

# Perinatal Services BC Obstetric Guideline: Prenatal Screening for Down Syndrome, Trisomy 18, and Open Neural Tube Defects

June 2020

## Table of Contents

EXECUTIVE SUMMARY . . . . .	2
1. INTRODUCTION . . . . .	3
SIPS, IPS, Quad, NIPT . . . . .	3
Open Neural Tube Defects (ONTDs). . . . .	4
Counselling . . . . .	4
Table 1: Summary of Prenatal Genetic Screening Tests. . . . .	5
Table 2: Screening options available through the BC Prenatal Genetic Screening Program . . . . .	6
2. MANAGEMENT . . . . .	7
3. RESOURCES. . . . .	10
BC Prenatal Genetic Screening Program Website . . . . .	10
Other Useful Websites . . . . .	10
4. BIBLIOGRAPHY . . . . .	11
APPENDIX 1 . . . . .	12
Risk of Down Syndrome and Other Chromosome Abnormalities in Live Births by Maternal Age . . . . .	12
APPENDIX 2 . . . . .	13
Screen Cut-Offs and Performance of Screening Tests . . . . .	13
APPENDIX 3 . . . . .	14
Prenatal Genetic Diagnostic Testing (CVS and Amniocentesis) . . . . .	14
APPENDIX 4 . . . . .	15
Soft Markers Identified on Detailed Ultrasound. . . . .	15

## BC Prenatal Genetic Screening Program

Tel: 604-877-2121

[www.bcprenatalscreening.ca](http://www.bcprenatalscreening.ca)



**Perinatal Services BC**

Tel: 604-877-2121

[www.perinatalservicesbc.ca](http://www.perinatalservicesbc.ca)



While every attempt has been made to ensure that the information contained herein is clinically accurate and current, Perinatal Services BC and the BC Prenatal Screening Program acknowledge that many issues remain controversial, and therefore may be subject to practice interpretation.

## Executive Summary

Prenatal genetic screening estimates the risk of Down syndrome, trisomy 18, and open neural tube defect. The results will assist in determining the need for further testing. The screening tests offered will vary according to the gestational age at the time of presentation, maternal age at the time of delivery, and whether the pregnancy is a singleton or twin gestation.

BC has adopted a serum-based approach to prenatal genetic screening, with nuchal translucency (NT) ultrasound added for women at higher risk of having a fetus with Down syndrome or trisomy 18 and women with twin pregnancies. Non-Invasive Prenatal Testing (NIPT) is now also an option for some higher risk women.

This guideline refers to screening options that are available in the public health care system. In BC, Serum Integrated Prenatal Screen (SIPS) is available and should be offered to all pregnant women. The following women are eligible for NT ultrasound as a component of Integrated Prenatal Screen (IPS = SIPS in combination with NT):

- a) Women  $\geq 35$  years old at expected date of delivery (EDD)<sup>1</sup>;
- b) Women with twin pregnancies;
- c) Women pregnant following in vitro fertilization with intracytoplasmic sperm injection (IVF with ICSI).

Certified (Fetal Medicine Foundation – UK) nuchal translucency ultrasound sites are established in all BC health authorities.

For women 40 years or older with a singleton pregnancy, or 35 years or older with a multiple gestation pregnancy, amniocentesis is also an option.

Provincially funded NIPT is available for the following eligible women:

- a) Women with a positive screen result from IPS, SIPS, or Quad;
- b) Women who have a documented history of a previous child or fetus with Down syndrome, trisomy 18, or trisomy 13;
- c) Women whose risk of Down syndrome is equal to or greater than 1/300 based on the finding of ultrasound marker(s) and results of SIPS/IPS/Quad.

---

<sup>1</sup> In order to ensure quality NT ultrasounds, every certified sonographer must annually perform a minimum number of ultrasounds. As such, pregnant women 30 years and older in Northern Health Authority and the East Kootenay Boundary Region of Interior Health Authority are also eligible for NT ultrasounds as part of IPS.

## 1. Introduction

The purpose of prenatal genetic screening is to identify pregnancies at increased risk of chromosome disorders or structural anomalies. Serum integrated prenatal screen (SIPS), integrated prenatal screen (IPS), quad marker screen (Quad), NIPT, and a detailed second trimester ultrasound<sup>2</sup> are some of the options available for prenatal genetic screening.

The risks for fetal Down syndrome, trisomy 18, and open neural tube defects (ONTDs) are calculated using a combination of variables which may include: biochemical serum markers collected from blood work, maternal age, maternal ethnicity, maternal weight, maternal diabetic status, maternal smoking, and, if available, nuchal translucency (NT) ultrasound measurement. There are four different screening tests: SIPS, IPS, Quad (Table 1) and NIPT. The screening tests offered will vary according to the woman's pregnancy history, the gestational age at the time of presentation, maternal age at the time of delivery, and whether the pregnancy is a singleton or twin gestation (Table 2). Depending on the results of the screening tests, other more accurate tests may also be offered (such as NIPT<sup>3</sup> and amniocentesis).

### SIPS, IPS, Quad, NIPT

**SIPS** involves measurement of first trimester pregnancy-associated plasma protein A (PAPP-A) and second trimester quad markers in two separate blood tests. Quad markers include alpha-fetoprotein (AFP), unconjugated estriol (uE3), human chorionic gonadotropin (hCG) and inhibin-A. The first blood test is collected between 9 – 13<sup>+6</sup> weeks (best at 10 – 11<sup>+6</sup> weeks) and the second between 14 – 20<sup>+6</sup> weeks (best at 15 – 16 weeks). Test results are available within 10 days after the second blood test. Both blood tests can be collected in the woman's local community with samples being sent to the Prenatal Biochemistry Laboratory at Children's and Women's Health Centre (C&W) for analysis.

**IPS** involves measurement of first trimester serum PAPP-A and a nuchal translucency (NT) ultrasound and second trimester serum quad markers (AFP, uE3, hCG and inhibin-A). The blood tests are collected as per the timing for SIPS and the NT measurement is done between 11 – 13<sup>+6</sup> weeks (best at 12 – 13<sup>+3</sup> weeks). Given that NT must be performed by a certified sonographer or sonologist, this test is available only in a select number of publicly funded centres<sup>4</sup> located around BC and use of the service is prioritized to serve those at higher risk of having a fetus with Down syndrome or trisomy 18 and women with multiple gestations. IPS test results are available within 10 days after the second blood test. If the NT measurement is high and results in a positive screen, counselling and further testing are offered (such as NIPT, chorionic villi sampling (CVS), or amniocentesis) prior to completing the second blood test.

The **Quad** screen involves the measurement of second trimester serum quad markers (AFP, uE3, hCG and inhibin-A) in one blood test. Blood is collected in the woman's local community between 14 – 20<sup>+6</sup> weeks (best at 15 – 16 weeks). The blood sample is sent to the Prenatal Biochemistry Laboratory at C&W for analysis. Test results are available within 10 days after the blood test. Quad screen should only be offered to women who present late for prenatal care (2nd trimester) as SIPS/IPS have better screening performance with lower false positive rates.

**NIPT** (Non-Invasive Prenatal Testing) is a blood test which analyzes cell free fetal DNA circulating in maternal blood, with a detection rate of Down syndrome in singleton pregnancies approaching 100%, and 97% for trisomy 18. NIPT is now funded in BC for women at increased risk for Down syndrome, trisomy 18, or trisomy 13 based on one of the following criteria:

- a) Women with a positive screen result from IPS, SIPS, or Quad;

<sup>2</sup> An accurate gestational age, determined by first trimester dating ultrasound, is important for accurate screening results. A dating ultrasound has additional benefits for obstetrical management.

<sup>3</sup> NIPT (non-invasive prenatal testing) is a blood test which analyzes cell free fetal DNA circulating in maternal blood with a detection rate of Down syndrome in singleton pregnancies approaching 100%, and 97% for trisomy 18.

<sup>4</sup> For a list of BC certified NT ultrasound centres, go to [www.bcprenatalscreening.ca](http://www.bcprenatalscreening.ca). If an NT ultrasound is done in a private clinic or a centre outside BC by a Fetal Medicine Foundation (FMF) certified sonographer or sonologist, these results can still be used in the risk calculation.

## 1. Introduction, *cont'd*

- b) Women who have a documented history of a previous child or fetus with Down syndrome, trisomy 18, or trisomy 13;
- c) Women whose risk of Down syndrome is equal to or greater than 1/300 based on the finding of ultrasound marker(s) and results of SIPS/IPS/Quad.

More details about how to access funded NIPT, including a BC-specific NIPT lab requisition, for your patient are available at [www.bcprenatalscreening.ca/NIPT](http://www.bcprenatalscreening.ca/NIPT).

Private self-pay NIPT is also available in BC for those women who do not meet the above criteria but who wish to pursue NIPT. More details on accessing private NIPT are available at [www.bcprenatalscreening.ca/NIPT](http://www.bcprenatalscreening.ca/NIPT).

**Download the (IPS/SIPS/Quad) serum lab requisition at [www.bcprenatalscreening.ca](http://www.bcprenatalscreening.ca).**

**Download the NIPT lab requisition for women eligible for funded NIPT at [www.bcprenatalscreening.ca/NIPT](http://www.bcprenatalscreening.ca/NIPT).**

### Open Neural Tube Defects (ONTDs)

As part of SIPS, IPS and Quad, maternal serum alpha-fetoprotein (MSAFP) is measured and is used to screen for open neural tube defects (ONTDs). However, the detection rate of open neural tube defect using MSAFP is only 70%. Given a detailed ultrasound at 18–20 weeks gestation has a higher detection rate for neural tube defects, women who decline screening for Down syndrome, or who have Down syndrome screening via NIPT, should be screened for ONTDs by detailed ultrasound and not by MSAFP. Maternal serum “AFP only” screening for an ONTD should be limited to women with a BMI  $\geq 40$ , or those with limited access to a quality 18–20 weeks ultrasound.

### Counselling

Women should understand that it is their choice to undertake genetic screening. Information about prenatal screening for Down syndrome, trisomy 18, and open neural tube defects should be given to pregnant women at the first contact with a healthcare professional. This should occur in the first trimester, ideally prior to 10 weeks gestational age in order to ensure that the appropriate early tests are performed, if desired. Women who choose screening should ideally be sent for the blood test #2 (SIPS/IPS) or the Quad as early as possible within the allotted (14 – 20<sup>+6</sup> weeks) timeframe. Although blood test #2 can be collected and analyzed up to 20<sup>+6</sup> weeks, the ideal time is much earlier (best at 15 – 16 weeks) to allow for earlier results and follow-up (NIPT or amnio) testing if necessary. To assist women and their families with prenatal screening information, patient brochures in multiple languages, decision aids, and a video are available at [bcprenatalscreening.ca](http://bcprenatalscreening.ca).

#### ***Specific counselling information should include:***

- The age-based a priori risk for each woman for having a fetus with a chromosomal abnormality (Appendix 1)
- The available tests for each woman (Table 2)
- The screening pathway for both screen positive and screen negative results
- The decisions that need to be made at each point along the pathway and their consequences
- The fact that screening does not provide a definitive diagnosis but only an estimate of risk
- The fact that women with a positive screen will have the option of further screening or testing such as funded NIPT, chorionic villi sampling (CVS), or amniocentesis (further testing options offered will be dependent on the woman’s level of risk from the positive screen)
- Information about chorionic villus sampling (CVS) and amniocentesis including the risks of these procedures (Appendix 3)
- Balanced and accurate information about Down syndrome, trisomy 18, trisomy 13 and ONTD

## 1. Introduction, *cont'd*

**Table 1: Summary of Prenatal Genetic Screening Tests**

Screen Name	Markers / Measurements	Possible Timeframes	Best Timeframes
Serum Integrated Prenatal Screen (SIPS)			
• SIPS blood test #1	PAPP-A	9 – 13 <sup>+6</sup> wks	10 – 11 <sup>+6</sup> wks
• SIPS blood test #2	AFP uE3 hCG Inhibin-A	14 – 20 <sup>+6</sup> wks	15 – 16 wks
Integrated Prenatal Screen (IPS)	Same as SIPS (blood tests #1 & #2) with addition of NT ultrasound <sup>5</sup>	See SIPS for blood tests 11– 13 <sup>+6</sup> wks	See SIPS for blood tests 12 – 13 <sup>+3</sup> wks
Quad blood screen	Same as SIPS blood test #2	14 – 20 <sup>+6</sup> wks	15 – 16 wks
Non-Invasive Prenatal Testing (NIPT)	Cell-free fetal DNA, collected from maternal blood	10 weeks and onwards	varies by indication

<sup>5</sup> If an NT ultrasound is performed, a separate first trimester dating ultrasound is not necessary if LMP date is certain.

## 1. Introduction, *cont'd*

**Table 2: Screening options available through the BC Prenatal Genetic Screening Program<sup>6</sup>**

Characteristics of woman	Gestational Age at the First Prenatal Visit		
	≤ 13+6 weeks	14–20+6 weeks	≥ 21 weeks (no prior screening)
<35 years	<ul style="list-style-type: none"> <li>• SIPS</li> </ul>	<ul style="list-style-type: none"> <li>• Quad</li> </ul>	<ul style="list-style-type: none"> <li>• Detailed ultrasound</li> </ul>
35–39 years	<ul style="list-style-type: none"> <li>• IPS; or</li> <li>• If NT not available, SIPS</li> </ul>	<ul style="list-style-type: none"> <li>• Quad</li> </ul>	<ul style="list-style-type: none"> <li>• Detailed ultrasound; and</li> <li>• Amnio</li> </ul>
40+ years	<ul style="list-style-type: none"> <li>• IPS; or</li> <li>• If NT not available, SIPS; or</li> <li>• CVS or Amnio without prior screening</li> </ul>	<ul style="list-style-type: none"> <li>• Quad; or</li> <li>• Amnio without prior screening</li> </ul>	<ul style="list-style-type: none"> <li>• Detailed ultrasound; and</li> <li>• Amnio</li> </ul>
Personal/family history that increases risk of fetus with Down syndrome, trisomy 18, or trisomy 13	<ul style="list-style-type: none"> <li>• NIPT; or</li> <li>• CVS or Amnio without prior screening</li> </ul>	<ul style="list-style-type: none"> <li>• NIPT; or</li> <li>• Amnio without prior screening</li> </ul>	<ul style="list-style-type: none"> <li>• Detailed ultrasound; and</li> <li>• NIPT; or</li> <li>• Amnio</li> </ul>
Personal/family history that increases risk of fetus with chromosomal abnormality other than Down syndrome, trisomy 18, or trisomy 13	<ul style="list-style-type: none"> <li>• CVS or Amnio without prior screening</li> </ul>	<ul style="list-style-type: none"> <li>• Amnio without prior screening</li> </ul>	<ul style="list-style-type: none"> <li>• Detailed ultrasound; and</li> <li>• Amnio</li> </ul>
Twin gestation <sup>7</sup>	<ul style="list-style-type: none"> <li>• IPS; or</li> <li>• If NT not available, SIPS; or</li> <li>• If ≥ 35, Amnio without prior screening</li> </ul>	<ul style="list-style-type: none"> <li>• Quad; or</li> <li>• If ≥ 35, Amnio without prior screening</li> </ul>	<ul style="list-style-type: none"> <li>• Detailed ultrasound; and</li> <li>• If ≥ 35, Amnio</li> </ul>
Pregnant following In vitro fertilization with intracytoplasmic sperm injection	<ul style="list-style-type: none"> <li>• IPS; or</li> <li>• If NT not available, SIPS; or</li> <li>• CVS or Amnio without prior screening</li> </ul>	<ul style="list-style-type: none"> <li>• Quad; or</li> <li>• Amnio without prior screening</li> </ul>	<ul style="list-style-type: none"> <li>• Detailed ultrasound; and</li> <li>• Amnio</li> </ul>

<sup>6</sup> SIPS/IPS/Quad and NIPT for particular high risk cases are publically available through the provincial program. Private pay options available in BC are: First Trimester Screening (measures free beta hCG, PAPP-A and ultrasound markers in the 10–13+6 wk time period) and Non Invasive Prenatal Testing (NIPT) based on cell free DNA in maternal blood (from 10 wks onwards) available to those who do not qualify for the funded NIPT.

<sup>7</sup> Screening in triplets and higher multiples will remain based on NT ultrasound alone. If NT is not available and the woman is ≥ 35 years old, amniocentesis is an option.

## 2. Management

- A. After a discussion of the pros and cons, all pregnant women regardless of age should be offered prenatal screening for Down syndrome, trisomy 18, and ONTDs. Ideally this discussion needs to occur prior to 10 weeks gestational age (GA) so that the best possible screen for the patient is available. After receiving the information, it is the woman's choice to proceed with or decline screening. Discussion of prenatal screening and the result should be documented on the BC antenatal record.
- B. The prenatal screen offered will depend upon the woman's gestational age at her first prenatal visit, her previous pregnancy history, maternal age at the time of delivery, and whether the pregnancy is a singleton or twin gestation. NT ultrasound assessment is available only to women at higher risk of having a fetus with Down syndrome or trisomy 18<sup>8</sup> and women with multiple gestations.
- C. Women at increased risk of having a fetus with a chromosomal abnormality<sup>9</sup> should be referred early in their pregnancy to Medical Genetics in Vancouver or Victoria for genetic counselling regarding their screening and diagnostic options.
- D. Women who have had a first trimester screen<sup>10</sup>, NIPT, and/or CVS, and women who have declined a SIPS, IPS, or Quad screen for Down Syndrome and trisomy 18 should be screened for ONTDs by a detailed ultrasound examination at 18–20 weeks gestation. The exception is if they have a BMI of 40 or greater or they have limited access to a quality detailed ultrasound examination. In those two circumstances, an alpha-fetoprotein (AFP) serum screen between 15–20<sup>+6</sup> (best 15–16 weeks) to screen for ONTDs should be offered.
- E. For women who choose to have (private-pay) NIPT as a first tier screen, IPS/SIPS is not indicated and should not be offered. An NT ultrasound scan should not be done if the woman is having NIPT, given the limited utility of NT measurement in pregnancies with a negative NIPT result and limited NT resources.
- F. CVS and amniocentesis for fetal karyotyping will not be offered without prior screening except for women 40 years or older at expected date of delivery, women at increased risk of having a fetus with a chromosomal abnormality,<sup>11</sup> and women with multiple gestations who are  $\geq 35$  years old at expected date of delivery.
- G. For women of any age found to have an NT measurement of 3.0 mm or greater, a screen risk will be calculated based on NT only (or NT and PAPP-A if available). If the risk is 1/300 or greater, a report will be issued without waiting for SIPS part 2 (blood test #2). The woman should then be offered further testing: either funded NIPT or CVS/amnio. If the screen risk is negative (less than 1/300) based on NT alone (or NT and PAPP-A), no report will be generated, and the woman will continue with serum screening (blood test #2) and the full IPS risk result will be reported 10 days after the collection of blood test #2.
- H. The finding of an NT measurement  $\geq 3.5$  mm increases the risk of congenital heart defects, genetic syndromes, and chromosomal abnormalities other than the common aneuploidies. A referral to Medical Genetics in Vancouver or Victoria is recommended.

<sup>8</sup> This includes women anticipated to be 35 years or older at the time of delivery or when the pregnancy is conceived by *in vitro* fertilization with intracytoplasmic sperm injection (IVF with ICSI).

<sup>9</sup> This includes a woman or her partner who (a) has a history of a previous child or fetus with Down syndrome, trisomy 18 or trisomy 13; or (b) is a carrier of a translocation, deletion, insertion, or inversion that increases the risk of having a fetus with an unbalanced chromosomal complement; or (c) has a history of a previous child or fetus with an unbalanced chromosomal complement; or (d) a woman with a pregnancy conceived by IVF with ICSI.

<sup>10</sup> First trimester screen (FTS) involves a blood test (PAPP-A and free beta hCG) and ultrasound scan. FTS is offered in the public system in some Canadian provinces and in private clinics in BC.

<sup>11</sup> See footnote 9.

## 2. Management, *cont'd*

- I. If a screen result is positive for Down syndrome and the screen was calculated based on last menstrual period (LMP), gestational age should be confirmed by ultrasound as soon as possible (see points J and K).
- J. Although dating ultrasounds in the first trimester are not required for screening, ultrasound is the preferred method for calculating gestational age, as opposed to using LMP. If a first trimester ultrasound is done, the calculated gestational age from the scan should be provided to the Prenatal Biochemistry Laboratory at C&W (by attaching the scan report if available to the lab serum requisition or by faxing the scan report to 604-875-3008) to ensure most accurate screen results. If an NT ultrasound is done, the calculated gestational age from this scan will be used.
- K. For any screen calculated based on LMP, if dating by second trimester ultrasound differs by eight days or more from original dates, fax the ultrasound report to the Prenatal Biochemistry Laboratory at C&W for recalculation of risk (fax 604-875-3008). The only exception would be when a screen result is positive for trisomy 18 and dating by LMP and second trimester ultrasound differ. In these cases, the screen will not be recalculated (because trisomy 18 is frequently associated with intrauterine growth restriction).
- L. If the SIPS/IPS/Quad prenatal screen result is positive for Down syndrome (assuming gestational dating is confirmed) or trisomy 18, women should be counselled by their health care provider and offered further testing. All women with a positive screen for trisomy 18 should be offered funded NIPT or amniocentesis. For women with a positive screen for Down syndrome and a risk between 1:900 and 1:301, only funded NIPT should be offered. For women with a positive screen for Down syndrome and a risk equal or greater than 1:300, the option of funded NIPT or amniocentesis should be offered.

**NIPT** is a blood test which analyzes cell free fetal DNA circulating in maternal blood and tests for Down syndrome, trisomy 18, trisomy 13, and sex aneuploidy. The detection rate for Down syndrome is close to 100% with less than 0.1% false positives; the detection rate for trisomy 18 is around 97% with less than a 0.1% false positive rate. For more information on NIPT, how it compares to amniocentesis, and how to access testing, go to [www.bcprenatalscreening.ca/NIPT](http://www.bcprenatalscreening.ca/NIPT).

Women who qualify for funded NIPT and amniocentesis and who are undecided regarding the best option for them can be referred for genetic counselling to the Medical Genetics departments either in Vancouver or Victoria (both genetic departments offer face-to-face and telehealth counselling; telephone counselling could be done if telehealth is not available). The decision to refer for genetic counselling should be a joint decision between the health care provider and woman.

- M. Women with a positive NIPT result should be referred to Medical Genetics in Vancouver or Victoria for counselling and diagnostic testing. The positive predictive value of a positive NIPT result varies depending on the prior risk of the patient. Amniocentesis is recommended for diagnostic confirmation of the positive NIPT result prior to any irrevocable obstetrical decision.

Women with a positive IPS/SIPS/Quad screen result who then go on to have a negative NIPT result would no longer qualify for amniocentesis. The woman should be reassured, as the negative predictive value of NIPT is very high.

- N. Women with an abnormal serum analyte, defined as PAPP-A  $\leq 0.15$  MoM,  $uE3 \leq 0.4$  MoM, AFP  $\geq 2.5$  MoM, hCG  $\geq 4.0$  MoM and Inhibin A  $\geq 3.0$  MoM, are at increased risk of adverse obstetrical outcomes. They should be assessed for the presence of additional risk factors (medical history, obstetrical history, blood pressure, uterine artery Doppler if available).

Refer to [www.bcprenatalscreening.ca](http://www.bcprenatalscreening.ca) for more details including an algorithm for obstetrical risk management.



## 2. Management, *cont'd*

- O. If the prenatal screen result is positive for an open neural tube defect, and dating is confirmed, women should be referred to Medical Genetics or a Maternal Fetal Medicine specialist for a detailed ultrasound to assess fetal anatomy, counselling and, if indicated, diagnostic testing.
- P. A detailed second trimester ultrasound (18–20 weeks) to assess fetal anatomy and growth should be offered to all pregnant women. An 18–20 week ultrasound without soft markers or anomalies is capable of reducing the estimated risk of Down syndrome by approximately 50% (Smith-Bindman, 2007).
- Q. Soft markers or anomalies on the 18–20 week ultrasound increase the risk for aneuploidy and should be interpreted in conjunction with the prenatal screening (SIPS, IPS, or Quad) result. See Appendix 4 for detailed soft marker information.
- R. Women who are found on cytogenetic analysis of amniocytes or chorionic villi to carry a fetus with a chromosomal abnormality may be referred to the Vancouver or Victoria Medical Genetics departments for counselling.

### 3. Resources

#### BC Prenatal Genetic Screening Program Website

The full guideline *Prenatal Genetic Screening for Down Syndrome, Trisomy 18, and Open Neural Tube Defects* and related teaching resources (prenatal screening and diagnostic testing) are available on the BC Prenatal Genetic Screening Program website: [www.bcprenatalscreening.ca](http://www.bcprenatalscreening.ca).

Perinatal Services BC, ph: (604) 877-2121; website: [www.perinatalservicesbc.ca](http://www.perinatalservicesbc.ca)

#### Other Useful Websites

(The following list is provided as a courtesy and should not be construed as an endorsement of content by the BC Prenatal Genetic Screening Program)

Canadian Down Syndrome Society, ph: (800) 883-5608; e-mail: [info@cdss.ca](mailto:info@cdss.ca); website: [www.cdss.ca](http://www.cdss.ca)

ChildHealth BC, website: [www.childhealthbc.ca](http://www.childhealthbc.ca)

Down Syndrome Resource Foundation (Burnaby, BC), ph: (604) 444-3773 or toll-free in Canada at 1-888-464-DSRF; website: [www.dsrf.org](http://www.dsrf.org)

Genetics Home Reference (US National Library of Medicine), website: [www.ghr.nlm.nih.gov](http://www.ghr.nlm.nih.gov)

Healthy Families BC, website: [www.healthyfamiliesbc.ca](http://www.healthyfamiliesbc.ca)

Lower Mainland Down Syndrome Society (BC), ph: (604) 591-2722; website: [www.lmdss.com](http://www.lmdss.com)

Society of Obstetricians and Gynaecologists, Clinical Practice Guidelines (Canada), website: [www.sogc.org](http://www.sogc.org)

Spina Bifida and Hydrocephalus Association of BC, ph: (604) 878-7000; e-mail: [info@sbhabc.org](mailto:info@sbhabc.org); website: [www.sbhabc.org](http://www.sbhabc.org)

Support Organization For Trisomy 18, 13, and Related Disorders (SOFT; US), website: [www.trisomy.org](http://www.trisomy.org)

## 4. Bibliography

- Agathokleous M, Chaveeva P, Poon LCY, Koosinski P, Nicolaidis KH. Meta-analysis of second trimester markers for trisomy 21. *Ultrasound Obstet Gynecol* 2013; 41:247-261.
- Audibert F, Gagnon A. 2011. Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada; Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists. Prenatal screening for and diagnosis of aneuploidy in twin pregnancies. *J Obstet Gynaecol Can Jul*;33(7):754-67.
- Chitayat D, Langlois S, Wilson RD. 2011. Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada; Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists. Prenatal screening for fetal aneuploidy in singleton pregnancies. *J Obstet Gynaecol Can Jul*;33(7):736-50.
- Davies G and Wilson RD. 2003. Amniocentesis and women with Hepatitis B, Hepatitis C, or Human Immunodeficiency Virus, *J Obstet Gynaecol Can* 25(2): 145-8.  
[www.sogc.org/wp-content/uploads/2013/01/123E-CPG-February20031.pdf](http://www.sogc.org/wp-content/uploads/2013/01/123E-CPG-February20031.pdf).
- Gagnon A, Wilson RD, et al. 2008. Obstetrical complications associated with abnormal maternal serum marker analytes. *JOGC* 30: 918-932. [www.sogc.org/wp-content/uploads/2013/01/gui217CPG0810.pdf](http://www.sogc.org/wp-content/uploads/2013/01/gui217CPG0810.pdf).
- Hecht CA and Hook EB. 1996. Rates of Down syndrome at live birth by one-year maternal age intervals in studies with apparent close to complete ascertainment in populations of European origin; a proposed revised rate schedule for use in genetic and prenatal screening. *Am J Med Genet* 62:376-385.
- Malone FD, Canick JA, Ball RH, Nyberg DA, Comstock CH, Bukowski R, et al. 2005. First- and Second-Trimester Evaluation of Risk (FASTER) research consortium. First-trimester or second-trimester screening, or both, for Down's syndrome. *N Engl J Med* 353:2001-11.
- Norton ME, Jacobsson B, Swamy GK, Laurent LC, Ranzini AC, et al. 2015. Cell-free DNA Analysis for Noninvasive Examination of Trisomy. *N Engl J Med* 372:1589-1597.
- Odibo AO, Stamilio DM, Nelson DB, Sehdev HM, Macones GA. 2005. A cost-effectiveness analysis of prenatal screening strategies for Down syndrome. *Obstet Gynecol* 106:562-8.
- Perinatal Services BC (PSBC). 2012. Obstetrical Ultrasound Assessment Standards. PSBC.  
[www.perinatalservicesbc.ca/Documents/Guidelines-Standards/Standards/Ultrasound/PSBCUltrasoundAssessmentStandards.pdf](http://www.perinatalservicesbc.ca/Documents/Guidelines-Standards/Standards/Ultrasound/PSBCUltrasoundAssessmentStandards.pdf)
- Smith-Bindman R, Chi P, Goldberg JD. 2007. Second trimester prenatal ultrasound for the detection of pregnancies at increased risk of Down syndrome. *Prenatal Diagnosis* 27:535-544.
- Stokowski R, Wang E, White K, Batey A, Jacobsson B, et al. 2015. Clinical performance of non-invasive prenatal testing (NIPT) using targeted cell-free DNA analysis in maternal plasma with microarrays or next generation sequencing (NGS) is consistent across multiple controlled clinical studies. *Prenatal Diagnosis* 35:1-4.
- Wald JN, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM. 2003. First and second trimester antenatal screening for Down's syndrome: the result of the Serum, Urine and Ultrasound Screening Study (SURUSS). *J Med Screen*10:56-104.
- Wald NJ, Rish S. 2005. Prenatal Screening for Down Syndrome and Neural Tube Defects in Twin Pregnancies. *Prenat Diagn* 25(9):740-5.
- Wapner R, Thom E, Simpson JL, Pergament E, Silver R, Filkins K, et al. 2003. First-trimester screening for trisomies 21 and 18. *N Engl J Med* 349:1405-13.

### Risk of Down Syndrome and Other Chromosome Abnormalities in Live Births by Maternal Age

Maternal Age (At Term)	Risk		Maternal Age (At Term)	Risk		Maternal Age (At Term)	Risk	
	Down Syndrome	Total Chromosome Abnormality		Down Syndrome	Total Chromosome Abnormality		Down Syndrome	Total Chromosome Abnormality
25	1 in 1,250	1 in 476	32	1 in 637	1 in 323	39	1 in 125	1 in 81
26	1 in 1,190	1 in 476	33	1 in 535	1 in 286	40	1 in 94	1 in 63
27	1 in 1,111	1 in 455	34	1 in 441	1 in 224	41	1 in 70	1 in 49
28	1 in 1,031	1 in 435	35	1 in 356	1 in 179	42	1 in 52	1 in 39
29	1 in 935	1 in 417	36	1 in 281	1 in 149	43	1 in 40	1 in 31
30	1 in 840	1 in 385	37	1 in 217	1 in 123	44	1 in 30	1 in 21
31	1 in 741	1 in 385	38	1 in 166	1 in 105	≥45	≥1 in 24	≥1 in 19

Note: numbers do not include mosaicism, translocations, or marker chromosomes.

Source: Hecht CA and Hook EB. 1996 Rates of Down syndrome at live birth by one-year maternal age intervals in studies with apparent close to complete ascertainment in populations of European origin; a proposed revised rate schedule for use in genetic and prenatal screening. Am J Med Genet 62:376-385.

The a priori risk of having a pregnancy with an open neural tube defect is 1/1000. Maternal age is not a factor.

## Appendix 2

### Screen Cut-Offs and Performance of Screening Tests<sup>12</sup>

	Serum Integrated Prenatal Screen (SIPS)	Integrated Prenatal Screen (IPS)	Quad Screen (QUAD)	Non-Invasive Prenatal Testing (NIPT)
<b>DOWN SYNDROME</b>	<b>1:900</b>	<b>1:200</b>	<b>1:900</b>	
Screen cut-off				
Detection rate	<35 yrs: 87% 35–39 yrs: 92% ≥40 yrs:100% <sup>13</sup>	<35 yrs:100% <sup>13</sup> 35–39 yrs: 95% ≥40 yrs:100% <sup>13</sup>	<35 yrs: 88% 35–39 yrs: 94% ≥40 yrs:100% <sup>13</sup>	>99%
False positive rate	<35 yrs: 7% 35–39 yrs: 20% ≥40 yrs: 39%	<35 yrs: 4% 35–39 yrs: 7% ≥40 yrs: 16%	<35 yrs: 9% 35–39 yrs: 25% ≥40 yrs: 44%	<0.1%
Chance a screen negative result is a false negative result	<0.1%	<0.1%	<0.1%	<0.01%
<b>TRISOMY 18</b>	<b>1:300</b>	<b>1:300</b>	<b>1:300</b>	
Screen cut-off				
Detection rate	86%	92%	70%	~97%
False positive rate <sup>14</sup>	0.3%	1%	0.4%	<0.1%
Chance a screen negative result is a false negative result	<0.1%	<0.1%	<0.1%	<0.01%

Sources: SIPS/IPS/Quad data from Perinatal Services BC. British Columbia Perinatal Data Registry.  
 Years Provided: April 1, 2013 to March 31, 2018. Resource type: Tabulated data  
 NIPT data from published studies of the Harmony test, Ariosa Diagnostics, Inc.

<sup>12</sup> Performance of screening tests applies to singleton pregnancies.

<sup>13</sup> The detection rates listed are based on the small cohort of Down syndrome pregnancies in BC. SIPS, IPS, and Quad are screening tests so may not have 100% detection rate.

<sup>14</sup> Higher false positive rate of IPS reflects that this test is done in women who are at a higher a priori risk.

## Appendix 3

### Prenatal Genetic Diagnostic Testing (CVS and Amniocentesis)

	<b>Chorionic Villus Sampling (CVS)<sup>15</sup></b>	<b>Amniocentesis</b>
Time period for performing tests	11–13 <sup>+2</sup> weeks gestation	≥ 15 weeks gestation <sup>16</sup>
Sample	Placental villi	Amniotic fluid
Pregnancy loss rate	1–2 in 100 (1–2%)	1 in 200 (0.5%)
Other risks associated with the procedure	<p>Bleeding, cramping, infection</p> <p>Possible increased risk of fetal limb malformations (arms, legs, hands, or feet)</p> <ul style="list-style-type: none"> <li>• With no procedure, the risk is 1 in every 2000 to 5000 births; after CVS, the risk is 1 in every 1000 to 2000 births.</li> <li>• Risk is primarily associated with CVSs done prior to 10 weeks.</li> </ul> <p>Failure to obtain results due to insufficient sample or poor cell growth</p>	<p>Bleeding, amniotic fluid leakage, cramping, infection</p> <p>Failure to obtain results due to insufficient sample or poor cell growth</p>
Result Turn-Around Time	<p>Depends on the indication and the type of test that is performed.</p> <ul style="list-style-type: none"> <li>• Rapid Aneuploidy Detection (RAD) of chromosomes 13, 18, 21, and sex chromosomes only: takes 2–3 days.</li> <li>• Full karyotype: 2 weeks</li> <li>• Chromosomal microarray: 2 weeks</li> </ul>	

<sup>15</sup> CVS services are available only at B.C. Women’s Hospital & Health Centre. CVS is ideally performed between 11–13<sup>+2</sup> weeks gestation. On a case by case basis, CVS may be performed outside this timeframe.

<sup>16</sup> For amniocenteses performed between 22 and 24 weeks gestation, counselling of the patient should include a discussion of the risks of preterm labour. For amniocenteses performed at or after 24 weeks, consultation with a Maternal Fetal Medicine specialist should take place prior to the amniocentesis.

## Appendix 4

### Soft Markers Identified on Detailed Ultrasound

Several markers identified on second-trimester ultrasound examination are associated with increased risk of Down syndrome. The markers are not equally suggestive of Down syndrome. Based on the presence or absence of these markers, positive or negative likelihood ratios can be applied to the risk calculation for Down syndrome from SIPS/IPS/Quad allowing modification of a patient's risk<sup>17</sup>. Some markers are also indicative of increased risk of condition(s) other than Down syndrome.

#### Markers that significantly increase the risk of Down syndrome include:

- increased nuchal thickness (NTh)  $\geq 6$  mm
- echogenic bowel (equal or greater than bone)
- ventriculomegaly
- **absent** nasal bone (second trimester) (not routinely looked for)
- aberrant right subclavian artery (not routinely looked for)

#### Markers with only a small impact on the risk of Down syndrome include:

- echogenic intracardiac focus (EICF)
- pyelectasis (5 mm–10 mm)
- abnormal femur/foot ratio ( $\leq 0.9$ ).

#### Markers that increase the risk of condition(s) other than Down syndrome include:

- increased nuchal thickness (NTh)  $\geq 6$  mm
- echogenic bowel
- ventriculomegaly
- pyelectasis (5 mm–10 mm)

#### Recommended management:

1. If ultrasound detects NTh  $\geq 6$  mm, echogenic bowel (brightness  $\geq$  bone), **absent** nasal bone (second trimester), aberrant right subclavian artery, or more than one marker, referral to Medical Genetics is recommended.
2. If ultrasound detects ventriculomegaly, referral to the Fetal Diagnosis Service is recommended.
3. If ultrasound detects isolated pyelectasis, abnormal femur/foot ratio ( $\leq 0.9$ ) or echogenic intracardiac focus (EICF), and the Down syndrome screen (SIPS/IPS/Quad or NIPT) showed a negative screen (low risk), no further prenatal testing is recommended. If no screening has been done and patient is less than 20 weeks and 6 days gestation, Quad screening should be offered.
4. If ultrasound detects pyelectasis, a postnatal renal ultrasound between 5–30 days of age is recommended.
5. If Choroid plexus cyst (CPC) is detected, referral to Medical Genetics is recommended **only** if CPC is seen in combination with structural abnormalities or growth restriction. No further testing is indicated if CPC is identified in isolation and the patient's SIPS/IPS/Quad or NIPT is screen negative for trisomy 18 (for SIPS/IPS/Quad, risk only appears on report when screen positive). If no screening has been done and patient is less than 20 weeks and 6 days gestation, Quad screening should be offered.

<sup>17</sup> Agathokleous M, Chaveeva P, Poon LCY, Koosinski P, Nicolaidis KH. Meta-analysis of second trimester markers for trisomy 21. *Ultrasound Obstet Gynecol* 2013; 41:247-261.

# BC Prenatal Genetic Screening Program

Tel: 604-877-2121

[www.bcprenatalscreening.ca](http://www.bcprenatalscreening.ca)



**Perinatal  
Services BC**

Provincial Health Services Authority

**Perinatal Services BC**

Tel: 604-877-2121

[www.perinatalservicesbc.ca](http://www.perinatalservicesbc.ca)



**Provincial Health  
Services Authority**

Province-wide solutions.  
Better health.

While every attempt has been made to ensure that the information contained herein is clinically accurate and current, Perinatal Services BC and the BC Prenatal Screening Program acknowledge that many issues remain controversial, and therefore may be subject to practice interpretation.

© Perinatal Services BC, 2020