was no meaningful serial correlation since the test statistic was very close to 2 (with 2 indicating no autocorrelation at all). When incorporating a one-month time lag to the introduction of self-pay NIPT, the adjusted model estimated that the rate of invasive diagnostic testing decreased by 9.8% (95% CI: 0.81 to 1.00). The level change of invasive diagnostic testing was not statistically significant (adjusted RR: 0.94; 95% CI: 0.84 to 1.04) at the introduction of self-pay NIPT with a two-month time lag. The trend of decrease within the second period was estimated to be approximately 1.8% (95% CI: 0.98 to 0.99) and 1.9% (95% CI: 0.97 to 0.99) per month when having a one-month and two-month time lag, respectively.

Table 3. Log-binomial interrupted time-series models estimating the impact of introducing self-pay and publicly-funded NIPT on utilization of invasive diagnostic testing in BC, April 1, 2011 - April 30, 2017.

	Crude model		Adjusted model	
	Risk ratio	**95% Confidence interval**	**Risk ratio**	**95% Confidence interval**
Intercept (β_0)	0.58	(0.54, 0.63)	0.45	(0.37, 0.55)
Time (β_1)	1.00	(0.99, 1.00)	0.99	(0.99, 1.00)
Self-pay NIPT (β_2) (No NIPT as reference)	0.87	(0.79, 0.97)	0.87	(0.79, 0.97)
Time after self-pay NIPT (β_3)	0.98	(0.98, 0.99)	0.98	(0.98, 0.99)
Publicly-funded NIPT (β_4) (Self-pay NIPT as reference)	0.52	(0.40, 0.67)	0.52	(0.40, 0.68)
Time after publicly-funded NIPT (β_5)	1.01	(0.99, 1.04)	1.01	(0.99, 1.04)
Maternal age at estimated delivery date (β_6)	-		1.00	(1.00, 1.01)
Race (β_7) (Caucasian as reference)	-		-	

	Crude model		Adjusted model	
	Risk ratio	95% Confidence interval	Risk ratio	95% Confidence interval
Black	-		0.78	(0.57, 1.08)
East Asian	-		1.12	(1.05, 1.19)
South Asian	-		1.17	(1.08, 1.27)
First Nations	-		0.85	(0.69, 1.05)
Other	-		1.21	(1.10, 1.33)

3.3.4 Interrupted time-series analysis – introduction of publicly-funded NIPT

The rate of invasive diagnostic testing expected by our adjusted model decreased from 21.8% in October 2015, the last month with self-pay NIPT, to 11.4% in November 2015, the beginning of the publicly-funded NIPT period. This corresponded to a 47.8% (95% CI: 0.40 to 0.68) decrease in the utilization of invasive diagnostic testing associated with the introduction of publicly-funded NIPT after adjusting for maternal age and race. There was no further change in the rate of invasive diagnostic testing within the third period (adjusted RR: 1.01; 95% CI: 0.99 to 1.04).

In our sensitivity analysis of adding time lags of one and two months to the introduction of publicly-funded NIPT, there was an estimated decrease of 45.7% (95% CI: 0.41 to 0.72) and 40.7% (95% CI: 0.44 to 0.79) in the rate of invasive diagnostic testing when adding a one-month and a two-month time lag, respectively. Once again, there was no change in the trend of the rate of invasive diagnostic testing within the third period even with both one-month (adjusted RR: 1.02; 95% CI: 0.99 to 1.04) and two-month time lags (adjusted RR: 1.02; 95% CI: 0.99 to 1.05).

3.4 Discussion

3.4.1 Main findings

In BC, the introduction of publicly-funded NIPT in November 2015 for women at a high risk of having a Down syndrome or trisomy 18 pregnancy resulted in a pronounced and immediate decrease in the use of invasive diagnostic testing (a reduction by nearly 50%). In the time period following the introduction of publicly-funded NIPT, the rate of invasive diagnostic testing plateaued at approximately 10%; this aligns with the reality that there will always be pregnancies requiring amniocentesis due to maternal choice or following clinical standards/guidelines. However, we also found that significant decreases in the utilization of CVS and amniocentesis had already occurred as a result of the introduction of self-pay NIPT in February 2013, both immediately after its introduction, and through a continued decrease in the months following its introduction. In fact, most of the overall reduction in utilization of invasive testing occurred within the second period when self-pay NIPT was available, as evidenced from an average of approximately 45.5% to 21.8%.

The continuous decrease within the second period with self-pay NIPT fits with implementation of a program in the real-world setting. Since not all private laboratories began providing self-pay NIPT at the same time, and there was likely a steady increase in awareness of self-pay NIPT through recommendations from healthcare providers and marketing material from the laboratories, this would be expected to create more gradual increases in the uptake of self-pay NIPT and hence, more gradual reductions in the use of invasive diagnostic testing. Similar decrease in slope after the introduction of a new intervention has been reported previously, suggesting that effects of an intervention may manifest over a longer time period. For example,

this effect was observed in a study examining the effect of routine childhood immunization with pneumococcal conjugate vaccine in the United States.(66)

3.4.2   Comparison with the literature

Our findings on the impact of self-pay NIPT on invasive diagnostic test utilization align with previous studies from the United States, Australia, China, and the Netherlands. The California Prenatal Screening Program offers the same screening test as the BC Prenatal Genetic Screening Program.(51) Contingent NIPT is offered free of charge to eligible women enrolling in California's public health insurance.(42,53) Chetty et al. examined the impact of NIPT with 1,036 women with a positive screening result in their Prenatal Diagnosis Center in California.(42) The introduction of NIPT in March 2012 was associated with a statistically significant decrease in the use of invasive diagnostic testing from 47% to 39%, and the association remained the same after controlling for race, advanced maternal age, and insurance payer.(42) Other single-site studies identified decreases in the use of invasive diagnostic testing with the introduction of self-pay NIPT to high-risk women as well.(43–46) Khalifeh et al. conducted a retrospective cohort study of 88,135 pregnancies at the four hospitals of the Main Line Health System in Pennsylvania to assess the impact of NIPT on the use of invasive diagnostic testing.(47) They found that the introduction of NIPT resulted in a significant decrease of invasive diagnostic testing by 64%.(47) Other studies with smaller sample sizes and shorter study period had similar findings from multiple hospitals within a private health system.(48,55)

In a population-based longitudinal study from Australia conducted by Robson and Hui, the number of CVS and amniocenteses dropped significantly by 37% and 51%, respectively, in the time period that coincided with the introduction of NIPT.(40) However, the study did not have direct data on NIPT eligibility or uptake. Poon et al. compared the use of invasive diagnosis testing before and after the introduction of contingent NIPT in a public hospital in Hong Kong.(49) After the introduction of self-pay NIPT, the use of CVS and amniocentesis decreased from 52% to 45% and from 37% to 28%, respectively.(49) In a study from the Netherlands, Oepkes et al. found that a high uptake of NIPT was associated with an estimated reduction of 62% in invasive diagnostic testing performed.(50) However, the uptake of first trimester screening (FTS) is low ($< 30\%$) in the Netherlands.(50)

There is limited evidence on the real-world impact of introducing population-based publicly-funded NIPT on invasive diagnostic test utilization rates. Ontario, a province in Canada offers provincially-funded prenatal genetic screening and publicly-funded NIPT with a similar set of eligibility criteria as BC's.(23) Okun et al. estimated that the implementation of contingent NIPT with current performance of FTS would result in fewer amniocenteses over a single year (from 4,247 to 1,358) in Ontario(27). However, no studies have examined the real impact after the introduction of publicly-funded NIPT in Ontario.

Our results show that meaningful reductions in the utilization of invasive diagnostic testing can be achieved through public-funding of NIPT, although the largest reductions in our setting occurred following the introduction of self-pay NIPT. We did not have data on women's socio-economic position or supplementary private insurance status; however, we speculate that the

introduction of publicly-funded NIPT could have had a more pronounced impact among women from disadvantaged socio-economic positions.

3.4.3 Strengths and limitations

An important strength of this study is its use of data from all prenatal biochemistry and cytogenetic laboratories in the province, enabling us to analyze all known pregnancies that received provincially-funded SIPS, IPS, Quad, CVS, and amniocentesis during the study period. The majority of previous studies examined the impact of NIPT on invasive diagnostic testing in pregnant women at a single healthcare site/system, which may be prone to selection bias due to underlying hospital referral patterns or geographic differences. The findings from our population-based study provide a more comprehensive understanding of how the introduction of NIPT influences the use of invasive diagnostic testing for health services decision-makers.

Another strength of this study is our use of the interrupted time series design, a rigorous quasi-experimental design used when randomized controlled trials are impractical or infeasible.(59,60) It is methodologically superior to the pre-post study design often used to evaluate the introduction of a new policy or practice because it controls for the underlying time trends.(59) The visual presentation of an interrupted time series can also show clearly the impact of the intervention as an immediate, delayed, lasting, or temporary effect.(59,60) Our sensitivity analysis identified that several of the estimated level changes remained statistically significant even when a time-lagged intervention was specified. The estimated level changes when the introduction of NIPT was modelled with time lags were smaller in magnitude than the level changes estimated with the correctly-specified intervention periods. We speculate that the strong

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decreasing rate of invasive diagnostic testing in period 2, which was the steep slope shown in Figure 1, was sufficiently pronounced to overcome any small misclassification of intervention timing, rather than reflecting the influence of an unrelated factor in invasive diagnostic testing.

The uptake of prenatal genetic screening is 55% in BC, implying that the remaining 45% of pregnancies either declined screening or opted for self-pay NIPT as a first-line screening test.(3) As a result, our findings may not be generalizable to settings with markedly different patterns in the uptake of prenatal genetic screening. We were only able to identify women who were eligible for publicly-funded NIPT following positive SIPS, IPS, or Quad results and could not include women eligible due to obstetrical history or ultrasound markers of aneuploidy. While these latter groups of women only comprise 12% of women who accessed publicly-funded NIPT in BC(Langlois S. and MacFarlane J. Perinatal Services BC. Personal communication. 19th June 2017.), we cannot rule out systematic differences between these women and those included in our study.

In this study, we were able to account for maternal age at estimated date of delivery and maternal race only. Another potential confounder is pre-pregnancy obesity. Obese women may not have sufficient cell-free fetal DNA fraction of the maternal blood sample and hence, increased likelihood of test failure.(23) Due to the higher possibility of failed test, obese women may be more likely to choose invasive diagnostic testing over NIPT. We were unable to adjust for body mass index in our modelling because such variable was not included in the laboratory data; however, it is unlikely that there were abrupt changes in obesity in BC coinciding with the specific dates of NIPT introduction, limiting its role as a confounder. Finally, administrative and

clinical datasets used in our study did not provide the reason why a woman chose invasive diagnostic testing over publicly-funded NIPT. Such information would be valuable in informing us on how to better support a woman's decision-making process.

3.4.4   Conclusions/implications for practice

The introduction of publicly-funded NIPT in November 2015 was associated with a significant decrease in the number of CVS and amniocenteses performed in BC among women who screened positive with provincially-funded SIPS, IPS, or Quad. The introduction of self-pay NIPT in February 2013 was also associated with a significant decrease in the rate of invasive diagnostic testing. The results from this research can be used as evidence for policy recommendations and informed decision making on providing publicly-funded NIPT in other Canadian provinces that do not currently fund this technology. Future cost consequences studies should be conducted to examine the real-world implications of publicly-funded NIPT in BC.

Our findings also have implications for several aspects of obstetrical practice. The reduced volume of CVS and amniocentesis observed in our study raises concerns related to the maintenance of proficiency among maternal-fetal medicine specialists in performing these invasive diagnostic tests. Revisions to the competency requirements and/or increased use of simulation training may be needed to adapt to the decrease in number of invasive diagnostic tests performed by each specialist or trainee. Further, ethical concerns are raised if pregnant women chose to terminate their pregnancy based on NIPT results without confirmatory diagnostic testing. Maternity care providers should be trained to provide comprehensive counselling on the

strengths and limitations of NIPT and invasive diagnostic testing in order to better guide a

woman's decision-making process.

4   Exploring the cost-consequences of publicly-funded NIPT in BC

4.1   Introduction

Many previous studies used theoretical cohorts to estimate the costs and benefits of introducing NIPT as either a first-line or contingent screening test.(24–39) These studies used simulation to combine estimates for multiple relevant parameters, such as the anticipated uptake of NIPT and use of invasive diagnostic testing given a positive screening result, derived from the literature, in an attempt to predict what the consequences of NIPT introduction would be. Most studies concluded that the introduction of contingent NIPT increased clinical performance of screening, decreased use of invasive diagnostic testing, and reduced procedure-related pregnancy losses at a lower cost.(24,26,38,27,28,31–33,35–37) However, cost-benefit analyses of NIPT introduction based on real-world implementation are scarce. This chapter provides a preliminary exploration of some of the cost-consequences of introducing publicly-funded NIPT in BC.

As outlined in Chapter 3, our study population included all known singleton pregnancies in BC between April 1, 2011 and April 30, 2017 with a positive result from provincially-funded SIPS, IPS, or Quad. The study population was derived from population-level data from the provincial prenatal biochemistry laboratory and provincial cytogenetic laboratories. There were a total of three study periods; period 1 with no NIPT from April 1, 2011 to January 31, 2013, period 2 with self-pay NIPT from February 1, 2013 to October 31, 2015, and the last period with publicly-funded NIPT from November 1, 2015 to April 31, 2017. The primary outcome of this exploratory cost-consequences analysis was the direct public healthcare cost per screen-positive pregnancy, which was defined as the total cost based on the number of invasive diagnostic tests

and publicly-funded NIPT performed over the total number of pregnancies with a positive SIPS, IPS, or Quad result.

4.2   Cost estimates

The uptake of publicly-funded NIPT among women with a positive SIPS, IPS, or Quad result was assumed to be 90% based on the average uptake of NIPT between November 1, 2016 and October 31, 2017 from an unpublished Perinatal Services BC report.(Langlois S. and MacFarlane J. Perinatal Services BC. Personal communication. 5th February 2018.) We assumed that CVS and amniocentesis are associated with a risk of pregnancy loss between 0.5% and 2% based on existing literature.(13,14) The number of estimated pregnancy losses due to invasive diagnostic testing was rounded to the nearest integer.

Since data from the laboratories did not include information on cost per procedure performed, we obtained the cost of CVS and amniocentesis through published literature. In the cost-effectiveness analysis conducted by Nshimyumukiza et al, the baseline cost of CVS and amniocentesis in Quebec were $1090.40 and $782.20, respectively.(28) As of February 2016, Dynacare Laboratories has been selected as the sole vendor for providing publicly-funded NIPT in BC.(19) Therefore, we used the cost of their test, Harmony NIPT, to obtain our cost per NIPT performed. We considered two different NIPT cost scenarios, one for the low cost of $495 per test and another for the high cost of $650 per test.

4.3 Findings

Table 4 shows the actual number of CVS and amniocenteses, and estimated procedure-related pregnancy losses and publicly-funded NIPT performed in each period according to availability of NIPT. In the third period, the total number of CVS, amniocenteses, and publicly-funded NIPT conducted was greater than the total number of pregnancies because pregnancies with a positive result from publicly-funded NIPT are advised to undergo amniocentesis and hence, are double-counted in both publicly-funded NIPT and amniocentesis categories. Based on the number of CVS and amniocenteses performed in the first period, the estimated number of pregnancy losses was 3.03 and 1.73 per 1,000 screen-positive pregnancies (with the conventional risk of 1% following CVS and 0.5% following amniocentesis) for the first period with no NIPT and the second period with self-pay NIPT, respectively. In contrast, the estimated number of pregnancy losses decreased to 0.92 per 1,000 screen-positive pregnancies in the third period with publicly-funded NIPT.

Table 4. Utilization of invasive diagnostic testing and publicly-funded NIPT among 8,649 singleton pregnancies in BC with a positive SIPS, IPS, or Quad result according to availability of NIPT, April 1, 2011 - April 30, 2017.

	Period 1 No NIPT (April 2011-Jan 2013) N	Period 2 Self-pay NIPT (Feb 2013-Oct 2015) N	Period 3 Publicly-funded NIPT (Nov 2015-April 2017) N
Pregnancies with a positive SIPS, IPS, or Quad result	2,573	3,943	2,133
CVS	19	18	6
Amniocentesis	1,405	1,261	212

	Period 1 No NIPT (April 2011-Jan 2013) N	Period 2 Self-pay NIPT (Feb 2013-Oct 2015) N	Period 3 Publicly-funded NIPT (Nov 2015-April 2017) N
Estimated publicly-funded NIPT	0	0	1,920
Estimated procedure-related pregnancy losses	8	7	2

The costs associated with these events are shown in Table 5. The public healthcare cost per screen-positive pregnancy was $435.18 and $255.13 in the first and second period, respectively. When publicly-funded NIPT was priced at $495 in the third period, the cost per screened positive pregnancy was $526.38. Cost increased to $665.90 in the third period when we factored in the higher cost of $650 per NIPT. When comparing the third period with publicly-funded NIPT with the second period with self-pay NIPT only, the cost per screen-positive pregnancy to the health care system doubled but the number of procedure-related pregnancy losses was reduced by almost 50%.

Table 5. Direct public healthcare cost based on the number of invasive diagnostic tests and publicly-funded NIPT performed among 8,649 singleton pregnancies in BC with a positive SIPS, IPS, or Quad result according to availability of NIPT, April 1, 2011 - April 30, 2017.

	Period 1 No NIPT (April 2011-Jan 2013)	Period 2 Self-pay NIPT (Feb 2013-Oct 2015)	Period 3 Publicly-funded NIPT (Nov 2015-April 2017)
CVS	$20,717.60	$19,627.20	$6,542.40
Amniocentesis	$1,098,991	$986,354.20	$165,826.40

	Period 1 No NIPT (April 2011-Jan 2013)	Period 2 Self-pay NIPT (Feb 2013-Oct 2015)	Period 3 Publicly-funded NIPT (Nov 2015-April 2017)
Publicly-funded NIPT			
i) Low cost	$0	$0	$950,400
ii) High cost	$0	$0	$1,248,000
Cost per screen-positive pregnancy			
i) Low cost	$435.18	$255.13	$526.38
ii) High cost	$435.18	$255.13	$665.90

4.4 Discussion

This descriptive cost-consequences analysis explored the estimated direct costs of invasive

diagnostic testing and publicly-funded NIPT to BC's public healthcare system. Publicly-funded

NIPT as a contingent screening test resulted in the highest cost per screen-positive pregnancy,

while self-pay NIPT resulted in the lowest cost per screen-positive pregnancy. In spite of the

high cost in the third period, there were likely fewer pregnancy losses due to invasive diagnostic

procedures in this time period. Additional healthcare cost might incur because of miscarriages;

for example, follow-up appointments with healthcare providers, and further ultrasound exams

and/or blood tests might be needed for confirmation. Not being able to include all these

additional costs was a limitation of this exploratory analysis. Nonetheless, this chapter provides a

preliminary understanding of the magnitude of the costs and benefits of publicly-funded NIPT

derived from population-level administrative and clinical data in BC. As more follow-up tests are

conducted for women who have a positive screening result, cost per Down syndrome case

diagnosed should be examined to account for the additional tests done. Further studies examining

the impact of publicly-funded NIPT on a broader range of associated healthcare costs should be conducted in order to help policy-makers to fully understand its economic cost consequences.

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Appendices

Appendix A: Screening tests available through the BC Prenatal Genetic Screening Program.

	Serum integrated prenatal screen (SIPS)	**Integrated prenatal screen (IPS)**	**Quad marker screen (Quad)**	**NIPT**
Eligibility	Women with their first prenatal visit < 14 weeks of gestation and < 35 years old	Women with their first prenatal visit < 14 weeks of gestation and: • are ≥ 35 years old, • have a maternal/family history that increases risk of Down syndrome or trisomy 18, • have a twin pregnancy, • are HIV positive, or • have in vitro fertilization with intracytoplasmic sperm injection	Women with their first antenatal visit 14 – 20+6 weeks of gestation	Women with: • a positive screening result from SIPS, IPS, or Quad, • a previous Down syndrome, trisomy 18, or trisomy 13 pregnancy, or • an increased risk of Down syndrome based on screening results and ultrasound markers

	Serum integrated prenatal screen (SIPS)		Integrated prenatal screen (IPS)			Quad marker screen (Quad)	NIPT
Sample type	Blood test #1	Blood test #2	Blood test #1	NT ultrasound	Blood test #2	Blood test	Blood test
Markers/Measurements	PAPP-A	AFP uE3 hCG Inhibin-A	PAPP-A	Width of fluid-filled space at the back of the fetus's neck	AFP uE3 hCG Inhibin-A	AFP uE3 hCG Inhibin-A	Cell-free fetal DNA
Collection timeframes (Gestational age in weeks+days)	9 – 13+6	14 – 20+6	9 – 13+6	11 – 13+6	14 – 20+6	14 – 20+6	≥ 10
Detection rate — **Down syndrome**	73 – 100%		86 – 100%			78 – 100%	> 99%
Detection rate — **Trisomy 18**	90%		90%			80%	~ 97%
Detection rate — **Trisomy 13**	Not applicable (N/A)		N/A			N/A	~ 93%
False positive rate — **Down syndrome**	3 – 19%		4 – 18%			4 – 27%	< 0.1%
False positive rate — **Trisomy 18**	0.4%		1.7%			0.4%	
False positive rate — **Trisomy 13**	N/A		N/A			N/A	

Appendix B: Invasive diagnostic testing available through the BC Prenatal Genetic Screening Program.

		CVS	Amniocentesis
Eligibility by gestational age at first antenatal visit	**≤ 13+6 weeks**	Women without prior screening and: • are ≥ 40 years old, • have a maternal/family history that increases risk of Down syndrome, trisomy 18, or trisomy 13, • have a maternal/family history that increases risk of other chromosomal abnormalities, or • have in vitro fertilization with intracytoplasmic sperm injection	Same as CVS with the additional of women without prior screening who are ≥ 35 years and have a twin pregnancy
	14 – 20+6 weeks	Not applicable (N/A)	Same as above
	≥ 21 weeks	N/A	Women without prior screening and: • are ≥ 35 years old, • are ≥ 35 years old and have a twin pregnancy, • have a maternal/family history that increases risk of Down syndrome, trisomy 18, or trisomy 13, • have a maternal/family history that increases risk of other chromosomal abnormalities, or • have in vitro fertilization with intracytoplasmic sperm injection
Sample type		Placental tissue	Amniotic fluid
Markers/Measurements		Quantitative Fluorescence Polymerase Chain Reaction or Microarray	Quantitative Fluorescence Polymerase Chain Reaction or Microarray

	CVS	Amniocentesis
Collection timeframes (Gestational age in weeks)	11 – 13	≥ 15
Detection rate **Down syndrome** **Trisomy 18** **Trisomy 13**	100%	100%
False positive rate **Down syndrome** **Trisomy 18** **Trisomy 13**	0%	0%