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# No. 348-Joint SOGC-CCMG Guideline: Update on Prenatal Screening for Fetal Aneuploidy, Fetal Anomalies, and Adverse Pregnancy Outcomes

**This Clinical Practice Guideline has been prepared by the Society of Obstetricians and Gynaecologists of Canada (SOGC) Genetics Committee and the Canadian College of Medical Geneticists (CCMG) Clinical Practice Committee,* and approved by the Boards of the SOGC and CCMG.**

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**Key Words:** Prenatal screening, cell-free DNA, aneuploidy, congenital anomalies

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## Abstract

**Objective:** To review the available prenatal screening options in light of the recent technical advances and to provide an update of previous guidelines in the field of prenatal screening.

**Intended Users:** Health care providers involved in prenatal screening, including general practitioners, obstetricians, midwives, maternal fetal medicine specialists, geneticists, and radiologists.

**Target Population:** All pregnant women receiving counselling and providing informed consent for prenatal screening.

**Evidence:** Published literature was retrieved through searches of Medline, PubMed, and the Cochrane Library in and prior to March 2016 using an appropriate controlled vocabulary (prenatal diagnosis, amniocentesis, chorionic villi sampling, non-invasive prenatal screening) and key words (prenatal screening, prenatal genetic counselling). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies written in English and published

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Women have the right and responsibility to make informed decisions about their care in partnership with their health care providers. To facilitate informed choice, women should be provided with information and support that is evidence based, culturally appropriate, and tailored to their needs. The values, beliefs, and individual needs of each woman and her family should be sought, and the final decision about the care and treatment options chosen by the woman should be respected.

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from January 1985 to May 2016. Searches were updated on a regular basis and incorporated in the guideline. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical speciality societies.

**Guideline update:** Evidence will be reviewed 5 years after publication to determine whether all or part of the guideline should be updated. However, if important new evidence is published prior to the 5-year cycle, the review process may be accelerated for a more rapid update of some recommendations.

**Summary Statements**

1. Where available with documented expertise, the first trimester ultrasound (11 to 14 weeks' gestation) offers many advantages including accurate dating, determination of twin chorionicity, early detection of major structural abnormalities, and aneuploidy screening (II-2A).
2. In women with a low risk of aneuploidy following first trimester aneuploidy screening, the presence of specific ultrasound "soft markers" associated with fetal trisomy 21 (echogenic intracardiac focus) or trisomy 18 (choroid plexus cysts) identified during the second trimester ultrasound (18 to 22 weeks) are not clinically relevant due to poor predictive value and do not warrant further testing (II-2A).
3. Second trimester serum alpha fetoprotein screening to rule out open neural tube defects is no longer necessary unless there is a barrier to good quality ultrasound examination (II-2A).
4. In twin pregnancies, fetal nuchal translucency (NT) combined with maternal age is an acceptable first trimester screening test for aneuploidies (II-2A). First trimester serum screening combined with NT may also be considered and improves the screening accuracy (II-3B). Integrated screening with NT plus first and second trimester serum screening is also an option. Further prospective studies are required in this area because this protocol has not been validated in large prospective studies in twins (III-C).
5. Maternal plasma cell-free DNA is a highly effective form of early prenatal screening of common trisomies (21, 18, 13) after 10 weeks' gestation (II-2A).
6. Currently, offering maternal plasma cell-free DNA to all women as a primary screening method is not fiscally feasible in most provinces. Offering cell-free DNA in a contingent model is an affordable option that has the potential to achieve improved performance while maintaining the benefits of conventional screening serum analyte and early ultrasound (III).

**Recommendations**

1. All pregnant women in Canada, regardless of age, should be offered, through an informed counselling process, the option of a prenatal screening test for the most common fetal aneuploidies (II-A).
2. First trimester nuchal translucency should be interpreted for risk assessment only when measured by sonographers or sonologists trained and accredited for this fetal screening service and when there is ongoing quality assurance (II-2A). For aneuploidy, it should be offered as a screen with maternal serum biochemical markers in singleton pregnancies (II-2B).
3. Maternal age alone is a poor minimum standard for prenatal screening for aneuploidy, and it should not be used as a basis for recommending invasive fetal diagnostic testing when prenatal screening for aneuploidy is available (II-2D).
4. Health care providers should be aware of the prenatal screening modalities available in their province or territory (III-B). A reliable prenatal system needs to be in place ensuring timely reporting of results (III-C). Prenatal screening programs should be implemented with resources that support audited screening and diagnostic laboratory services, ultrasound, genetic counselling services, patient and health care provider education, and high-quality diagnostic testing, as well as resources for administration, annual clinical audit, and data management. In addition, there must be the flexibility and funding opportunities to adjust the program to new technology and protocols (II-3B).
5. A discussion of the risks, benefits, and alternatives of the various prenatal diagnoses and screening options, including the option of no testing, should be undertaken with all patients prior to any prenatal screening. Following this counselling, patients should be offered (1) no aneuploidy screening, (2) standard prenatal screening based on locally offered paradigms, (3) ultrasound-guided invasive testing when appropriate indications are present, or (4) maternal plasma cell-free DNA screening where available, with the understanding that it may not be provincially funded (II-2B).
6. Regardless of aneuploidy screening choice, all women should be offered a fetal ultrasound (optimally between 11 and 14 weeks) to confirm viability, gestational age, number of fetuses, chorionicity in multiples, early anatomic assessment, and nuchal translucency (NT) evaluation where available. The NT measurement for aneuploidy risk estimation (combined with maternal serum) should not be performed if cell-free DNA screening has been used. Every effort should be made to improve access to high-quality first trimester ultrasound for all Canadian women. In areas where NT assessment is not available, a first trimester dating ultrasound improves the accuracy of maternal serum screening and the management of pregnancy (II-1A).
7. A large nuchal translucency ($>$3.5 mm) should be considered a major marker for fetal chromosomal and structural anomalies and requires genetic counselling, an offer of invasive testing with chromosomal microarray analysis, and detailed second trimester ultrasound follow-up (II-2A).
8. Women who are considering undergoing maternal plasma cell-free DNA (cfDNA) screening should be informed that:
   - It is a highly effective screening test for the common fetal trisomies (21, 18, 13), performed after 10 weeks' gestation (II-1A).

## ABBREVIATIONS

| | |
|---|---|
| cfDNA | cell-free DNA |
| CNV | copy number variant |
| CPM | confined placental mosaicism |
| CVS | chorionic villus sampling |
| DNA | deoxyribonucleic acid |
| IPS | integrated prenatal screening |
| GA | gestational age |
| LR | likelihood ratio |
| MoM | multiple of the median |
| MSS | maternal serum screening |
| NIPT | non-invasive prenatal testing |
| NT | nuchal translucency |
| PCR | polymerase chain reaction |
| PPV | positive predictive value |
| SCA | sex chromosome aneuploidy |
| T13 | trisomy 13 |
| T18 | trisomy 18 |
| T21 | trisomy 21 |



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- There is a possibility of a failed test (no result available), false negative or positive fetal result, and an unexpected fetal or maternal result (II-1A).
- All positive cfDNA screening results should be confirmed with invasive fetal diagnostic testing prior to any irrevocable decision (II-1B).
- Management decisions, including termination of pregnancy, require diagnostic testing and should not be based on maternal plasma cfDNA results alone because it is not a diagnostic test (II-2B).
- If a fetal structural abnormality is identified in a woman regardless of previous screening test results, the woman should undergo genetic counselling and be offered invasive diagnostic testing with rapid aneuploidy detection and reflex to microarray analysis if rapid aneuploidy detection is normal or inconclusive (II-2B).
- Although cfDNA screening for aneuploidy in twin pregnancy is available, there is less validation data than for a singleton pregnancy and it should be undertaken with caution (II-2C).
- Routine cfDNA screening for fetal microdeletions is not currently recommended (II-2B).

9. If a fetal structural abnormality is identified, regardless of previous screening test results, genetic counselling and invasive fetal diagnostic testing should be offered, with rapid aneuploidy detection and reflex to microarray analysis if rapid aneuploidy detection is normal or inconclusive (II-2A).
10. The presence of an isolated fetal soft marker in the second trimester, with the exception of increased nuchal fold, should not be used to adjust the a priori risk for fetal aneuploidy (II-2D).
11. Universal screening for adverse pregnancy outcomes using maternal serum markers is currently not recommended outside of an investigational protocol with informed consent (II-2D).

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## INTRODUCTION

The landscape of prenatal screening and diagnosis has changed considerably in the last decade with the rapid development of new technologies, particularly the introduction of (1) NIPT using circulating maternal plasma cfDNA and (2) chromosomal microarray analysis of amniotic fluid or chorionic villi. These new tools are associated with additional complexity with respect to patient counselling and interpretation of conventional tests such as ultrasound, MSS, and invasive fetal testing.

The objective of this guideline was to summarize these advances for maternity care providers, provide guidance for the incorporation of new technologies, and discuss the impact they may have on prenatal counselling, screening, and diagnosis (Table 1). This guideline replaces the following previous guidelines from the SOGC Genetics Committee and Canadian College of Medical Geneticists Prenatal Diagnosis Committee:

- Current Status in Non-Invasive Prenatal Detection of Down Syndrome, Trisomy 18, and Trisomy 13 Using Cell-Free DNA in Maternal Plasma[1]
- Obstetrical Complications Associated With Abnormal Maternal Serum Markers Analytes[2]
- Fetal Soft Markers in Obstetric Ultrasound[3]

This guideline also provides an update to the following two previous guidelines:

- Prenatal Screening for Fetal Aneuploidy in Singleton Pregnancies[4]
- Prenatal Screening for and Diagnosis of Aneuploidy in Twin Pregnancies[5]

## GENERAL CONSIDERATIONS FOR PRENATAL SCREENING

All pregnant women should be offered the option to accept or decline screening for fetal aneuploidy and major congenital anomalies. The following factors modify the risk of fetal aneuploidy, genetic disorders, and/or structural abnormalities and should be interpreted together, rather than separately, for individual risk estimation and counselling:

1. Maternal history, including maternal age, previous pregnancy affected by aneuploidy, maternal or paternal chromosome rearrangements with an increased risk for chromosomal imbalance, history of congenital anomalies, or recurrent spontaneous abortions of unknown etiology.
2. First trimester (11 to 13 weeks) ultrasound evaluation, where available with documented expertise: offers many advantages including accurate dating, determination of twin chorionicity, early detection of major structural abnormalities such as anencephaly, and aneuploidy screening using NT. A large NT (above 3.5 mm) is associated with an increased risk of specific fetal conditions, in particular congenital heart disease, fetal akinesia, structural malformations, some single gene disorders (such as Noonan syndrome and many others), chromosome abnormalities, and poor pregnancy outcome including fetal demise. The American Institute of Ultrasound in Medicine[6] and the International Society of Ultrasound in Obstetrics and Gynecology[7]

**Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care**

| Quality of evidence assessment[a] | Classification of recommendations[b] |
|---|---|
| I: Evidence obtained from at least one properly randomized controlled trial. | A. There is good evidence to recommend the clinical preventive action. |
| II-1: Evidence from well-designed controlled trials without randomization. | B. There is fair evidence to recommend the clinical preventive action. |
| II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group. | C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making. |
| II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in the category. | D. There is fair evidence to recommend against the clinical preventive action. |
| III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees. | E. There is good evidence to recommend against the clinical preventive action. |
| | I. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making. |

[a]The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.

[b]Recommendations included in these guidelines have been adapted from the Classification of recommendations criteria described in The Canadian Task Force on Preventive Health Care.



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support the continued measurement of NT in the first trimester even if it is not used in the context of screening for aneuploidy. SOGC encourages NT measurement with adequate quality control. In areas where first trimester ultrasound is not available, a "second trimester ultrasound only" approach is acceptable, although every effort should be made to improve access to high-quality first trimester ultrasound for all Canadian women. In areas where NT ultrasound is not available, a first trimester dating ultrasound improves the accuracy of MSS and the management of pregnancy.[8]

3. Second trimester (18 to 22 weeks) ultrasound evaluation: should be offered for structural anomalies in a centre or with an imaging provider with demonstrated expertise in fetal ultrasound.
4. First and/or second trimester maternal serum aneuploidy screening: using placental and fetal biochemical analytes with or without NT, as part of first trimester screening, IPS, or serum IPS. The 2011 recommendations regarding the aneuploidy screening options in singleton and twin pregnancies are still valid.
5. NIPT using circulating maternal plasma cfDNA.

**Recommendations**

1. All pregnant women in Canada, regardless of age, should be offered, through an informed counselling process, the option of a prenatal screening test for the most common fetal aneuploidies (II-A).
2. First trimester nuchal translucency should be interpreted for risk assessment only when measured by sonographers or sonologists trained and accredited for this fetal screening service and when there is ongoing quality assurance (II-2A). For aneuploidy, it should be offered as a screen with maternal serum biochemical markers in singleton pregnancies (II-2B).
3. Maternal age alone is a poor minimum standard for prenatal screening for aneuploidy, and it should not be used as a basis for recommending invasive fetal diagnostic testing when prenatal screening for aneuploidy is available (II-2D).
4. Health care providers should be aware of the prenatal screening modalities available in their province or territory (III-B). A reliable prenatal system needs to be in place ensuring timely reporting of results (III-C). Prenatal screening programs should be implemented with resources that support audited screening and diagnostic laboratory services, ultrasound, genetic counselling services, patient and health care provider education, and high-quality diagnostic testing, as well as resources for administration, annual clinical audit, and data management. In addition, there must be the flexibility and funding opportunities to adjust the program to new technology and protocols (II-3B).
5. A discussion of the risks, benefits, and alternatives of the various prenatal diagnoses and screening options, including the option of no testing, should be undertaken with all patients prior to any prenatal screening. Following this counselling, patients should be offered (1) no aneuploidy screening, (2) standard prenatal screening based on locally offered paradigms, (3) ultrasound-guided invasive testing when appropriate indications are present, or (4) maternal plasma cell-free DNA screening where available, with the understanding that it may not be provincially funded (II-2B).
6. Regardless of aneuploidy screening choice, all women should be offered a fetal ultrasound (optimally between 11 and 14 weeks) to confirm viability, gestational age, number of fetuses, chorionicity in multiples, early anatomic assessment, and nuchal translucency (NT) evaluation where available. The NT measurement for aneuploidy risk estimation (combined with maternal serum) should not be performed if cell-free DNA screening has been used. Every effort should be made to improve access to high-quality first trimester ultrasound for all Canadian women. In areas where NT assessment is not available, a first trimester dating ultrasound improves the accuracy of maternal serum screening and the management of pregnancy (II-1A).
7. A large nuchal translucency (>3.5 mm) should be considered a major marker for fetal chromosomal and structural anomalies and requires genetic counselling, an offer of invasive testing with chromosomal microarray analysis, and detailed second trimester ultrasound follow-up (II-2A).
9. If a fetal structural abnormality is identified, regardless of previous screening test results, genetic counselling and invasive fetal diagnostic testing should be offered, with rapid aneuploidy detection and reflex to microarray analysis if rapid aneuploidy detection is normal or inconclusive (II-2A).


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**Summary Statement**

1. Where available with documented expertise, the first trimester ultrasound (11 to 14 weeks' gestation) offers many advantages including accurate dating, determination of twin chorionicity, early detection of major structural abnormalities, and aneuploidy screening (II-2A).

## PRENATAL SCREENING FOR ANEUPLOIDY: ROLE OF MATERNAL PLASMA CFDNA BASED NIPT

Current prenatal screening protocols for fetal T21, T18, and T13 are based on combinations of maternal serum biochemical markers with or without an NT measurement.[4] The recent introduction of maternal plasma cfDNA–based technology, with its superior performance for fetal aneuploidy screening, has had a dramatic impact on this traditional screening approach. Widely referred to as NIPT, maternal plasma cfDNA screening (preferred nomenclature) is based on genomic sequencing of maternal plasma cfDNA fragments using either "massively parallel" sequencing or targeted-sequencing methods (either chromosome selective or single nucleotide polymorphism-based) combined with advanced bio-informatic analysis. Data from recent meta-analyses of published clinical validation and implementation studies show high sensitivity and specificity for fetal T21, T18, and T13, regardless of the method used (Table 2).[9–13]

cfDNA screening can also be used to determine fetal sex, to identify the presence of a Rh-positive fetus in a Rh-negative mother, and to detect certain paternally derived autosomal genetic abnormalities.

In the context of aneuploidy screening, current SOGC guidelines[1] (February 2013) recommend that cfDNA screening should be an option for women at increased risk of fetal trisomies who wish to avoid invasive testing. Although the current recommendations remain valid, women and their health care providers need to fully understand that cfDNA screening *is not a substitute* for invasive diagnostic testing and that this approach may delay diagnosis and miss some fetuses with aneuploidy. This section discusses the risks, benefits, and limitations of cfDNA screening identified through its clinical use in average and high-risk populations and provides an updated implementation model and counselling considerations.

### Interpretation of Maternal Plasma cfDNA Screening Results

The average turn-around time for cfDNA screening results is currently 4 to 10 days. Report formats vary from a simple "positive" or "negative" screening result to a numerical risk (e.g., >99% [high risk] or <1/10 000 [low risk]). The American Congress of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine recommend that the PPV (i.e., the chance that a positive result is a true positive) and the residual risk (the chance that a negative result is false) be included in cfDNA screening reports.[14] Although the sensitivity and specificity of cfDNA screening have been shown to be similar in the general obstetric population to those in the high-risk population, the PPV is lower in the general population, given the lower prevalence of fetal aneuploidy. Thus, far fewer women with a positive result in the general obstetric population will have an affected fetus and there will be more false positive results (Table 2). Other factors influencing the PPV include previous serum screening results, ultrasound findings, incidence of the aneuploidy, and GA. For women who receive a negative result, the likelihood that the fetus does not have one of the common aneuploidies (negative predictive value) also depends on multiple factors, but is overall very high (>99%).[15] The odds of being affected, given a positive result, is another calculation to assist with counselling and understanding because it does not vary as much as the age-based prevalence in PPV. This information is important for health care providers and patients to understand in order to enable more accurate and informative counselling for patients regarding their screening results.

### cfDNA Test Failures and the Importance of Fetal Fraction

Provision of a cfDNA screening result depends on the maternal plasma DNA sample being of sufficient quality and the fetal fraction (%) being adequate to allow for an accurate separation of normal and abnormal results. The fetal fraction is the percentage of fetal cfDNA in the maternal sample (which consists of maternal and placental [fetal surrogate] cfDNA).

Factors affecting the fetal fraction include GA, maternal obesity, and the presence of a chromosome aneuploidy in either the placenta or the mother. The median fetal fraction between 11 to 14 weeks' gestation is 10% and failure rates are low at this GA. At earlier GAs, the fetal fraction is not consistently adequate and therefore screening prior to 10 to 11 weeks is not recommended. Maternal obesity is inversely related to fetal fraction and for women >110 kg, the failure rate of cfDNA screening is over 10%.[16–18] The likely mechanism is a dilutional effect combined with increased adipocyte turnover, resulting in increased maternal relative to fetal serum



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**Table 2. cfDNA Test Performance[14]**

| | Sensitivity, % | Specificity, % | Age 25 years PPV, % | Age 40 years PPV, % |
|---|---|---|---|---|
| T21 | 99.3 | 99.8 | 33 | 87 |
| T18 | 97.4 | 99.8 | 13 | 68 |
| T13 | 91.6 | 99.6 | 9 | 57 |
| SCA | 91 | 99.6 | - | - |

This table is modeled on 25- and 40-year-old patients based on aneuploidy prevalence at 16 weeks' gestation. The PPV for SCAs vary by condition but range 20% to 40%.

The PPV (true positives divided by true positives plus false positives) is directly related to the prevalence of the condition in the population being screened. Given a prevalence of 1/1000 for T21 in a 25-year-old, only 1 in 3 women with an abnormal result will have an affected fetus (i.e., PPV 33%), whereas if the prevalence is 1/75 (40-year-old), the PPV is 87%.

Adapted with permission from Committee Opinion No. 640: Cell-free DNA screening for fetal aneuploidy. Obstet Gynecol 2015;126:e31–7.[14]

cfDNA.[19] CfDNA samples with a low fetal fraction (<4%) may not produce an interpretable result and should be reported as "no-call."

The overall probability of a failed (no-call) result ranges from 1% to 8% depending on the laboratory and method used.[20,21] Women for whom first screening results are inconclusive due to low fetal fraction should be counselled and be offered a redraw with a 50% to 60% likelihood of getting an interpretable result, but they need to be informed that the process may significantly delay diagnosis. Given that test failure due to low fetal fraction is associated in itself with an increased risk of fetal aneuploidy (as high as 5%),[22] women with "no call" should be offered genetic counselling to discuss invasive fetal chromosome investigations. The follow-up should include an ultrasound examination (if not recently done) because the presence of fetal abnormalities would further guide management.

### False Positive Rate and Confirmation of Abnormal Results

cfDNA screening is associated with an overall false positive rate for the common aneuploidies of approximately 1%.[15,20,21] This is because the specificity for each screening condition is reported separately, so false positive rates are cumulative.[14] There are several biological and non-biological explanations for positive NIPT results other than fetal aneuploidy, including confined placental mosaicism,[23–25] maternal aneuploidy,[26,27] maternal CNVs,[28] maternal malignancy,[29,30] or a co-twin demise.[31]

Invasive diagnostic testing, either CVS or amniocentesis, is thus recommended after a positive cfDNA fetal aneuploidy screen, and no irrevocable pregnancy decision or procedure should be taken solely based on a "positive" cfDNA screening result. Because cfDNA screening is frequently performed in the first trimester, CVS may be the invasive procedure method offered so that an early definitive diagnosis can be achieved. However, if mosaicism is identified on CVS, confirmatory amniocentesis is recommended due to the possibility of discordance based on CPM.

CPM refers to the presence of a chromosome abnormality in the placenta with a normal fetal karyotype and occurs in 1% to 2% of placental samples obtained using CVS.[32,33] Because fetal cfDNA originates mainly from apoptosis of the trophoblast layer of the chorionic villi and not the fetus,[34] cfDNA screening can be considered equivalent to a "non-invasive CVS"; hence a similar incidence of CPM is expected.

T21 and T18 have a low probability of CVS mosaicism; therefore, CVS may be appropriate as a confirmatory diagnostic procedure. Because T13 and monosomy X have a higher incidence of placental mosaicism on CVS, waiting for an amniocentesis would appear to be the most appropriate step.[35]

### Role of cfDNA Screening in Twins

Although cfDNA screening is available for T21, T18, and T13 in twins, less large cohort validation data are available than for singleton pregnancies, and cfDNA should be undertaken with caution.

The main challenge of screening twin pregnancies is that the cfDNA in the maternal circulation is derived from both fetal placentas. Therefore, the results are reported for the entire pregnancy, not for each individual fetus. Invasive testing is required to determine which fetus, if any, is affected. In addition, multiple gestation results in a lower per fetus fetal fraction than does a singleton pregnancy. One approach, therefore, is to base the assessment of risk in dichorionic twins on the lower fetal fraction of the twins, rather than on the total fetal fraction.[22,36] Although this improves performance, it is also associated with higher failure rates. Additional validation studies including better evaluation of monochorionic and dichorionic twin cohorts are needed before cfDNA screening can be recommended in twins.

### Microdeletion Syndromes

Some companies offer screening for specific chromosome microdeletion syndromes through maternal plasma cfDNA analysis in addition to aneuploidy screening. Peer-reviewed data validating the performance of these investigations are few, and given the low incidence of each of these microdeletions, the PPV is very low.[37] Fetal submicroscopic chromosomal changes are individually rare but are reported to have an estimated cumulative incidence of


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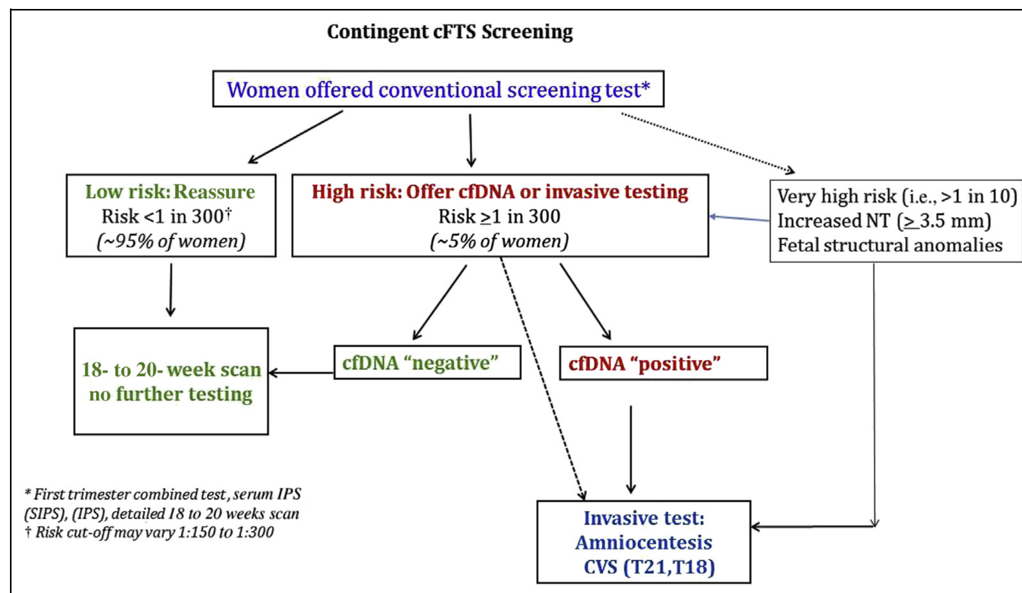
**Figure. Contingent combined first trimester screening (cFTS) cFTS screening. Low risk: Women identified on screening to be at a low risk (i.e., <1:300) for common fetal aneuploidies should be offered no further screening/testing other than 18- to 22-week detailed fetal anatomic survey. High risk: Women identified on screening to be at a high risk (i.e., >1:300) for fetal aneuploidy following first trimester screening, serum IPS, or IPS should be offered invasive fetal testing or cfDNA screening. Women who chose cfDNA screening should be counselled that cfDNA is limited in its ability to detect all chromosome abnormalities. Very high risk: For women identified on screening to have a very high risk (i.e., >1:10) for fetal aneuploidy, increased NT (>3.5 mm), or fetal anomaly on ultrasound, diagnostic testing should be offered rather than cfDNA screening.**




about 1% to 1.5% in the population. Unlike fetal trisomies, the risk for these chromosomal microdeletions/duplications is independent of maternal or paternal age.

The National Institute of Child Health and Human Development study evaluated more than 4400 women who had an invasive diagnostic karyotype.[38] Approximately 1.7% of pregnancies with advanced maternal age or a positive prenatal screen and a normal standard karyotype had a pathogenic or likely pathogenic CNV detected by the microarray. Among women presenting with abnormal ultrasound and a normal standard karyotype, additional microarray testing identified a CNV pathogenic result in 2.8% and a possible clinically significant result in 3.2% (total 6.0%).

Although proof of concept studies and case reports have conveyed the capacity of cfDNA to detect fetal microdeletions on maternal blood,[37] there are currently few studies[39] to support the use of cfDNA for such expanded fetal screening. One genetic study reported an overall PPV ranging from 60% to 100% for 7 particular subchromosomal changes.[40] In that study, half of the patients with a correctly reported fetal microdeletion by cfDNA had undergone testing due to abnormal ultrasound findings or a positive family history.

Given the low incidence of each individual submicroscopic chromosome change, the PPV is expected to be low in pregnancies without fetal anomalies and will increase the risk of false-positive results.[41,42] Low PPVs and the false-positive result will, in turn, lead back to what cfDNA was designed to avoid, which is unnecessary invasive procedures. Moreover, use of cfDNA screening in the context of fetal anomalies may delay diagnosis through conventional invasive testing. Screening for microdeletions involves complex issues of pre-test and post-test counselling that are currently unresolved. For these reasons, routine cfDNA screening for fetal microdeletions is currently not recommended.

## Fetal Sex Determination

Several common DNA sequences specific to the Y chromosome allow for the determination of fetal sex as early as the seventh postmenstrual week, with nearly 100% determination by the 10th postmenstrual week. PCR testing of maternal blood for these sequences generates the sex determination: if Y chromosome sequences are present, the fetus is presumed to be male. The only clinical indication for prenatal fetal sex determination is to determine the risk of transmission of an X-linked genetic disorder (e.g., Duchenne



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muscular dystrophy or X-linked hemophilia) or to determine the potential risk of virilisation in a pregnancy at risk of congenital adrenal hyperplasia. Fetal sexing alone is not indicated, even with patient autonomy considerations.

## SCA

Testing for fetal sex determination will result in the potential discovery of fetal SCA; hence couples will need to decide whether they wish to receive this information. Genetic counselling following the prenatal discovery of 47,XXX; 47,XXY; and 47,XYY is complex, and the identification through cfDNA screening is particularly challenging because detection rates and false positive rates are lower than for T21, T18, and T13 and the PPV is not available for these karyotypes. All women with positive results should be offered invasive testing to determine whether the cytogenetic abnormality is actually present in the fetus. Discussing the potential implications of screening for fetal sex determination and SCA, and obtaining the patient's consent prior to screening are recommended.

## Models for Clinical Implementation of cfDNA Screening

### Contingent-cfDNA screening

Based on available data and considering the current cost of cfDNA testing to our publically funded health care system, a contingent-cfDNA screening model would seem to be the most appropriate current strategy.[43] Contingent-cfDNA screening refers to the use of cfDNA screening as a follow-up test for women with a positive or "high-risk" conventional screening result who wish to avoid an invasive diagnostic test. Cost and performance modeling studies[44–46] have demonstrated that contingent screening with cut-off adjustment* can approach the same detection rates and false positive rates as those with primary cfDNA screening (especially when considering the test-failure or "no-call" rate of cfDNA), while maintaining the benefits of the 11- to 14-week fetal ultrasound within a multiple marker screening system.[44,46] Funding for contingent-cfDNA screening has been approved in 2 provinces in Canada (British Columbia and Ontario) and should be considered by the provincial governments of the remaining provinces. A simple algorithm of cfDNA-contingent screening is described in Figure.

* Although the sensitivity of cfDNA for T21 is 99.3%, the overall detection rate using a contingent protocol will only be as good as the primary screening test (80% to 85%). A recommended strategy is to adjust the initial screen cut-off upward (i.e., to 1/500 or 1/1000) to create an intermediate-risk category eligible for cfDNA screening. Modelling data show this would result in 15% to 20% of women being eligible for cfDNA and overall detection would approach that of primary screening (96% to 98%).

**Table 3. Interpretation of second trimester ultrasound soft markers**

| Ultrasound variant/marker | SOGC 2005[3] LR[a] | Meta-analysis 2013[47] LR[a] marker | Meta-analysis 2013[47] LR[a] isolated marker |
|---|---|---|---|
| Nuchal fold | 17 | 23.3 | 3.8 |
| Echogenic cardiac focus | 2 | 5.8 | 0.95 |
| Echogenic bowel | 6 | 11.4 | 1.65 |
| Ventriculomegaly | 9 | 27.5 | 3.8 |
| Choroid plexus cysts | 7 (T18 only) | - | - |
| Hypoplastic/absent nasal bone | - | 23.3 | 6.6 |

[a]LR for T21.

### Primary cfDNA screening

Work in Ontario has recently shown that a primary cfDNA model with 100% screening uptake would approximately quadruple the total program cost of screening for aneuploidy.[46] The predicted price of cfDNA screening for a cost-neutral universal screening program was calculated to be approximately $226. Universal access to cfDNA as a first tier screening is thus currently not feasible but may be offered based on provincial funding arrangements, via private insurers, or on an informed consent self-pay basis.

## Pre-Screen Counselling in the Era of cfDNA

A discussion of the risks, benefits, and alternatives of the various prenatal diagnoses and screening options, including the option of no testing, should be undertaken with all patients prior to any prenatal screening. Women should have further discussion regarding local and provincial options available to them for prenatal genetic screening. Following this, they should be offered (1) no aneuploidy screening, (2) standard prenatal screening based on locally offered paradigms, (3) ultrasound guided-invasive testing, or (4) maternal plasma cfDNA screening where available, with the understanding that it may not be provincially funded.

Regardless of aneuploidy screening choice, all women should be offered a baseline fetal ultrasound (optimally between 11 and 14 weeks) to confirm viability, GA, number of fetuses, chorionicity in multiples, early anatomic assessment, and NT evaluation (if an accredited sonographer is available). The NT measurement for aneuploidy risk estimation (combined with MSS) should not be performed if cfDNA screening is used.

In summary, maternal plasma cfDNA is a highly effective form of prenatal aneuploidy screening that can facilitate

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early detection of common trisomies (21, 18, 13) and provide early reassurance when a pregnancy is deemed to be at increased risk. Implementation of maternal plasma cfDNA screening in clinical practice requires changes in patient referral patterns, pre-screen counselling, and management of women with positive results. Currently, offering cfDNA to all women as a primary screening method is not feasible in most provinces due to cost issues. Offering cfDNA in a contingent model with cut-offs set to optimize detection is an affordable option that has the potential to achieve improved performance while maintaining the benefits of conventional screening through early ultrasound, which has applications beyond age-based aneuploidy detection.

**Recommendations**

8. Women who are considering undergoing maternal plasma cell-free DNA (cfDNA) screening should be informed that:
   - It is a highly effective screening test for the common fetal trisomies (21, 18, 13), performed after 10 weeks' gestation (II-1A).
   - There is a possibility of a failed test (no result available), false negative or positive fetal result, and an unexpected fetal or maternal result (II-1A).
   - All positive cfDNA screening results should be confirmed with invasive fetal diagnostic testing prior to any irrevocable decision (II-1B).
   - Management decisions, including termination of pregnancy, require diagnostic testing and should not be based on maternal plasma cfDNA results alone because it is not a diagnostic test (II-2B).
   - If a fetal structural abnormality is identified in a woman regardless of previous screening test results, the woman should undergo genetic counselling and be offered invasive diagnostic testing with rapid aneuploidy detection and reflex to microarray analysis if rapid aneuploidy detection is normal or inconclusive (II-2B).
   - Although cfDNA screening for aneuploidy in twin pregnancy is available, there is less validation data than for a singleton pregnancy and it should be undertaken with caution (II-2C).
   - Routine cfDNA screening for fetal microdeletions is not currently recommended (II-2B).

## PRENATAL SCREENING: ROLE OF ULTRASOUND SOFT MARKERS

The SOGC Clinical Practice Guideline *Fetal Soft Markers in Obstetrical Ultrasound* was published in June 2005 as an aid to help recalculate the risk for fetal aneuploidy when the anatomic ultrasound demonstrated findings suggestive of an increased risk of aneuploidy.[3] Although more sensitive screening options with serum markers with or without NT were available, accessibility across Canada varied. Because all pregnant women were being offered an ultrasound evaluation, this approach of "genetic ultrasound" was developed as an additive screening option.

The 5 ultrasound soft markers previously recommended for aneuploidy screening were enlarged nuchal fold, echogenic bowel, mild ventriculomegaly, echogenic heart focus, and choroid plexus cysts. Although none of these ultrasound-identified features is considered a malformation, all were shown to be associated with an increased relative risk of T21 and T18 (Table 3).[3,47] If a marker is present, the patient's a priori risk of aneuploidy is increased by a specific LR; conversely, the risk may be decreased if no markers are present. Of these, increased nuchal fold is the most powerful marker, with an LR of 23 (but only 3.8 if isolated) for T21, whereas choroid plexus cysts are only associated with a minimally increased risk of fetal T18. Echogenic intracardiac focus has an LR of 2 to 5.8 for T21, but only 0.95 if isolated. Echogenic bowel is associated with a slightly increased risk for fetal T21 but has additional implications including an increased risk of cystic fibrosis (2%), fetal infection (3%), and gastrointestinal malformation (6%). Mild fetal ventriculomegaly is associated with an increased risk of fetal T21 as well as CNS malformations or intracranial infection and some other inherited conditions. Hypoplastic or absent nasal bone in the second trimester has a relatively high LR, but the reproducibility of this marker has not been adequately studied.[48]

Many of the studies on soft markers were performed in women who did not undergo first trimester screeing. Given the much reduced incidence of aneuploidies in the second trimester following effective screening in the first and/or early second trimester, the relative LRs are also markedly reduced, and some have suggested that 2 of these specific to only T21 (echogenic intracardiac focus) or T18 (choroid plexus cysts) are no longer relevant if they exist in isolation.

Fetal soft marker screening in the second trimester should not be used in isolation and should be used cautiously if effective first or second trimester aneuploidy screening has been carried out and not at all if maternal cfDNA screening has been performed. This recommendation is also supported by the International Society for Ultrasound in Obstetrics and Gynecology, which states that the so-called genetic sonogram "should not be performed in women with a normal NIPT result due to its high false-positive rate and poor positive predictive value."[7]



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In summary, the presence of specific ultrasound "soft markers" associated with fetal T21 (echogenic intracardiac focus) or T18 (choroid plexus cysts) at the time of the anatomic survey (18 to 22 weeks) in women with a low risk of aneuploidy is not clinically relevant and does not warrant further testing. The presence of an isolated soft marker, with the exception of increased nuchal fold, on the routine second trimester scan should not be used to adjust the a priori risk for T21.

**Summary Statement**

2. In women with a low risk of aneuploidy following first trimester aneuploidy screening, the presence of specific ultrasound "soft markers" associated with fetal trisomy 21 (echogenic intracardiac focus) or trisomy 18 (choroid plexus cysts) identified during the second trimester ultrasound (18 to 22 weeks) are not clinically relevant due to poor predictive value and do not warrant further testing (II-2A).

**Recommendation**

10. The presence of an isolated fetal soft marker in the second trimester, with the exception of increased nuchal fold, should not be used to adjust the a priori risk for fetal aneuploidy (II-2D).

## SCREENING FOR PREGNANCY COMPLICATIONS: ROLE OF SERUM BIOMARKERS

A recognized association exists between abnormal serum analytes detected at the time of aneuploidy screening and adverse obstetrical outcomes such as preeclampsia and intrauterine growth restriction.[2]

Screening for adverse pregnancy outcomes is seen as a potential secondary benefit of genetic screening for aneuploidies, taking advantage of the fact that similar markers of placental origin are both associated with aneuploidies and adverse outcomes, mostly related to placental insufficiency. However, with the rapid development of maternal plasma cfDNA for aneuploidies and the potential decrease of the use of serum markers for aneuploidy, the question is raised about the relevance of MSS for pregnancy outcomes as a stand-alone test.

The recommendations proposed by the Genetics Committee of the SOGC in 2008 were as follows[2]:

> In the first trimester, an unexplained low pregnancy-associated plasma protein A (<0.4 MoM) and/or a low hCG [human chorionic gonadotropin] (<0.5 MoM) are associated with an increased frequency of adverse obstetrical outcomes, and, at present, no specific protocol for treatment is available. In the second trimester, an unexplained elevation of maternal serum alpha-fetoprotein (>2.5 MoM), hCG (>3.0 MoM), and/or inhibin-A (>or=2.0 MoM) or a decreased level of maternal serum AFP [alpha-fetoprotein] (<0.25 MoM) and/or unconjugated estriol (<0.5 MoM) are associated with an increased frequency of adverse obstetrical outcomes, and, at present, no specific protocol for treatment is available.

Since the publication of those recommendations, numerous studies have confirmed the association between abnormal maternal serum markers and adverse pregnancy outcomes, mostly preeclampsia and to a lesser extent intrauterine growth restriction and intrauterine fetal demise. However, it appears that the most promising approach in screening for preeclampsia could be provided in the first trimester by a broader combination of maternal historical risk factors, mean arterial pressure, uterine artery Doppler, and maternal serum markers (such as pregnancy-associated plasma protein A and placental growth gactor).[49–51] The performance of this approach is currently being studied in large populations and in the context of routine screening rather than in experimental settings.

Moreover, the benefit of screening for adverse pregnancy outcome is still debated because there is still no compelling evidence to show what type of intervention could improve pregnancy outcomes in screen-positive women. Ongoing clinical trials are currently examining the role of low-dose aspirin in high-risk women based on first-trimester multiple-marker screening. Before the results of such trials become available, universal screening for adverse pregnancy outcomes using maternal serum markers is not recommended.

Another application of MSS was based on the long-known association of second trimester elevated AFP with open neural tube defects and abdominal wall defects. However, the Genetics Committee of the SOGC recently stated that (1) "the primary screening test for the detection of fetal structural abnormalities including neural tube defects is a second trimester anatomical ultrasound with detailed fetal cranial and spinal imaging and assessment" and (2) "the primary use of maternal serum alpha-fetoprotein for neural tube defects screening should be discontinued, except in some limited clinical exceptions."[52]

**Summary Statement**

3. Second trimester serum alpha fetoprotein screening to rule out open neural tube defects is no longer necessary unless there is a barrier to good quality ultrasound examination (II-2A).


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An additional uncommon clinical application of MSS is the detection of very low serum estriol as a marker of rare fetal and maternal conditions with important clinical implications. Very low (<0.15 MoM) or undetectable unconjugated estriol can be an indicator of a pregnancy affected with X-linked ichthyosis.[53] Moreover, women who are carriers of an affected pregnancy are at risk of obstetrical complications, such as failure to initiate labor and failure to progress, and a small increased risk of intrauterine fetal demise. Low unconjugated estriol can also be a marker of other monogenic conditions with significant clinical impact in the fetus, such as Smith-Lemli-Opitz sydrome,[54,55] congenital adrenal hypoplasia, multiple sulfatase deficiency, and Antley-Bixler syndrome.[56]

It remains to be determined whether, in an era in which cfDNA screening may be more generally accessible, there remains a value for maternal unconjugated estriol screening as a single marker for the aforementioned conditions.

**Recommendations**

11. Universal screening for adverse pregnancy outcomes using maternal serum markers is currently not recommended outside of an investigational protocol with informed consent (II-2D).

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