Perinatal Services BC Obstetric Guideline:

Prenatal Screening for Down Syndrome, Trisomy 18, and Open Neural Tube Defects

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BC Prenatal Genetic Screening Program

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Executive Summary

Prenatal genetic screening estimates the chance 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/individuals at higher chance of having a fetus with Down syndrome or trisomy 18 and women/individuals with twin pregnancies. Non-Invasive Prenatal Screening (NIPS) is now also an option for some higher risk women/individuals.

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/individuals. The following women/individuals are eligible for NT ultrasound as a component of Integrated Prenatal Screen (IPS = SIPS in combination with NT):

a) Women/individuals ≥35 years old at expected date of delivery (EDD)[1];

b) Women/individuals with twin pregnancies;

c) Women/individuals pregnant following in vitro fertilization with intracytoplasmic sperm injection (IVF with ICSI) without PGT-A.

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

For women/individuals 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 NIPS is available for the following eligible women/individuals:

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

b) Women/individuals who have a documented history of a previous child or fetus with Down syndrome, trisomy 18, or trisomy 13;

c) Women/individuals whose chance 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.

[1] In order to ensure quality NT ultrasounds, every certified sonographer must annually perform a minimum number of ultrasounds. As such, pregnant women/individuals 30 years and older in the 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 chance of chromosome disorders or structural anomalies. Serum integrated prenatal screen (SIPS), integrated prenatal screen (IPS), quad marker screen (Quad), NIPS, and a detailed second trimester ultrasound[2] are some of the options available for prenatal genetic screening.

The chance for fetal Down syndrome, trisomy 18, and open neural tube defects (ONTDs) is 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 NIPS. The screening tests offered will vary according to the woman's/individual'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 NIPS[3] and amniocentesis).

SIPS, IPS, Quad, NIPS

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^{+6} weeks (best at 10 – 11^{+6} weeks) and the second between 14 – 20^{+6} 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/individual'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^{+6} weeks (best at 12 – 13^{+3} 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[4] located around BC and use of the service is prioritized to serve those at higher chance of having a fetus with Down syndrome or trisomy 18 and women/individuals 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 NIPS, 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/individual's local community between 14 – 20^{+6} 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/individuals who present late for prenatal care (2nd trimester) as SIPS/IPS have better screening performance with lower false positive rates.

NIPS (Non-Invasive Prenatal Screening) is a blood test which analyzes cell free fetal DNA circulating in maternal blood, with a detection rate of Down syndrome in singleton pregnancies of approximately 98%, and 85% for trisomy 18. NIPS is funded in BC for women/individuals at increased chance for Down syndrome, trisomy 18, or trisomy 13 based on one of the following criteria:

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

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2 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.

3 NIPS (non-invasive prenatal screening) is a blood test which analyzes cell free fetal DNA circulating in maternal blood with a detection rate of Down syndrome in singleton pregnancies approximately 98%, and 85% for trisomy 18.

4 For a list of BC certified NT ultrasound centres, go to 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 calculation.

b) Women/individuals who have a documented history of a previous child or fetus with Down syndrome, trisomy 18, or trisomy 13;

c) Women/individuals whose chance 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 NIPS, including a BC-specific NIPS lab requisition, for your patient are available at www.bcprenatalscreening.ca/NIPT.

Private self-pay NIPS is also available in BC for those women/individuals who do not meet the above criteria but who wish to pursue NIPS. More details on private NIPS are available at www.bcprenatalscreening.ca/NIPT.

Download the (IPS/SIPS/Quad) serum lab requisition at www.bcprenatalscreening.ca.

Download the NIPS lab requisition for women/individuals eligible for funded NIPS at 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/individuals who decline screening for Down syndrome, or who have Down syndrome screening via NIPS, 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/individuals with a BMI ≥40, or those with limited access to a quality 18–20 weeks ultrasound, or those with increased risk of a NTD. The latter includes women/individuals with a previous pregnancy or personal or family history of NTD, women/individuals with diabetes or those on anti-epileptic medication. The indication for ordering a maternal serum AFP only should be provided on the requisition.

Counselling

Women/individuals 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/individuals 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/individuals 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^{+6} weeks) timeframe. Although blood test #2 can be collected and analyzed up to 20^{+6} weeks, the ideal time is much earlier (best at 15 – 16 weeks) to allow for earlier results and follow-up (NIPS or amnio) testing if necessary. To assist women/individuals and their families with prenatal screening information, patient brochures in multiple languages, decision aids, and a video are available at bcprenatalscreening.ca.

Specific counselling information should include:

- The age-based a priori risk for each woman/individual for having a fetus with a chromosomal abnormality (Appendix 1)
- The available tests for each woman/individual (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
- The fact that women/individuals with a positive screen will have the option of further screening or testing such as funded NIPS, chorionic villi sampling (CVS), or amniocentesis (further testing options offered will be dependent on the woman's/individual's estimated chance of Down syndrome or trisomy 18 from the positive screen)
- Information about chorionic villus sampling (CVS) and amniocentesis including the chance of complications from these procedures (Appendix 3)
- Balanced and accurate information about Down syndrome, trisomy 18, trisomy 13 and ONTD

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^{+6} wks	10 – 11^{+6} wks
• SIPS blood test #2	AFP uE3 hCG Inhibin-A	14 – 20^{+6} wks	15 – 16 wks
Integrated Prenatal Screen (IPS)	Same as SIPS (blood tests #1 & #2) with addition of NT ultrasound[5]	See SIPS for blood tests 11– 13^{+6} wks	See SIPS for blood tests 12 – 13^{+3} wks
Quad blood screen	Same as SIPS blood test #2	14 – 20^{+6} wks	15 – 16 wks
Non-Invasive Prenatal Testing (NIPS)	Cell-free fetal DNA, collected from maternal blood	10 weeks and onwards	varies by indication

[5] If an NT ultrasound is performed, NT centers require a first trimester dating ultrasound to book NT ultrasound in appropriate time window.

Table 2: Screening options available through the BC Prenatal Genetic Screening Program[6]

Characteristics of woman/individual	Gestational Age at the First Prenatal Visit		
	≤13+6 weeks	14–20+6 weeks	≥21 weeks (no prior screening)
<35 years	• SIPS	• Quad	• Detailed ultrasound
35–39 years	• IPS; or • If NT not available, SIPS	• Quad	• Detailed ultrasound; and • Amnio
40+ years	• IPS; or • If NT not available, SIPS; or • CVS or Amnio without prior screening	• Quad; or • Amnio without prior screening	• Detailed ultrasound; and • Amnio
Personal/family history that increases the chance of fetus with Down syndrome, trisomy 18, or trisomy 13	• NIPS; or • CVS or Amnio without prior screening	• NIPS; or • Amnio without prior screening	• Detailed ultrasound; and • NIPS; or • Amnio
Personal/family history that increases the chance of fetus with chromosomal abnormality other than Down syndrome, trisomy 18, or trisomy 13	• CVS or Amnio without prior screening	• Amnio without prior screening	• Detailed ultrasound; and • Amnio
Twin gestation[7]	• IPS; or • If NT not available, SIPS; or • If ≥35, Amnio without prior screening	• Quad; or • If ≥35, Amnio without prior screening	• Detailed ultrasound; and • If ≥35, Amnio
Pregnant following In vitro fertilization with intracytoplasmic sperm injection without prior PGT-A	• IPS; or • If NT not available, SIPS; or • CVS or Amnio without prior screening	• Quad; or • Amnio without prior screening	• Detailed ultrasound; and • Amnio

6 SIPS/IPS/Quad and NIPS for eligible women/individuals 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 (NIPS) based on cell free DNA in maternal blood (from 10 wks onwards) available to those who do not qualify for the funded NIPS.

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

2. Management

A. After a discussion of the pros and cons, all pregnant women/individuals 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/individual'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/individual's gestational age at their first prenatal visit, their 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/individuals at higher chance of having a fetus with Down syndrome or trisomy 18[8] and women/individuals with multiple gestations.

C. Women/individuals with an increased chance of having a fetus with a chromosomal abnormality[9] 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/individuals who have had a first trimester screen[10], NIPS, and/or CVS, and women/individuals 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 exceptions are if they have a BMI of 40 or greater, or have limited access to a quality detailed ultrasound examination, or at increased risk of NTD (a previous pregnancy or personal or family history of NTD, women/individuals with diabetes or those on anti-epileptic medication). In those circumstances, an alpha-fetoprotein (AFP) serum screen between 15–20^{+6} (best 15 –16 weeks) to screen for ONTDs should be offered. The reason for the maternal serum AFP only should be provided on the requisition.

E. For women/individuals who choose to have (private-pay) NIPS 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/individual is having NIPS, given the limited utility of NT measurement in pregnancies with a negative NIPS result and limited NT resources.

F. CVS and amniocentesis for fetal karyotyping will not be offered without prior screening except for women/individuals 40 years or older at expected date of delivery, women/individuals at increased chance of having a fetus with a chromosomal abnormality,[11] and women/individuals with multiple gestations who are ≥ 35 years old at expected date of delivery.

G. For women/individuals of any age found to have an NT measurement of 3.0 mm or greater, a calculation will be made based on NT only (or NT and PAPP-A if available). If the result is 1/300 or greater, a report will be issued without waiting for SIPS part 2 (blood test #2). The woman/individual should then be offered further testing: either funded NIPS or CVS/amnio. If the screen result is less than 1/300 based on NT alone (or NT and PAPP-A), no report will be generated, and the woman/individual 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 ≥ 3.5 mm increases the chance 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.

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8 This includes women/individuals 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) without PGT-A.

9 This includes a woman/individual or their 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 chance 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/individual with a pregnancy conceived by IVF with ICSI and without PGT-A.

10 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.

11 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 chance (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/individuals should be counselled by their health care provider and offered further testing. All women/individuals with a positive screen for trisomy 18 should be offered funded NIPS or amniocentesis. For women/individuals with a positive screen for Down syndrome and a result between 1:900 and 1:301, only funded NIPS should be offered. For women/individuals with a positive screen for Down syndrome and a result equal or greater than 1:300, the option of funded NIPS or amniocentesis should be offered.

NIPS 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 approximately 98% with less than 0.1% false positives; the detection rate for trisomy 18 is around 85% with less than a 0.1% false positive rate. For more information on NIPS, how it compares to amniocentesis, and how to access testing, go to www.bcprenatalscreening.ca/NIPT.

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

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

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

Refer to www.bcprenatalscreening.ca for more details including an algorithm for obstetrical management.

O. If the prenatal screen result is positive for an open neural tube defect, and dating is confirmed, a detailed ultrasound should be immediately done, even if less than 19 weeks gestation. Management of the pregnancy will be dependent on the results of the detailed ultrasound. See Appendix 4 for follow-up of elevated MSAFP.

2. Management, *cont'd*

P. A detailed second trimester ultrasound (18–20 weeks) to assess fetal anatomy and growth should be offered to all pregnant women/individuals. An 18–20 week ultrasound without soft markers or anomalies is capable of reducing the estimated chance of Down syndrome by approximately 50% (Smith-Bindman, 2007).

Q. Soft markers or anomalies on the 18–20 week ultrasound increase the chance of aneuploidy and should be interpreted in conjunction with the prenatal screening (SIPS, IPS, or Quad) result. See Appendix 5 for detailed soft marker information.

R. Women/individuals 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.

Perinatal Services BC, ph: (604) 877-2121; website: 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; website: www.cdss.ca

ChildHealth BC, website: 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

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

Healthy Families BC, website: www.healthyfamiliesbc.ca

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

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

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

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

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

Maternal Age (At Term)	Chance		Maternal Age (At Term)	Chance		Maternal Age (At Term)	Chance	
	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 chance 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[12]

		Serum Integrated Prenatal Screen (SIPS)	Integrated Prenatal Screen (IPS)	Quad Screen (QUAD)	Non-Invasive Prenatal Testing (NIPS)
DOWN SYNDROME	**Screen cut-off**	**1:900**	**1:200**	**1:900**	
	Detection rate	<35 yrs: 86% 35–39 yrs: 96% ≥40 yrs:100%[13]	<35 yrs:100%[13] 35–39 yrs: 98% ≥40 yrs: 97%[13]	<35 yrs: 83% 35–39 yrs:100% ≥40 yrs:100%[13]	~98%
	False positive rate	<35 yrs: 8% 35–39 yrs: 21% ≥40 yrs: 44%	<35 yrs: 7% 35–39 yrs: 9% ≥40 yrs: 16%	<35 yrs: 9% 35–39 yrs: 24% ≥40 yrs: 45%	<0.1%
	Chance a screen negative result is a false negative result	<0.1%	<0.1%	<0.1%	<0.01%
TRISOMY 18	**Screen cut-off**	**1:300**	**1:300**	**1:300**	
	Detection rate	88%	90%	75%	~85%
	False positive rate[14]	0.6%	2%	1%	<0.1%
	Chance a screen negative result is a false negative result	<0.1%	<0.1%	<0.1%	<0.1% [15]

Sources: SIPS/IPS/Quad data from Perinatal Services BC. British Columbia Perinatal Data Registry.
Years Provided: April 1, 2016 to March 31, 2021. Resource type: Tabulated data
NIPS data from Perinatal Services BC based on 229 cases of T21 and 45 cases of Trisomy 18.

[12] Performance of screening tests applies to singleton pregnancies.

[13] 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.

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

[15] May be higher if ultrasound abnormalities present.

Appendix 3

Prenatal Genetic Diagnostic Testing (CVS and Amniocentesis)

	Chorionic Villus Sampling (CVS)[16]	Amniocentesis
Time period for performing tests	11–13^{+2} weeks gestation	≥15 weeks gestation[17]
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	Bleeding, cramping, infection Possible increased rate of fetal limb malformations (arms, legs, hands, or feet) • With no procedure, the rate is 1 in every 2000 to 5000 births; after CVS, the rate is 1 in every 1000 to 2000 births. • Risk is primarily associated with CVSs done prior to 10 weeks. Failure to obtain results due to insufficient sample or poor cell growth	Bleeding, amniotic fluid leakage, cramping, infection Failure to obtain results due to insufficient sample or poor cell growth
Result Turn-Around Time	Depends on the indication and the type of test that is performed. • Rapid Aneuploidy Detection (RAD) of chromosomes 13, 18, 21, and sex chromosomes only: takes 2–3 days. • Full karyotype: 2 weeks • Chromosomal microarray: 2 weeks	

[16] CVS services are available only at B.C. Women's Hospital & Health Centre. CVS is ideally performed between 11–13^{+2} weeks gestation. On a case by case basis, CVS may be performed outside this timeframe.

[17] 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

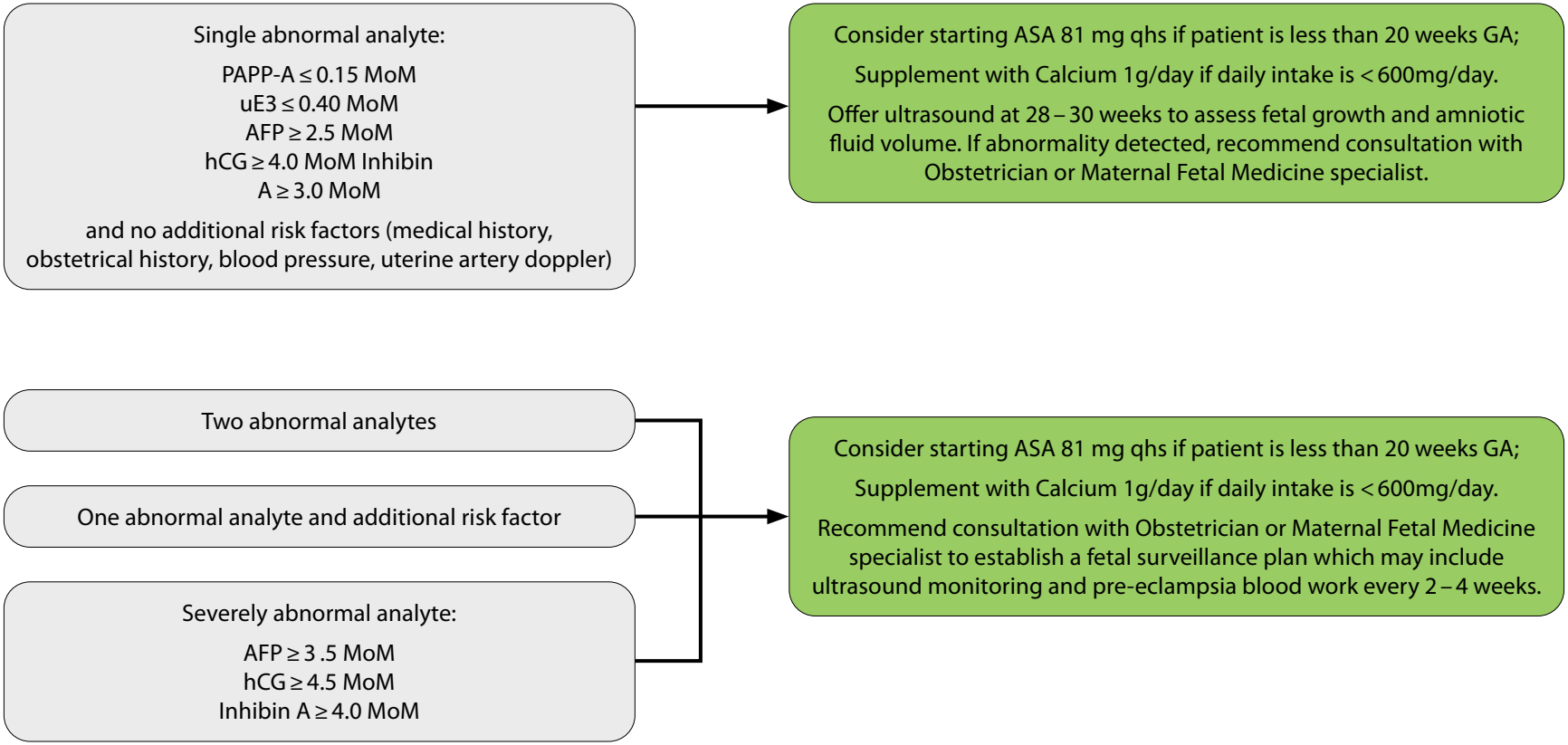
Recommended Approach For Patients With Elevated MSAFP

Approximately 1% of patients having screening for Down syndrome by SIPS/IPS/Quad are found to have an elevated maternal serum AFP (MSAFP) resulting in a positive screen for open neural tube defect. A review of close to 600 of cases of MSAFP with AFP >2.5MoM (positive screen for ONTD) seen in Medical Genetics over a period of 6 years shows that only 9% of those cases had a fetal structural abnormality related to the elevated MSAFP (spina bifida, anencephaly, omphalocele, gastroschisis, limb body wall complex). Another 5% had IUGR with or without oligohydramnios or echogenic bowel likely indicative of abnormal placentation. 5% of patients had fetal abnormalities unrelated to the elevated MSAFP, 3% had isolated echogenic bowel, 2% had other soft markers and 2% had fetal demise. As such, 73% had completely normal ultrasounds.

Based on these findings, it is no longer recommended that all patients with elevated MSAFP be referred to Medical Genetics. Instead, only patients with extremely high MSAFP (>400 µg/L) should be referred to Medical Genetics prior to doing any additional investigations. All other patients should have an ultrasound done in their local community as soon as possible even if less than 19 weeks gestation. The result of that ultrasound should be used to guide further management as follows:

1. Patients with fetal structural abnormality should be referred to the Fetal Diagnosis Service at BCWH: http://www.bcwomens.ca/our-services/pregnancy-prenatal-care/complications-in-pregnancy/fetal-diagnosis-service; or to the Antenatal Assessment Unit in Victoria (fax referral to 1-250-727-4441)
2. Patients with fetus with AC or EFW less than the 10th %le should be referred to an MFM specialist as per MFM Provincial Guideline: http://www.bcwomens.ca/health-professionals/refer-a-patient/ultrasound
3. Patients with soft markers on ultrasound should be managed as per the recommendations outlined in the PSBC Obstetric Guideline: Prenatal screening for Down syndrome, appendix 5 available at www.bcprenatalscreening.ca
4. Patients with no fetal abnormality identified on ultrasound but with incomplete anatomical screen (not all details seen) should have a repeat ultrasound between 19–21 weeks gestation.
5. All patients with MSAFP that is not explained by a fetal abnormality should be considered at increased chance of adverse obstetrical outcome and followed as per following algorithm:

Recommended Approach For Patients With Elevated MSAFP



Medical Genetics		Fetal Diagnosis Service (FDS)	Maternal Fetal Medicine		
Vancouver: T: 604-875-2818 F: 604-875-3484	Victoria: T: 250-727-4461 F: 250-727-4295	T: 604-875-2848 F: 604-875-3484	BC Women's Hospital: T: 604-875-2162 F: 604-875-3255	Surrey Jim Pattison: T: 604-582-4558 ext. 763995 F: 604-582-3798	Victoria General: T: 250-727-4266 F: 250-727-4441

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Appendix 5

Soft Markers Identified on Detailed Ultrasound

Several markers identified on second-trimester ultrasound examination are associated with increased chance 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 calculation of chance of Down syndrome from SIPS/IPS/Quad or maternal age allowing modification of a patient's chance[10]. Some markers are also indicative of increased chance of condition(s) other than Down syndrome.

Markers that significantly increase the chance of Down syndrome include:

- increased nuchal thickness (NTh) ≥ 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 chance of Down syndrome include:

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

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

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

Recommended management:

1. If ultrasound detects **absent** nasal bone (second trimester), aberrant right subclavian artery, or more than one marker, consult with or refer to Medical Genetics.

2. If ultrasound detects ventriculomegaly, referral to the Fetal Diagnosis Service (BCWH) or Victoria MFM is recommended.

3. If ultrasound detects increased nuchal thickness:
   - If NTh is between 6 – 7mm and cardiac views are reported as normal and patient had negative NIPS screen, no further testing is recommended.
   - If NTh is between 6 – 7mm and cardiac views are reported as normal and patient had SIPS/IPS/Quad, or no screen, the chance of Down syndrome should be recalculated using the Trisomy21 calculator (www.perinatalservicesbc.ca/health-professionals/professionalresources/screening/prenatal-genetic/trisomy-21-risk-calculator). Medical Genetics can be consulted for help with calculation as needed. If revised chance of Down syndrome is greater than 1 in 300, patient qualifies for amniocentesis or funded NIPS. If patient chooses funded NIPS, contact medical genetics (604-875-2157 BCWH, or 250-727-4461 Victoria) for NIPS code.

- If NTh is between 6–7mm and cardiac views are reported as not well seen, in addition to recalculation of the chance of Down syndrome using the Trisomy21 calculator, a prompt reassessment of the cardiac views is needed. For patients from VCH, NHA, IHA, this can be facilitated through referral to Medical Genetics at BCWH; for patients from FHA, referral to the Jim Pattison Maternal Fetal Medicine Service is recommended; for VIHA patients, referral to Medical Genetics at Victoria General Hospital is recommended.
- If NTh is 7mm or greater, referral to Medical Genetics (Vancouver or Victoria) is recommended.

4. If ultrasound detects echogenic bowel:
   - If associated dilated bowel loops, referral to the Fetal Diagnosis Service (FDS) is recommended.
   - If isolated echogenic bowel as bright as bone:
     - Chance of an intrauterine infection is increased. Recommend serology IgM and IgG for CMV, Toxoplasmosis and Parvovirus.
     - Chance of Down syndrome is increased. If patient had negative NIPS, chance of Down syndrome remains low. If patient had SIPS/IPS/Quad or no screen, the chance of Down syndrome should be recalculated using the Trisomy21 calculator (www.perinatalservicesbc.ca/healthprofessionals/professional-resources/screening/prenatal-genetic/trisomy-21-risk-calculator). Medical Genetics can be consulted for help with calculation as needed. If revised chance of Down syndrome is greater than 1 in 300, patient qualifies for amniocentesis or funded NIPS. If patient chooses funded NIPS, contact medical genetics for NIPS code.
     - Chance of cystic fibrosis is increased for Caucasian couples. Offer CF carrier screening on patient and partner (requisition available at www.genebc.ca). For midwifery patients, this can be facilitated through referral to Medical Genetics.
     - Risk of developing IUGR in third trimester is increased. A follow up ultrasound around 30–32 weeks gestation is recommended.

5. If ultrasound detects isolated pyelectasis, abnormal femur/foot ratio (≤0.9) or echogenic intracardiac focus (EICF), and the Down syndrome screen (SIPS /IPS /Quad or NIPS) showed a negative screen (low chance), no further prenatal testing is recommended. If no screening has been done and patient is less than 21 weeks and 6 days gestation, Quad screening should be offered. For patients with an ultrasound finding of pyelectasis, a postnatal renal ultrasound between 5–30 days of age is recommended.

6. 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 NIPS 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.

Medical Genetics		Fetal Diagnosis Service (FDS)	Maternal Fetal Medicine		
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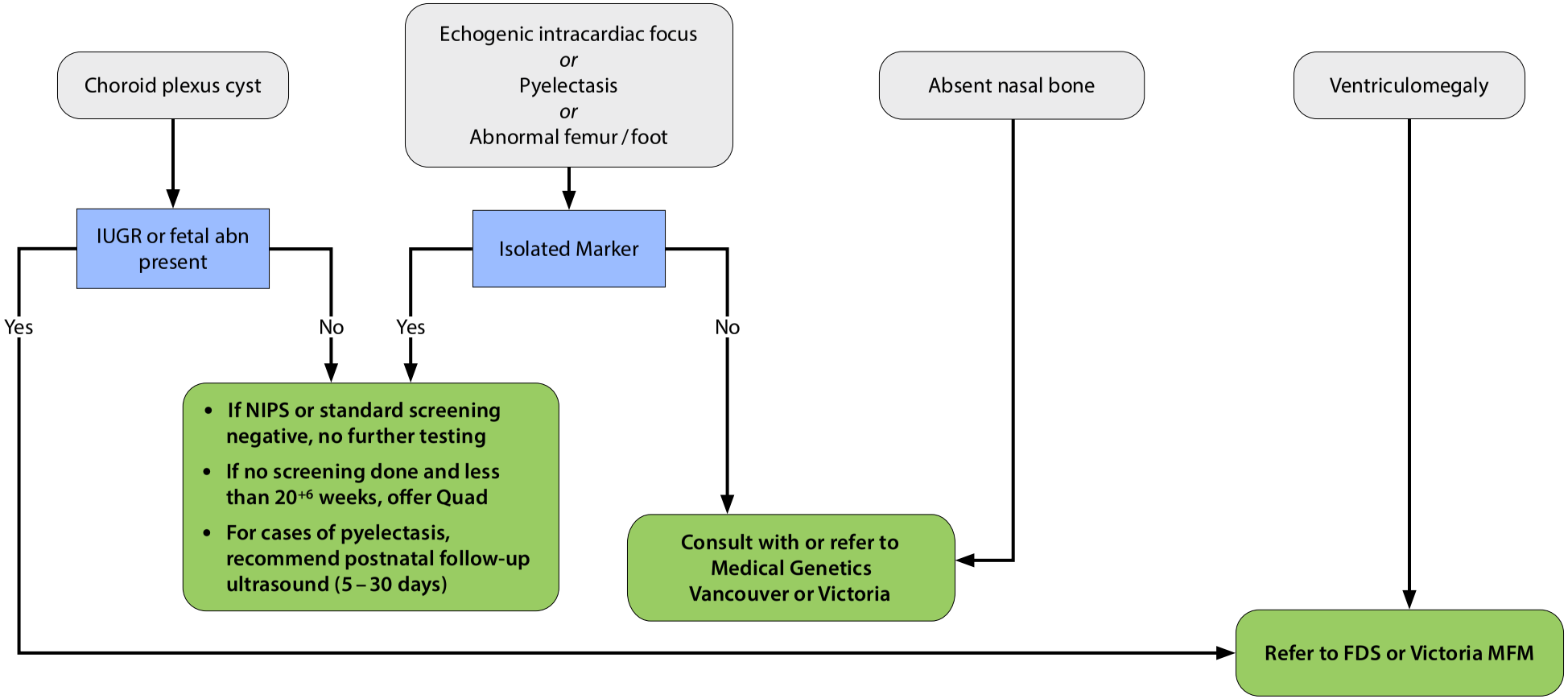
[10] Agathokleous M, Chaveeva P, Poon LCY, Koosinski P, Nicolaides KH. Meta-analysis of second trimester markers for trisomy 21. Ultrasound Obstet Gynecol 2013; 41:247-261.

Soft Markers on 2nd Trimester Ultrasound



NIPS: Non-Invasive Prenatal Screening

Medical Genetics		Fetal Diagnosis Service (FDS)	Maternal Fetal Medicine		
Vancouver: T: 604-875-2818 F: 604-875-3484	Victoria: T: 250-727-4461 F: 250-727-4295	T: 604-875-2848 F: 604-875-3484	BC Women's Hospital: T: 604-875-2162 F: 604-875-3255	Surrey Jim Pattison: T: 604-582-4558 ext. 763995 F: 604-582-3798	Victoria General: T: 250-727-4266 F: 250-727-4441

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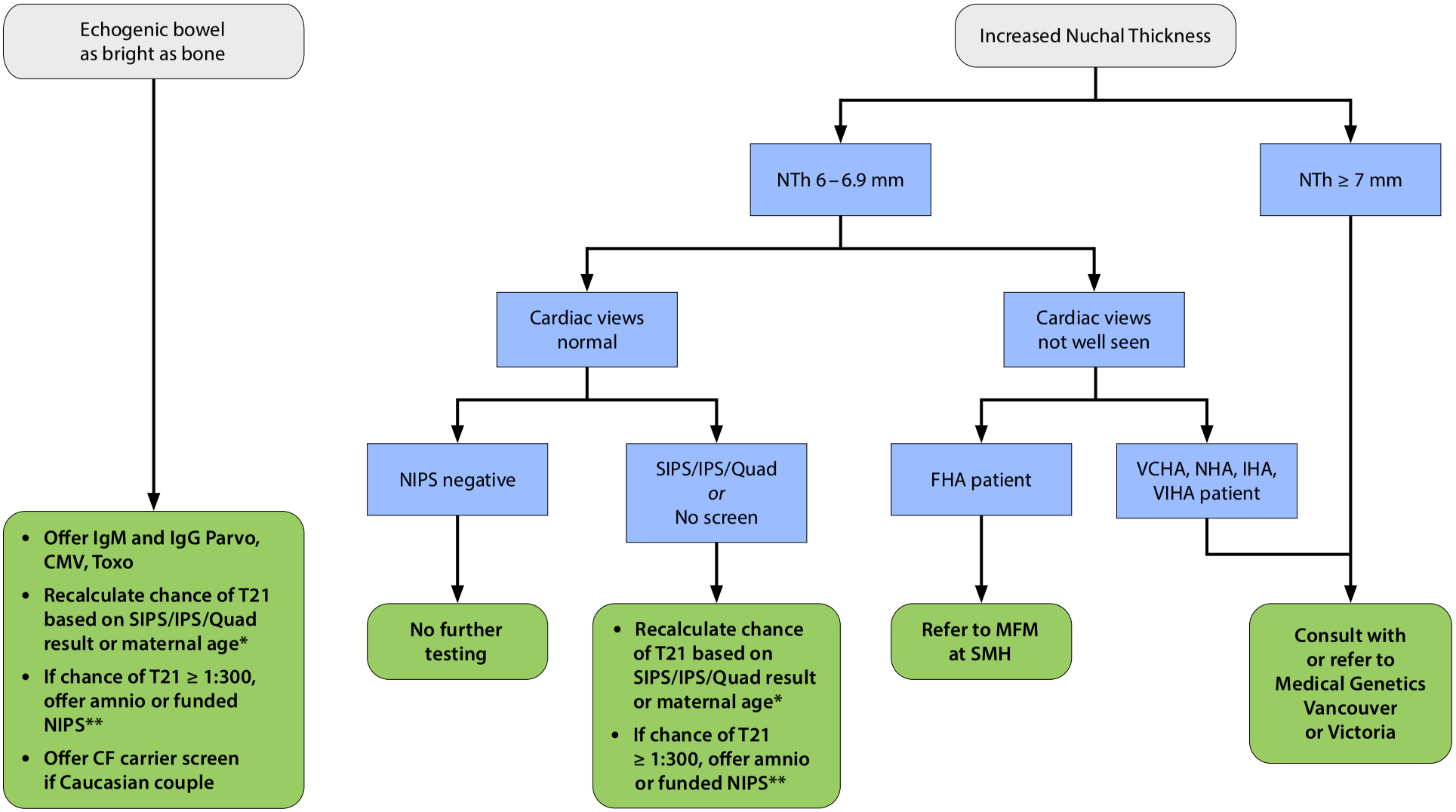
Soft Markers on 2nd Trimester Ultrasound



NIPS: Non-Invasive Prenatal Screening

* Use T21 risk calculator on PSBC website or consult medical genetics.

** Contact medical genetics (604-875-2157 BCWH, or 250-727-4461 Victoria) for NIPS code.

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