
This Committee Opinion 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 Board of the SOGC and the Board of the CCMG.

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Abstract

Objective: This guideline was written to update Canadian maternity care and reproductive healthcare providers on pre- and postconceptional reproductive carrier screening for women or couples who may be at risk of being carriers for autosomal recessive (AR), autosomal dominant (AD), or X-linked (XL) conditions, with risk of transmission to the fetus. Four previous SOGC–Canadian College of Medical Geneticists (CCMG) guidelines are updated and merged into the current document.

Intended Users: All maternity care (most responsible health provider [MRHP]) and paediatric providers; maternity nursing; nurse practitioner; provincial maternity care administrator; medical student; and postgraduate resident year 1 or are pregnant (preferably in the first trimester of pregnancy, but any gestational age is acceptable).

Target Population: Fertile, sexually active females and their fertile, sexually active male partners who are either planning a pregnancy or are pregnant (preferably in the first trimester of pregnancy, but any gestational age is acceptable).

ABBREVIATIONS

ACOG American Congress of Obstetricians and Gynecologists
AD autosomal dominant
AJ Ashkenazi Jewish
AR autosomal recessive
CCMG Canadian College of Medical Geneticists
CGG unstable triplet
CF cell free
CF cystic fibrosis
DNA deoxyribonucleic acid
DTC direct-to-consumer
DTC-GT DTC genetic testing
FMR1 Fragile X mental retardation 1
FSH follicle stimulating hormone
FXS Fragile X syndrome
Hb hemoglobin
HE hemoglobin electrophoresis
HHPLC hemoglobin high performance liquid chromatography
MRHP most responsible health provider
SC sickle cell
SMA spinal muscular atrophy
SMN1 survivor motor neuron 1 gene
SOGC Society of Obstetricians and Gynaecologists of Canada
XL X-linked

Options: Women and their partners will be able to obtain appropriate genetic carrier screening information and possible diagnosis of AR, AD, or XL disorders (preferably pre-conception), thereby allowing an informed choice regarding genetic carrier screening and reproductive options (e.g., prenatal diagnosis, preimplantation genetic diagnosis, egg or sperm donation, or adoption).

Outcomes: Informed reproductive decisions related to genetic carrier screening and reproductive outcomes based on family history, ethnic background, past obstetrical history, known carrier status, or genetic diagnosis.

SOGC Reproductive Carrier Screening Summary Statement (2016): Pre-conception or prenatal education and counselling for reproductive carrier screening requires a discussion about testing within the three perinatal carrier screening/diagnosis time periods, which include pre-conception, prenatal, and neonatal for conditions currently being screened for and diagnosed. New information should be added to the standard reproductive carrier screening protocols that are already being utilized by the most responsible maternity provider through the informed consent process with the patient. (III-A; GRADE low/moderate)

SOGC Overview of Recommendations Quality and Grade: There was a strong observational/expert opinion (quality and grade) for the genetic carrier literature with randomized controlled trial evidence being available only for the invasive testing. Both the Canadian Task Force on Preventive Health Care quality and classification and the GRADE evidence quality and grade are provided.

Evidence: MEDLINE; PubMed; government neonatal screening websites; key words/common reproductive genetic carrier screened diseases/previous SOGC Guidelines/medical academic societies (Society of Maternal-Fetal Medicine [SMFM]; American College of Medical Genetics and Genomics; American College of Obstetricians and Gynecologists [ACOG]; CCMG; Royal College Obstetrics and Gynaecology [RCOG] [UK]; American Society of Human Genetics [ASHG]; International Society of Prenatal Diagnosis [ISPD]/provincial neonatal screening policies and programs; search terms (carrier screening, prenatal screening, neonatal genetic/metabolic screening, cystic fibrosis [CF], thalassemia, hemoglobinopathy, hemophilia, Fragile X syndrome [FXS], spinal muscular atrophy, Ashkenazi Jewish carrier screening, genetic carrier screening protocols, AR, AD, XL).

Search Period: 10 years (June 2005-September 2015); initial search dates June 30, 2015 and September 15, 2015; completed final search January 4, 2016. Validation of articles was completed by primary authors RD Wilson and I De Bie.

Benefits, Harms, and Cost: Benefits are to provide an evidenced based reproductive genetic carrier screening update consensus based on international opinions and publications for the use of Canadian women, who are planning a pregnancy or who are pregnant and have been identified to be at risk (personal or male partner family or reproductive history) for the transmission of a clinically significant genetic condition to their offspring with associated morbidity and/or mortality. Harm may arise from having counselling and informed testing of the carrier status of the mother, their partner, or their fetus, as well as from declining to have this counselling and informed testing or from not having the opportunity for counselling and informed testing. Costs will ensue both from the provision of opportunities for counselling and testing, as well as when no such opportunities are offered or are declined and the birth of a child with a significant inherited condition and resulting morbidity/mortality occurs; these comprise not only the health care costs to the system but also the social/financial/psychological/emotional costs to the family. These recommendations are based on expert opinion and have not been subjected to a health economics assessment and local or provincial implementation will be required.
Guideline Update: This guideline is an update of four previous joint SOGC-CCMG Genetic Screening Guidelines dated 2002, 2006, 2008, and 2008 developed by the SOGC Genetic Committee in collaboration with the CCMG Prenatal Diagnosis Committee (now Clinical Practice Committee).

2016 Carrier Screening Recommendations: Primary principles for carrier screening

1. A primary discussion about the value and risk of reproductive carrier screening should be offered to all women/families considering a pregnancy (pre-conception) and to all pregnant women at their first prenatal visit, regardless of gestational age at the time of presentation. (III-A) (GRADE low/moderate)

2. Women should be asked, preferably in the pre-conception period, about a family history or personal manifestations of intellectual disability, muscular dystrophy, or bleeding disorders. Particular attention should be paid to X-linked conditions such as Fragile X syndrome, Duchenne/Becker muscular dystrophy (1/4000 male births), hemophilia A (1/5000 male births), and hemophilia B (1/30,000 male births). (III-A) (GRADE low/moderate)

3. A positive history of potential genetic/syndromic and chromosomal disorders as well as congenital anomalies, intellectual disability, stillbirth, sudden death, and other major health concerns such as cardiomyopathy, epilepsy, hearing loss, autism, and psychiatric disorders obtained as part of a three-generation pedigree review requires timely consultation referral to a reproductive genetic provider. (III-A) (GRADE low/moderate)

4. Genetic counselling should be offered to women/families identified as being at risk of transmission of an inherited condition based on a three-generation pedigree review, ethnic background, or past medical/obstetrical history. Information on ethnic origin and province/country of recent family residence may be helpful in choosing appropriate screening studies. Direct gene mutation or expanded next generation gene sequencing testing should be discussed as part of the informed consent process. (II-2A) (GRADE moderate/moderate)

5. When both reproductive partners are identified as carriers of the same autosomal recessive condition, the couple should be promptly referred for formal genetic counselling, preferably before conception or as early in the pregnancy as possible due to the complexity of the counselling/informed consent process and the 25% transmission risk to their offspring. (II-3A) (GRADE moderate/moderate)

Fragile X syndrome and related disorders

1. Fragile X syndrome is an X-linked condition with significant clinical implications for the carrier and her relatives. Any woman with a personal or family history of Fragile X- or Fragile X mental retardation 1–related disorders; unexplained intellectual disability or developmental delay; autism; ovarian insufficiency with elevated follicle stimulating hormone at age < 40 years of unknown etiology; or any woman with a family history of male relatives with developmental delay, autism, or isolated cerebellar ataxia and tremor should be offered screening for this condition. (II-2A) (GRADE moderate/moderate)

2. History alone is appropriate for consultation by a medical genetics specialist, as family confirmation can be difficult to obtain and may delay carrier testing, especially if pregnant. (II-2A) (GRADE moderate/moderate)

3. Fragile X carrier testing must only occur after detailed genetic counselling and informed consent from the woman to be tested has been obtained. (III-A) (GRADE low/moderate)

4. Population carrier screening for Fragile X syndrome in all women of reproductive age cannot be recommended at this time. (II-2D) (GRADE moderate/moderate)

X-linked hemophilia

1. A maternal family history of bleeding disorders in a woman’s male relatives (father, brother and/or maternal uncles) requires genetic counselling and the offer of carrier testing for the specific bleeding disorder in the family. If the diagnosis is unknown or cannot be confirmed, carrier testing for hemophilia A and B should be offered.

Thalassemia/hemoglobinopathies

1. Carrier screening for hemoglobinopathies should be offered to women/families from ethnic backgrounds with a reported increased carrier frequency, when red blood cell indices reveal a mean cellular volume < 80 fl, or electrophoresis reveals an abnormal hemoglobin type. However, the use of ethnicity alone in the carrier risk identification process may create screening inconsistency and missed opportunity for carrier identification, with both obstetrical and fetal implications. High clinical suspicion is required as well. Screening should be done in the pre-conception period or as early into the pregnancy as possible. (II-2A) (GRADE moderate/moderate)

2. Carrier screening for thalassemia/hemoglobinopathies should be offered by the most responsible health care provider or reproductive genetic provider and include:

- Complete blood count
- Hemoglobin (Hb) electrophoresis (HE) or Hb high performance liquid chromatography (HHPLC)
- Quantification of Hb alpha 2 and fetal Hb
- Serum ferritin/H bodies (blood smear stain using brilliant cresyl blue) if microcytosis (mean cellular volume < 80 fl) and/or hypocromia (mean cellular Hb < 27 pg) in the presence of a normal HE or HHPLC assessment. (II-2A) (GRADE moderate/moderate)

3. If the female thalassemia screening results are abnormal, a hemoglobinopathy screening protocol should be undertaken for the male partner. (II-A) (GRADE low/moderate)

4. If both reproductive partners are found to be carriers of thalassemia or a combination of thalassemia and hemoglobin variant, they should be referred for formal genetic counselling (reproductive risks, recommended prenatal testing, and diagnostic management). (II-3A) (GRADE moderate/moderate)

Cystic fibrosis

1. Cystic fibrosis carrier screening pre-conception or in pregnancy should be offered to women/families who may be at an increased risk of an affected child due to ethnic background, personal or family history, or clinical manifestations of this condition in themselves or the pregnancy. Pre-conception carrier screening is preferable. (II-2A) (GRADE moderate/moderate)

2. The routine screening of all pregnant women to determine their cystic fibrosis carrier status is not recommended at this time. (III-D) (GRADE low/moderate)

3. French Canadians with family origins from the Quebec regions of Saguenay Lac-St-Jean and Charlevoix should be routinely offered cystic fibrosis carrier status is not recommended at this time. (III-D) (GRADE low/moderate)

Ashkenazi Jewish population

1. The definition for an Ashkenazi Jewish (AJ) heritage is determined as having at least one grandparent of AJ background. (III-A) (GRADE moderate/moderate)

2. For couples of Ashkenazi Jewish heritage, routine carrier screening for Tay-Sachs disease (carrier frequency 1/30); Canavan disease (carrier frequency 1/37–1/53); and familial dysautonomia (carrier
3. When only one member of a couple is of Ashkenazi Jewish ancestry, screening for the couple should be offered for Tay-Sachs disease only using biochemical hexosaminidase enzyme activity. (II-2A) (GRADE moderate/moderate)

4. When only one member of a couple is of Ashkenazi Jewish (AJ) ancestry, screening should not be offered for familial dysautonomia and Canavan disease because of low carrier frequency in individuals who are not of AJ heritage and concurrent limitations of carrier screening in this situation. (III-D) (GRADE moderate/moderate)

5. Additional Ashkenazi Jewish carrier screening should be offered when a positive family is elicited for one of the conditions known to be present at an increased frequency in this population (associated carrier frequencies are listed): Bloom syndrome 1/104; Fanconi anemia group C 1/89; Niemann-Pick type A 1/90; mucolipidosis type IV 1/100–127; Gaucher disease 1/18; glycogen storage disease type 1a 1/64; familial hyperinsulinism 1/68; maple syrup urine disease 1/97; dihydrolipoamide dehydrogenase deficiency 1/107; CF 1/28; Usher syndrome 1/120; nemaline myopathy 1/168; Joubert syndrome 1/92; Walker-Warburg syndrome 1/150. (III-A) (GRADE moderate/high)

**Founder effects**

1. Women/families whose families have originated from the Quebec Bas-St-Laurent (Rimouski) and Gaspesie regions as well as from adjoining New Brunswick territories, or whose family history is positive for this condition, should be offered Tay-Sachs carrier screening due to carrier frequency of 1/14 in this particular geographic aggregate. (II-2A) (GRADE high/high) As well, couples for whom each partner has at least one grandparent originating from Saguenay Lac-St-Jean/Charlevoix region should be offered screening for the four common conditions present at a higher carrier frequency in this population due to founder effects: Tyrosinemia type I (carrier frequency 1/19), congenital lactic acidosis from Saguenay Lac-St-Jean (Leigh syndrome French Canadian type, carrier frequency 1/23), spastic ataxia, Charlevoix-Saguenay type (carrier frequency 1/23), and agenesis of the corpus callosum with peripheral neuropathy (carrier frequency 1/23).

2. Careful three-generation family review for couples originating from regions with founder effects is mandatory, as other clinically relevant conditions may present with a higher incidence in these populations (e.g., cerebro-oculo-facio-skeletal syndrome in aboriginal Manitoba populations; myotonic dystrophy type I, congenital disorder of glycosylation type 1B, Tay-Sachs disease, and mucolipidosis II in populations from Saguenay Lac-St-Jean; and neuronal ceroid-lipofuscinosis and Bardet Biedl in populations originating from Newfoundland). The maternity care provider should remain alert to these specific regional founder effects.

3. Women/families of Cree ancestry should be asked about previous screening for Cree leukoencephalopathy and Cree encephalitis, two devastating congenital neurodegenerative disorders with a founded effect in this population, for whom screening programs have been developed in their regional communities. If the couple has not been screened or does not recall their screening results, screening for these conditions should be undertaken as early as possible, ideally in the pre-conception period.

4. Women/families with a possible heritage from Amish, Mennonite, and Hutterite religious groups based on family history and/or geographic or religious settlement locality should have a three-generation pedigree with founder effect considerations and referral to provincial medical genetic services if increased or possible connection is identified.

**Spinal muscular atrophy**

1. Routine spinal muscular atrophy (SMA) reproductive carrier screening cannot be recommended at this time as laboratory infrastructures as well as clinical and counselling resources are not universally available across Canada. However, a family history of SMA should alert the provider to an increased carrier risk for one member of the couple. Prompt referral to a reproductive medical genetics provider is strongly recommended (education and counselling). (II-2D) (GRADE moderate/moderate)

**Diagnosis and follow up**

1. Directed diagnostic fetal or neonatal laboratory (genetic/metabolic) testing or directed diagnostic postmortem pathology/autopsy evaluation is recommended to allow for appropriate diagnostic and recurrence risk counselling. (III-A) (GRADE low/moderate)

2. A timely postnatal follow up by the most appropriate or available primary care physician, geneticist, obstetrician, neonatologist, or maternal fetal medicine provider(s) should be offered for any couple with a pregnancy established to be affected with an inherited condition identified by either prenatal or neonatal testing. (III-A) (GRADE low/moderate)

3. Parents should be advised and educated about the estimated genetic recurrence risk in a subsequent pregnancy. (III-A) (GRADE low/moderate)

**Direct-to-consumer or self-pay physician ordered carrier testing**

1. Women/families who choose to undergo testing though either direct-to-consumer genetic testing or self-pay physician ordered testing, and who are subsequently found to be carriers of an inherited condition, have to be made aware prior to testing that access to formal genetic counselling may be limited. As well, additional confirmatory testing may be required but access may be limited by local resources or availability of the test in accredited laboratories. Ideally, individuals or couples who have been identified to be “at risk” for the transmission of a clinically significant genetic condition to their offspring by their primary care giver should be referred in the pre-conception period to a reproductive medical genetic provider for education and discussion of the implications for the couple and their offspring. (III-A) (GRADE low/moderate)
INTRODUCTION

This reproductive genetic carrier screening guideline is targeted for the most responsible health provider (MRHP) in collaboration with reproductive genetic medicine providers. It provides an updated review of the recommended genetic screening assessment and testing for establishing the potential carrier risk status for all pregnant females due to the rapidly developing laboratory technology and techniques and new screening considerations. Reproductive genetic carrier assessment, counselling, and management will rely on a timely maternity/multidisciplinary collaboration.

Reproductive genetic carrier screening, DTC testing, self-pay provider ordered carrier screening, and neonatal metabolic screening have synergy and clinical overlap but present significant challenges to both health care providers and patients with respect to education, ethical use, timing of screening, cost effectiveness, and clinical utility. Molecular technology, with next generation sequencing, provides comprehensive gene sequencing analysis for a panel of over 100 carrier genes with a three-week turnaround time but at a cost that provincial health care will not cover. The option of this technology should be part of the informed consent process.

Harper defines a carrier as “an individual who possesses in a heterozygous state, the mutated gene determining an inherited disorder and who is essentially healthy at the time of study.” This definition highlights several important points:

1. Consideration for screening is usually made for single gene disorders (monogenic inheritance).
2. The health status of a heterozygote is usually unaffected for AR conditions.
3. Generally, the carrier is healthy at the time of screening, but the age of onset for AD and XL conditions will impact the carrier’s state of health or the recognition of an underlying genetic condition with diagnostic testing. It is important, for these undiagnosed adult onset disease(s), which could be identified through prenatal carrier testing, that this possibility is discussed with the patient/couple prior to undertaking investigations.
4. While the risk of transmission of a heterozygous variant to the offspring is 50%, the risk for an affected child is generally low for AR conditions in the general population with no family history (unless consanguinity is present) but is 50% for AD and XL conditions.

This document provides evidence based clinical guidance towards pre-conception, prenatal, and neonatal carrier status screening for both the primary care, low-risk, maternity provider (midwifery, family medicine, nursing) and the complex obstetrical and neonatal providers (obstetrics, maternal fetal medicine, reproductive genetics, neonatology, reproductive endocrinology infertility).

Screening Approaches/Options: Prenatal/Pre-conception Genetic Carrier Identification (by the Conventional or DTC Testing or Private Pay Physician Ordered Carrier Testing) and Newborn Metabolic Screening

There are three current scenarios amenable to reproductive screening for inherited monogenic disorders:

1. The traditional “medical guideline recommended” pre-conception/prenatal screening process;
2. The postnatal provincial newborn metabolic screening programs;
3. The more recent access to DTC or private pay physician ordered pan ethnic expanded pre-conception carrier testing with next generation sequencing technology.

The MRHP should have an understanding about the differences in these screening approaches, their diagnostic impact, and the timing of testing in relation to counselling for the pregnancy.

For medically recommended carrier screening, the methods of carrier detection are variable and include, but are not restricted to, molecular analysis, enzymatic or biochemical testing, and cytogenetic studies. Timing of testing can be either pre-conception or during the prenatal period.

The accepted criteria for a carrier screening protocol are:

- AR/AD/XL disorders with expected significant clinical impact and morbidity during an individual’s lifetime
- Intervention is available and alters the clinical outcome
- High frequency of expected carriers in the population
- Availability of cost effective but reliable testing (high positive predictive value and detection rate; low false positive rate)
- Appropriate access for the patient to genetic counselling and an informed consent process
- Voluntary participation or request by the patient

The new consideration and discussion with the pre-conception or pregnant woman is related to the mandated postnatal newborn metabolic screening.
programs that occur in every province with an extensive list of screened conditions.

The third and newer industry and technology driven approach, the DTC or the private pay physician ordered expanded pre-conception carrier testing, can have a broad and a very different meaning based on the area of medical investigation or the reason(s) for undertaking testing. DTC-GT (also known as at-home genetic testing) refers to genetic tests that are marketed directly to consumers via the media. This form of testing provides access to a person’s genetic information without necessarily involving a health care professional or insurance company in the process.3

DTC testing has so far targeted the following areas:

- Non-invasive fetal sex determination
- Non-invasive paternity testing
- Carrier screening for inherited disorders or ethnic directed testing, such as AJ heritage testing or pan ethnic testing due to increasing inter-ethnic pregnancies
- Predisposition to disease susceptibility

There are, at this time, no standards regulating this industry and accuracy, validity, sensitivity, specificity, and clinical utility are generally not discussed or disclosed to the consumer. As stated in the National Institute of Health Genetics Home Reference on DTC, “This genetic testing has significant risks and limitations. Consumers are vulnerable to being misled by the results of unproven or invalid tests. Without guidance from a healthcare provider, they may make important decisions about treatment or prevention based on inaccurate, incomplete, or misunderstood information about their health. Consumers may also experience an invasion of genetic privacy if testing companies use their genetic information in an unauthorized way… Genetic testing provides only one piece of information about a person’s health—other genetic and environmental factors, lifestyle choices, and family medical history also affect a person’s risk of developing many disorders. These factors are discussed during a consultation with a doctor or genetic counselor, but in many cases are not addressed by DTC genetic tests.”5

Precision medicine (formerly called personalised medicine), on the other hand, is an emerging practice of medicine that uses an individual’s genetic profile to guide decisions with respect to the prevention, diagnosis, and treatment of disease. Examples of such testing would include:

- Genotyping of cancer type for specific targeted treatment
- Pharmacogenomics

These different screening approaches have identified and opened complex opportunities for individualized care and patient choice based on the potential genetic variations identified.

For this reproductive genetic guideline, the DTC or private pay approach will focus on personal genetic knowledge, informed choice, and situations where this evaluation has been completed pre-conception. However, concerns remain about the ability to integrate DTC or private pay genetic testing with appropriate genetic counselling such that individuals can make fully informed decisions based on their test results.

The Ethics of Parental Reproductive Genetic Carrier Testing

Pergament and Pergament stated, “Screening connotes a non-invasive approach to evaluating a pregnancy either by means of testing the prospective parents for their carrier status for single gene mutations or by the use of ultrasound and maternal serum markers for determining the risk of aneuploidy, open neural tube defects, and other structural anomalies associated with developmental and genetic syndromes. Screening provides a quantitative assessment of risk for a genetic disorder, compared with a diagnostic test, which leads to a ‘yes’/affected or ‘no’/unaffected result.”4

Population carrier screening for single gene disorders may reduce the risks for birth of an affected offspring. However, a negative carrier test result does not completely eliminate the risk of carrier status. This information is not always well understood or communicated to patients undergoing carrier screening testing. False negative carrier status, for example, when not all genes or variants for a particular condition are being evaluated, presents a potential risk for the couple to still have an affected child. In addition, issues of undisclosed non-paternity may add to the reproductive counselling challenge.5 Pregnancy outcomes that parents and health care providers aim to achieve from carrier testing will need to be defined in each case as well as the best personal or gestational timing for the carrier and pregnancy testing.5

Preconception screening

A recent editorial summarizes the issues around the expanded preconception carrier screening debate very well.5 The high throughput genotyping and sequencing approaches allow for the efficient and simultaneous screening of hundreds of genetic conditions. Recent endorsement for the use of this expanded carrier screening testing with genetic counselling and appropriate support for identified carriers indicated that benefits such as pre-conception planning,
prenatal diagnosis, condition specific counselling, and condition specific care could be met. Significant challenges underlying this approach are that patients will turn to providers for guidance on whether they (the patient) have a responsibility to optimize the conditions under which they will conceive. Providers will wrestle with this question, as they will have to balance between two desired outcomes consequent to testing; one focusing on the well-being of the future child (pre-conception beneficence), the other primarily considering the needs of the prospective parents. These implications related to the availability of DTC carrier testing remain unresolved at this time.

The provincial postnatal newborn metabolic screening program, on the other hand, is a provincially supported universal neonatal screening plan for which the needed medical and counselling structures are available to the population to whom screening is directed.

However, The Globe and Mail published an article in 2013 reporting that “Canada has no national standard for newborn screening” and highlighted the significant discrepancies between provinces regarding the number of conditions covered and the infrastructures available to the screened population, underlining the discrepancies in access to care across Canada.

**Neonatal diagnosis**

The provincially mandated newborn screening programs will likely impact the parental screening choices and their approaches/options for pre-conception and prenatal reproductive carrier screening. The lack of parental knowledge, prior to birth, about this postnatal newborn screening process is an important issue that needs to be considered by providers. Screening for conditions such as CF and certain hemoglobinopathies could be achieved either by the option of pre-conception/prenatal screening with prenatal diagnostic testing or by postnatal testing/screening (diagnosis). The list of newborn metabolic/endocrine conditions covered through newborn screening programs that would not usually be part of a prenatal screening/diagnosis protocol, unless the couple had been identified as carriers or had previously had an affected pregnancy, should be provided to the parents prenatally (Table 1).

**Prenatal or preconception screening and diagnosis**

Skirton et al. comment that newer maternal plasma cfDNA testing is an “easy test but a hard decision.” They studied the ethical issues concerning cfDNA testing for some AR disorders. They used a qualitative cross-sectional design (focus groups or interviews) to study 27 individuals of reproductive age, who were carriers of one of four AR conditions (thalassemia, SC disease, CF, or SMA). Participants were aware of the routine availability of invasive DNA testing for these AR disorders and that cfDNA testing for these conditions would only determine if the fetus was carrier of the paternal variant (i.e., invasive testing would be required to determine if the fetus was only carrier or affected).

Based on the conclusions of this study it is suggested that for such testing:

1. Written consent should be obtained
2. Adequate time (and possible repeat counselling) should be allowed for decision making
3. When a pregnant women requests fetal testing but the biologic father declines carrier testing, he should be made aware that fetal results may reveal his carrier status. Strategies to manage this situation should be anticipated and put into place.

This study concluded that non-invasive prenatal diagnosis has numerous advantages for couples at risk of affected offspring by AR disease, but that it is important for health professionals to be aware of the potential ethical issues that may arise and that they should be prepared to address them proactively. Moreover, cfDNA testing (usually undertaken at around 10 weeks of gestation) may delay timely access to invasive diagnostic testing by chorionic villous sampling (usually performed between 10 and 12 weeks and prior to 13 weeks gestation).

Hill et al. used a similar interview approach for carriers of CF, SC, and thalassemia. They found the patient opinions about cfDNA usage to be usually positive. The participants valued the opportunity to have safe and early gestational testing. The authors anticipated an increased uptake of the testing even amongst women who may have previously declined such analysis.

Additional issues were highlighted and included:

1. Participants’ concerns were directed at ensuring the need for high accuracy for tests that may lead to decisions concerning pregnancy termination.
2. There were also concerns that less consideration may be given to having a simple blood test compared to undertaking invasive fetal testing (amniocentesis, chorionic villus sampling).
3. Participants felt that cfDNA testing should be offered through specialist (non-generalist) services to ensure appropriate non-directive genetic counselling and support.
4. Maintenance of all testing options was important (non-invasive, invasive) for maximal patient choice.

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(HEAR: hearing screening; CH: congenital hypothyroidism; CAH: congenital adrenal hyperplasia; HB S/S: Sickle cell anemia; HB S/C: Sickle-C disease; HB S/A: S-beta thalessemia; BIO: biotinidase; GALT: transferase deficient galactosemia (classic); CF: cystic fibrosis; CCHD: critical congenital heart disease; SCID: severe combined immunodeficiency)
Table 1. continued
Core Conditions Part II
(A universally offered but not yet required; B offered to selected populations; C testing required or offered universally but not yet implemented; U screened by urine)

<table>
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<tr>
<th>Province Territory</th>
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(FAD: fatty acid disorders; OAD: organic acid disorders; AAD: amino acid disorders; CUD: carnitine uptake defect; LCHAD: long-chain hydroxyacyl-CoA dehydrogenase; MCAD: medium-chain acyl-CoA dehydrogenase; TFP: trifunctional protein; VLCAD: very long-chain acyl-CoA dehydrogenase; GA-1: glutaric academia type 1; HMG: 3-hydroxy 3-methylglutaric aciduria; IVA: isovaleric acidemia; 3-MCC: 3-methylcrotonyl-CoA carboxylase; CBL: A,B methylmalonic academia (vitamin B12 disorder); BKT: beta ketothiolase; MUT: methylmalonic academia (methylmalonyl-CoA mutase); PROP: propionic academia; MCD: multiple carboxylase; ASA: argininosuccinate academia; CIT: citrullinemia type 1; HCY: homocystinuria; MSUD: maple syrup urine disease; PKU: phenylketouria / hyperphenylalaninemia; TYR-1: tyrosinemia type 1)
Previous Recommendations by the SOGC and the CCMG on Reproductive Carrier Screening

The SOGC Genetic Committee in collaboration with the CCMG Clinical Practice Committee has published a number of reproductive carrier screening guidelines for directed gene mutation testing:

- Thalassemia/Hemoglobinopathies carrier testing (October 2008)
- Fragile X syndrome (September 2008)
- AJ descent carrier testing (April 2006)
- CF carrier testing (August 2002)

The recommendations from those previous SOGC guidelines (using the Canadian Task Force on Preventive Health Care evidence statements and grading) included:

1. All carrier screening should ideally be undertaken in the pre-conception period (III-A).
2. For CF, universal CF carrier screening was not recommended (III-A), screening should be offered only to at-risk individuals determined by clinical manifestations or family history (II-2A).
3. For CF, routine screening for Tay-Sachs disease, Canavan disease, and familial dysautonomia is recommended while other AJ disease screening should only be considered with a positive family history (III-A).
4. For Fragile X female carrier screening is recommended for women with a positive family history of affected males. Fragile X tremor/ataxia, or premature ovarian failure should be offered to women who are identified as belonging to an ethnic population associated with a higher prevalence of hemoglobinopathy carriers (II-2A).
5. All carrier screening should ideally be undertaken in the pre-conception period (III-A).

2016 Carrier Screening Recommendations

- Primary principles for carrier screening:
  1. A primary discussion about the value and risk of reproductive carrier screening should be offered to all women/families considering a pregnancy (pre-conception) and to all pregnant women at their first prenatal visit, regardless of gestational age at the time of presentation. (III-A) (GRADE low/moderate)

- Table 1. continued

Secondary Target Conditions Part III

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<th>Prov/Territory</th>
<th>FA</th>
<th>CPT-1a</th>
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(FA: fatty acid disorders; OA: organic acid disorders; AA: amino acid disorders; CACT: carnitine acylcarnitine translocase; CPT-1a: carnitine palmitoyltransferase I; CPT-2: carnitine palmitoyltransferase II; DE-RED: dienoyl-CoA reductase; GA-II: glutaric academia type II; MCKAT: medium-chain ketoxacyl-CoA thiolase; M/SCHAD: medium/short chain L-3-hydroxy acyl-CoA dehydrogenase; SCAD: short-chain acyl-CoA dehydrogenase; 2M3HBA: 2-methyl-3-hydroxybutyric aciduria; 2MBG: 2-methylbutyryl-CoA dehydrogenase; CBL C,D: methylmalonic academia C, D; IBG: isobutyryl-CoA dehydrogenase; MAL: malonic academia; ARG: arginemia; BIOPT-BS: defects of biotin cofactor biosynthetic; BIOPT-RG: defects of biotin cofactor regeneration; CIT-II: citrullinemia type II; H-PHE: benign hyperphenylalaninemia; MET: hypermethionemia; TYR-II: tyrosinemia type II; TYR-III: tyrosinemia type III; GALE: galactose epimerase; GALK: galactokinase; Hbg: variant haemoglobin)
2. Women should be asked, preferably in the pre-conception period, about a family history or personal manifestations of intellectual disability, muscular dystrophy, or bleeding disorders. Particular attention should be paid to X-linked conditions such as Fragile X syndrome, Duchenne/Becker muscular dystrophy (1/4000 male births), hemophilia A (1/5000 male births), and hemophilia B (1/30000 male births). (III-A) (GRADE low/moderate)

3. A positive history of potential genetic/syndromic and chromosomal disorders as well as congenital anomalies, intellectual disability, stillbirth, sudden death, and other major health concerns such as cardiomyopathy, epilepsy, hearing loss, autism, and psychiatric disorders obtained as part of a three-generation pedigree review requires timely referral to a reproductive genetic provider. (III-A) (GRADE low/moderate)

4. Genetic counselling should be offered to women/families identified as being at risk of transmission of an inherited condition based on a three-generation pedigree review, ethnic background, or past medical/obstetrical history. Information on ethnic origin and province/country of recent family residence may be helpful in choosing appropriate screening studies. Directed gene mutation or expanded next generation gene sequencing testing should be discussed as part of the informed consent process. (II-2A) (GRADE moderate/moderate)

5. When both reproductive partners are identified as carriers of the same autosomal recessive condition, the couple should be promptly referred for formal genetic counselling, preferably before conception or as early in the pregnancy as possible due to the complexity of the counselling/informed consent process and the 25% transmission risk to their offspring. (II-3A) (GRADE low/moderate)

What is the new evidence based information available to support a change in the SOGC recommendations for AR and XL reproductive carrier screening?

As molecular and biochemical technology has improved, women/families want and expect more information about genetic carrier screening and the technology value for prenatal screening and diagnosis.

Maruotti et al. report 20 years of experience with a population cohort undergoing screening for beta thalassemia, CF, and other inherited disorders. The reported indications for parental screening for this population were (1) an affected pregnancy/child, (2) cascade screening (screening based on a detailed family history review), (3) routine prenatal screening/pre-conception screening, (4) fetal ultrasound findings, and (5) history of one affected parent. In this cohort, 549 rare disorders were identified and diagnosed in the context of a positive family history. Of those, 12.6% were AD, 43.2% were AR, and 43.2% were XL. The prevalence of these rare genetic disorders was distributed as such: Incidence of 1/50 000 (67.8%), between 1/50 000 and 1/100 000 (18%), and < 1/100 000 (14.2%). The authors concluded that the level of required counselling expertise to screen for these rare disorders has increased due to the additional genetic knowledge available in the public arena. This need for more detailed prenatal counselling was echoed by Minkoff and Berkowitz. They concluded that “All women, not just those surpassing some poorly defined level of risk, deserve genetic counselling.”

The provincial reproductive genetic providers will need to plan and to strategize on how the carrier screening counselling and testing services can or will be available as the demand increases.

The inherited conditions for which prenatal screening is recommended or could be considered include XL conditions, hemoglobinopathies, CF, conditions more prevalent in the AJ population or those resulting from a regional founder effect, and SMA.

FXS
FXS is the most common form of inherited intellectual and developmental disability, with an estimated prevalence of 1/3600 males and 1/4000–1/6000 females. The diagnosis of FXS in the child can be delayed, with an average age at diagnosis of 3 years. FXS is an XL disorder caused in the majority of cases by an increased number of CGG trinucleotide repeats in the untranslated region of the Fragile X gene (FMR1 gene) located on the X chromosome. Four clinical presentations are classically associated with these CGG repeats, as they are transmitted from the parent via the gamete to the conceptus: unaffected < 45 repeats, intermediate 45–54 repeats, premutation 55–200 repeats, to full mutation > 200 repeats. The number of maternal CGG trinucleotide repeats correlates with the risk of expansion to a full mutation in the next generation (2% for repeat size of 60–69; 32% for repeat size of 70–79; 74% for repeat size of 80–89; 94% for repeat size of 90–99; 98% for repeat size of 100–200). The ACOG defined their criteria for FXS testing as:

- Any female with a personal or family history of FXS- or FMR1-related disorders, unexplained intellectual disability...
or developmental delay in males or females, autism, ovarian insufficiency with elevated FSH at age < 40 years with an unknown etiology (definition for the diagnosis of primary ovarian insufficiency can be made definitely in women younger than age 40 years with irregular menses in association with FSH concentrations in the post-menopausal range as defined by the measuring laboratory)

- Men with an isolated cerebellar ataxia with tremor or congenital cognitive impairment
- Female requesting Fragile X testing

Routine prenatal Fragile X carrier screening has been debated, with expert reproductive genetic opinion supporting routine prenatal maternal screening. If routine prenatal screening were to be adopted, female pre-conception testing with informed consent and counseling would be the preferred approach. The complexity of counseling given the potential change in the number of CGG repeats observed between generations and the clinical associations that these may have should not be underestimated.

At the present time, Fragile X carrier screening in Canada should be limited to those women with a positive personal or family history using the clinical scenarios listed below. Population carrier screening for FXS in all women of reproductive age cannot be recommended due to the inability for the Canadian reproductive genetic counselling resources to handle the service volume required.

### Carrier Screening Recommendations

1. Fragile X syndrome is an X-linked condition with significant clinical implications for the carrier and her relatives. Any woman with a personal or family history of Fragile X- or Fragile X mental retardation 1—related disorders; unexplained intellectual disability or developmental delay; autism; ovarian insufficiency with elevated follicle stimulating hormone at age < 40 years of unknown etiology; or any woman with a family history of male relatives with developmental delay, autism, or isolated cerebellar ataxia and tremor should be offered screening for this condition. (II-2A) (GRADE moderate/moderate)

### Table 3. Some common AD conditions are summarized along with their live born incidence as examples of conditions that could potentially be identified through family history taking

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Myotonic dystrophy</td>
<td>1/8000 live births</td>
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<tr>
<td>Neurofibromatosis type I</td>
<td>1/3000 live births</td>
</tr>
<tr>
<td>Adult onset polycystic kidney disease</td>
<td>1/800 live births</td>
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<tr>
<td>Tuberous sclerosis</td>
<td>1/5800 live births</td>
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</tbody>
</table>
2. History alone is appropriate for consultation by a medical genetics specialist, as family confirmation can be difficult to obtain and may delay carrier testing, especially if pregnant. (II-2A) (GRADE moderate/moderate)

3. Fragile X carrier testing must only occur after detailed genetic counselling and informed consent from the woman to be tested has been obtained. (III-A) (GRADE low/moderate)

4. Population carrier screening for Fragile X syndrome in all women of reproductive age cannot be recommended at this time. (II-2D) (GRADE moderate/moderate)

Other XL Conditions

Bleeding disorders

Hemophilia A (decreased factor VIII) and hemophilia B (factor IX mutations) are XL bleeding disorders with a prevalence in males of 1/5000 (A) and 1/30,000 (B). Carrier screening and prenatal diagnostic testing are preferably performed by molecular diagnosis of the familial related gene variant, but in certain situations, indirect methods may be required. For female relatives of affected males, knowledge of the familial mutation can facilitate education, counselling, carrier status determination, and prenatal diagnosis if carrier status is identified and patient provides informed consent.

2016 Carrier Screening Recommendations for X-linked hemophilia:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Duchenne/Becker muscular dystrophy</td>
<td>1/3000–1/4000 male births</td>
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<tr>
<td>Fabry's disease</td>
<td>1/80 000–1/117 000 male births</td>
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<tr>
<td>Fragile X mental retardation</td>
<td>1/5000 male births</td>
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<tr>
<td>Hemophilia A (factor VIII)</td>
<td>1/5500 male births</td>
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<tr>
<td>Hemophilia B (factor IX)</td>
<td>1/30 000 male births</td>
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<tr>
<td>Immune deficiency (SCID) XL and AR</td>
<td>1/30 000 live births</td>
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<td>XL adrenoleukodystrophy</td>
<td>1/20 000–1/50 000</td>
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<tr>
<td>XL hydrocephalus with stenosis of the aqueduct of Sylvius (L1 syndrome)</td>
<td>1/30 000</td>
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</table>

Thalassemia/Hemoglobinopathies

Hemoglobinopathies are reported to constitute the most common recessive monogenic disorders worldwide. Several guidelines are available for screening and management of these red blood cell Hb pathologies in pregnancy. Variants in the genes responsible for the synthesis of Hb chains result in altered synthesis (thalassemia) or structural changes (sickling). The clinical entities with severe outcomes requiring screening, counselling, and prenatal diagnosis are:

- Variants in the Hb alpha locus leading to Bart’s hydrops fetalis syndrome (homozygous deletion or alpha0 thalassemia)

The carrier testing protocol for the suspected hemoglobinopathies is well documented (complete blood counts, mean cellular volume size, hemoglobin pattern analysis, quantification of Hb alpha 2 and fetal Hb, iron status). Details are included in the references.

Geographic locations associated with increased hemoglobinopathy carrier prevalence are Southeast Asia, the Mediterranean region, and Africa. The alpha thalassemia trait prevalence in Hong Kong is 4% to 6% and 30% to 40% in Laos and Thailand. The predominant Southeast Asian mutation reported is alpha0 (−/−) while the Mediterranean populations have a carrier prevalence of 8% for alpha thalassemia, 8% for beta thalassemia, 2.5% for gamma globin gene variants, and 2% for beta globin gene variants. Southeast Asia and Northern Thailand demonstrate a high prevalence of Hb E (50%).

Carrier screening for thalassemia and hemoglobinopathies has received much attention related to the ethnic carrier prevalence in different geographic areas. Strategies for screening have been implemented and include screening at the school level, pre-conception screening, and screening in early pregnancy. Education, protocols, and guidelines assist practitioners in early identification of at risk females and their potential reproductive partners.

Ethnic identification, once the patient/couple has left their high prevalence geographic location, makes ethnic recognition a very poor screening tool. Laboratory evaluations should be used to identify the carrier status through high clinical suspicion, family history review, or other
investigative reasons for laboratory testing. Ethnic diversification has led to universal screening of pregnant women in some countries.

**Carrier Screening Recommendations for Thalassemia/Hemoglobinopathies**

The following individuals should be offered screening for this group of conditions:

1. Carrier screening for hemoglobinopathies should be offered to women/families from ethnic backgrounds with a reported increased carrier frequency, when red blood cell indices reveal a mean cellular volume < 80 fl, or electrophoresis reveals an abnormal hemoglobin type. However, the use of ethnicity alone in the carrier risk identification process may create screening inconsistency and missed opportunity for carrier identification, with both obstetrical and fetal implications. High clinical suspicion is required as well. Screening should be done in the pre-conception period or as early into the pregnancy as possible. (II-2A) (GRADE moderate/moderate)

2. Carrier screening for thalassemia/hemoglobinopathies should be offered by the most responsible health care provider or reproductive genetic provider and include:
   - Complete blood count
   - Hemoglobin (Hb) electrophoresis (HE) or Hb high performance liquid chromatography (HHPLC)
   - Quantification of Hb alpha 2 and fetal Hb
   - Serum ferritin/H bodies (blood smear stain using brilliant cresyl blue) if microcytosis (mean cellular volume < 80 fl) and/or hypochromia (mean cellular Hb < 27 pg) in the presence of a normal HE or HHPLC assessment. (II-2A) (GRADE moderate/moderate)

3. If the female thalassemia screening results are abnormal, an hemoglobinopathy screening protocol should be undertaken for the male partner. (III-A) (GRADE low/moderate)

4. If both reproductive partners are found to be carriers of thalassemia or a combination of thalassemia and hemoglobin variant, they should be referred for formal genetic counselling (reproductive risks, recommended prenatal testing, and diagnostic management). (II-3A) (GRADE moderate/moderate)

**CF**

CF is the most common clinically significant AR disorder in Northern Europe where the prevalence of this condition is approximately 1 in 2500 and the carrier frequency about 1 in 25. CF pathogenic variants show varying degrees of genotype-phenotype correlation with severity of lung and gastrointestinal symptoms.

Recommendations by the National Society of Genetic Counselors and ACOG #486 regarding CF molecular carrier testing emphasize that relationship between the CF transmembrane conductance regulator genotype and the CF phenotype has become complex and variable. They make ten recommendations including that “Carrier testing for CF should be offered to all women of reproductive age, regardless of ancestry, preferably during the period of pre-conception. CF carrier testing should also be offered to an individual with a family history of CF, and to partners of mutation carriers and people with CF.” Another recommendation deals with the residual risk associated with negative and indeterminate carrier screening results and states that, “Clients who have a negative CF carrier screening result should be informed of their reduced or residual risk to have a child with CF, and of the possibility of their child having an abnormal CF newborn screen if one partner is a CF carrier.” Finally, they state that “When both parents are known CF carriers, available prenatal and pre-implantation diagnostic testing should be offered. For couples ‘at risk’ of or who continue a pregnancy known to have an affected CF fetus, prenatal counselling with implementation of a plan for postnatal evaluation should be offered.”

Australian experiences with 10 CF carrier couples, found all couples were unprepared for a positive carrier screening result. All couples changed their reproductive behaviour as a result of their newly identified carrier status. Two couples with an affected pregnancy reported feelings of devastation and grief upon receiving their prenatal diagnosis result and terminated their pregnancy.

A specific Canadian geographic population has been identified at an increased risk for CF carrier status. For people with family origins from the Quebec regions of Saguenay Lac-St-Jean and Charlevoix, incidence of CF carrier status is 1/15 and 1/20, respectively. French Canadians from these two regions should be offered routine CF carrier screening. CF carrier screening is also offered to couples during a pregnancy when fetal echogenic bowel is identified by prenatal ultrasound. CF detection rate will vary depending on parental ethnicity.

A non-invasive prenatal assay for CF that could reliably predict paternal mutations in all control and maternal plasma samples has been reported. For 142 adults, either carriers of or affected by CF, only 43.5% reported a willingness to have invasive testing for CF, while
94.4% indicated that they would pursue a non-invasive approach. The use of a next generation sequencing panel to detect 10 common CF mutations could eventually provide a non-invasive prenatal screening option for around 30% of parents who are carriers of CF mutations. However, as for aneuploidy screening through non-invasive prenatal testing, confirmatory diagnostic testing using an invasive prenatal diagnosis method would be necessary prior to making irrevocable decisions regarding the pregnancy plan.

2016 Carrier Screening Recommendations for Cystic Fibrosis:

1. Cystic fibrosis carrier screening pre-conception or in pregnancy should be offered to women/families who may be at an increased risk of an affected child due to ethnic background, personal or family history, or clinical manifestations of this condition in themselves or the pregnancy. Pre-conception carrier screening is preferable. (II-2A) (GRADE moderate/moderate)

2. The routine screening of all pregnant women to determine their cystic fibrosis carrier status is not recommended at this time. (III-D) (GRADE: low/moderate)

3. French Canadians with family origins from the Quebec regions of Saguenay Lac-St-Jean and Charlevoix should be routinely offered cystic fibrosis carrier screening due to the increased carrier frequency of 1/15 and 1/20, respectively, in individuals originating from these regions. (II-2A) (GRADE high/high) (see glossary for identified Quebec geographic regions)

AJ Screening

Ferreira et al. have reviewed the AJ recommendations and provided their clinical opinion regarding an acceptable approach to carrier screening. They recommend that routine screening be offered to all individuals of AJ descent (defined as having at least one AJ grandparent) who are considering a pregnancy or are currently pregnant and have not as yet had screening completed for the following conditions with population identified carrier frequencies of 1/30—1/40; Tay-Sachs disease (1/30), Canavan disease (1/40), CF (1/28) and familial dysautonomia (1/32).

Tay-Sachs disease testing should include hexosaminidase enzymatic activity as sensitivity of the enzymatic assay is over 98% and is not moderated by ethnic/cultural background.

Molecular testing of two common variants has a detection rate of 94% in people of AJ descent, but the detection rate is unknown for other ethnicities.

The American College of Medical Genetics and Genomics suggests that Niemann-Pick type A (1/90), Mucopolysaccharidosis type IV (1/127), Gaucher disease (1/18), Fanconi anemia group C (1/89) and Bloom syndrome (1/100) could also be added to a minimal AJ carrier screening panel. Both members of the couple should undergo testing, and pre- and post-test counselling would be required, as a residual risk remains even with a negative screening result. In Canada, considerations should be given to the repercussions on clinical and laboratory resources to implementation of an extended AJ screening panel, particularly in the context of a universal health care system.

For example, Gaucher disease, although having a high incidence of carriers in the AJ population (1/18), is a condition that, like hereditary hemochromatosis, demonstrates extremely variable expression and a poor genotype-phenotype correlation, with some homozygous carriers of pathogenic variants being asymptomatic well into their adulthood. Carrier screening is thus made difficult by this lack of genotype-phenotype correlation. It is quite possible, during the process of screening, to uncover an asymptomatic affected homozygous individual. This makes counselling in a prenatal setting even more uncertain.

2016 Carrier Screening Recommendations for Ashkenazi Jewish Population:

1. The definition for an Ashkenazi Jewish (AJ) heritage is determined as having at least one grandparent of AJ background. (III-A) (GRADE moderate/moderate)

2. For couples of Ashkenazi Jewish heritage, routine carrier screening for Tay-Sachs disease (carrier frequency 1/30); Canavan disease (carrier frequency 1/37—1/53) and familial dysautonomia (carrier frequency 1/32) should be offered, preferably pre-conception or as early in pregnancy as is possible. (II-2A) (GRADE moderate/high)

3. When only one member of a couple is of Ashkenazi Jewish ancestry, screening for the couple should be offered for Tay-Sachs disease only using biochemical hexosaminidase enzyme activity. (II-2A) (GRADE moderate/moderate)

4. When only one member of a couple is of Ashkenazi Jewish (AJ) ancestry, screening should not be offered for familial dysautonomia and Canavan disease, because of low carrier frequency in individuals who are not of AJ heritage and concurrent limitations of carrier screening in this situation. (III-D) (GRADE moderate/moderate)

5. Additional Ashkenazi Jewish carrier screening should be offered when a positive family is elicited for one of the conditions known to be present at an increased
frequency in this population (associated carrier frequencies are listed): Bloom syndrome 1/104; Fanconi anemia group C 1/89; Niemann-Pick type A 1/90; Mucolipidosis type IV 1/100—1/127; Gaucher disease 1/18; glycogen storage disease type 1a 1/64; familial hyperinsulinism 1/68; maple syrup urine disease 1/97; dihydrolipoamide dehydrogenase deficiency 1/107; CF 1/28; Usher syndrome 1/120; nemaline myopathy 1/168; Joubert syndrome 1/92; Walker-Warburg syndrome 1/150. (II-3; GRADE moderate/high)

Founder effects
As recently stated by Jane Evans, “From the first arrivals over 10 000 years ago to the most recent immigrants, every person coming to Canada has carried with them a unique genetic contribution. Once here, forces such as the size of founder populations and isolation by geography or cultural practices have led to a high prevalence of specific genetic conditions in many diverse ethnic groups. Although an appreciation of such variation in disease frequency and population genetics principles has been around for some time, the application of modern methods for gene identification now has the potential to improve outcomes for patients, their families and communities.”

Examples of founder effects that have a significant clinical implications are listed below:

- One Tay-Sachs mutation (7.6 kb deletion) has been found to be present at a higher frequency in French Canadians from the Bas-St-Laurent (Rimouski) and Gaspésie regions as well as in people originating from adjacent New-Brunswick territories, with an estimated carrier frequency of 1/14. Tay-Sachs carrier screening should therefore be considered for couples/individuals who present a geographic connection to these regions or have a family history of this condition.

- Other similar founder effects have been demonstrated in isolate aggregates such as those of Newfoundland and Labrador or Saguenay Lac-St-Jean/Charlevoix regions, where carrier screening is now routinely offered for four conditions with a high carrier frequency in those populations. As well, founder mutations are present in Native Canadians of Cree or Inuit ancestry. Screening programs have been implemented in Cree communities of the James Bay region since 2006 in collaboration with the Cree Board of Social Services of James Bay.

- Amish, Mennonite, and Hutterite religious groups all arose in Europe during the Protestant reformation of the 16th century and due to persecution in Europe migrated to North America. Due to individual movement out of the population (10% to 20% of each generation as the Old Order Amish and Mennonite children chose to leave their communities), many rare disease alleles have entered the general population. Genetic linkage studies of Mennonites have led to gene discovery including hypophosphatasia and XL congenital stationary night blindness. An online Amish, Mennonite, and Hutterite genetic disorder database is available to assist the maternity provider with possible carrier risk (www.biochemgenetics.ca/plainpeople).

Local MRHPs have to remain alert to these regional founder effects, as couples may not present to their pre-conception or prenatal consultation with a positive family history.

### 2016 Carrier Screening Recommendations for Founder effects:

1. Women/families whose families have originated from the Quebec Bas-St-Laurent (Rimouski) and Gaspésie regions as well as from adjoining New Brunswick territories or whose family history is positive for this condition should be offered Tay-Sachs carrier screening due to carrier frequency of 1/14 in this particular geographic aggregate. (II-2A) (GRADE high/high) As well, couples for whom each partner has at least one grandparent originating from Saguenay Lac-St-Jean/Charlevoix region should be offered screening for the four common conditions present at a higher carrier frequency in this population due to founder effects: Tyrosinemia type I (carrier frequency 1/19); congenital lactic acidosis from Saguenay Lac-St-Jean (Leigh syndrome French Canadian type, carrier frequency 1/23), spastic ataxia, Charlevoix-Saguenay type (carrier frequency 1/23), and agenesis of the corpus callosum with peripheral neuropathy (carrier frequency 1/23).

2. Careful three-generation family review for couples originating from regions with founder effects is mandatory as other clinically relevant conditions may present with a higher incidence in these populations (e.g., cerebro-oculo-facio-skeletal syndrome in aboriginal Manitoba populations; myotonic dystrophy type I, congenital disorder of glycosylation type 1B, Tay-Sachs disease, and mucolipidosis II in populations from Saguenay Lac-St-Jean; and neuronal ceroid-lipofuscinosis and Bardet-Biedl in populations originating from Newfoundland). The maternity care provider should remain alert to these specific regional founder effects.
SMA

SMA is an AR disease with a prevalence of 1/10 000 live births and a carrier frequency of 1/35—1/117 in the Caucasian population. SMA is characterized clinically by progressive muscle weakness resulting from degeneration of the anterior horn cells in the spinal cord and the brain stem. Onset ranges from before birth to adolescence or young adulthood. SMA is classically subdivided into four subtypes based on age of onset and severity of motor deficit. Loss of function of the SMN1 allele is due to a large gene deletion in 99% of cases with the remaining 1% being the result of point mutations or microdeletions. Ninety-five percent of individuals with SMA are homozygous for a large SMN1 deletion while 5% are compound heterozygotes for a large deletion and a point mutation or microdeletion. Current molecular diagnosis assay is 95% reliable for the diagnosis of an affected individual. However, the use of this assay to determine carrier status is impaired by the fact that approximately 3% to 4% of the general population carry two SMN1 copies on one chromosome and no copies on the other and will therefore be incorrectly identified as being negative or not carriers of SMA. Another 2% of the general population carry SMN1 variants that are not detected by quantitative SMN1 dosage analysis. Therefore, the counselling of patients who are tested for carrier status must account for the residual risk present when carrier screening assay results are negative, particularly in patients from SMA affected families.36

MacDonald et al. undertook a meta-analysis of SMA carrier screening performance based on ethnicity specific allele frequencies, carrier rates, and screening test performance.57 Results indicated carrier screening detection rates performed better in non-Black populations (87% to 95% compared to 71%). Their conclusion was that SMA carrier screening could be considered for routine use but with caution in the Black population. However, a recent study on SMA carrier frequencies indicates significant differences among the major ethnic groups of the United States, ranging from about 1 in 35 in Caucasians to about 1 in 125 in Hispanics.58 Moreover, no pilot studies have been completed in the United States that would determine adequate pre- and post-test counselling SMA screening practices. In addition, there have been no studies to date to measure utility and cost effectiveness of widespread carrier screening for SMA.

The Association for Molecular Pathology stated that “A test used for population-based SMA screening, particularly screening advocated by professional organizations, should support widespread accessibility to patients, robust capacity, effective proficiency testing, continued innovation, and competitive pricing.”59

2016 Carrier Screening Recommendation for Spinal Muscular Atrophy

1. Routine spinal muscular atrophy (SMA) reproductive carrier screening cannot be recommended at this time as laboratory infrastructures as well as clinical and counselling resources are not universally available across Canada. However, a family history of SMA should alert the provider to an increased carrier risk for one member of the couple. The partner of a known SMA deletion carrier should have counselling and SMA carrier testing. Prompt referral to a reproductive medical genetics provider is strongly recommended (education and counselling). (II-2D) (GRADE moderate/moderate)

Fetal Diagnostic Testing for an At-Risk Pregnancy: Standard of Care Process in the Carrier Screening Pathway

The SOGC guideline (July 2015) summarizes the prenatal diagnostic procedures and techniques used to obtain fetal specimens or tissue.60 Invasive prenatal diagnostic testing by chorionic villus sampling, amniocentesis, and cordocentesis provide fetal tissue access during the first/second, second/third, and second/third trimesters, respectively.

Non-invasive prenatal screening using cfDNA from maternal plasma is, at present, mainly used for fetal aneuploidy screening. cfDNA technology has the ability to evaluate other types of fetal DNA variations and may, over time, become the primary technique for fetal genetic testing.
For an Affected Pregnancy with Postnatal Counselling and Confirmation of Prenatal Affected Diagnosis/Autopsy: Standard of Care Process in the Carrier Screening Pathway

Referral to a provider with medical genetic expertise, for complete postnatal counselling for the mother and her partner including a review of prenatal screening and diagnostic testing results as well as postnatal genetic testing or autopsy results as applicable, would be recommended in each case where diagnostic testing has been positive or where positive screening was not confirmed by diagnostic testing. This information may/will allow for a better prediction of recurrence risk in a future pregnancy.61

2016 Carrier Screening Recommendations for Diagnosis and Follow up:

| 1. Directed diagnostic fetal or neonatal laboratory (genetic/metabolic) testing or directed diagnostic postmortem pathology/autopsy is recommended to allow for appropriate diagnostic and recurrence risk counselling. (III-A) (GRADE low/moderate) |
| 2. A timely postnatal follow up by the most appropriate or available primary care physician, geneticist, obstetrician, neonatologist, or maternal fetal medicine provider(s) should be offered for any couple with a pregnancy determined to be affected with an inherited condition identified by either prenatal or neonatal testing. (III-A) (GRADE low/moderate) |
| 3. Parents should be advised and educated about the estimated genetic recurrence risk in a subsequent pregnancy. (III-A) (GRADE low/moderate) |

NEW Concept: An Integrated Approach to Genetic Screening with Combined Fetal/Newborn Education, Counselling, and Screening/Diagnosis Approach and with the understanding that both Pre-conception/Prenatal Maternal-Fetal Screening/Diagnosis and Neonatal Diagnosis Opportunities can be Utilized

The opportunity for women/families to understand and use a combined pre-conception/prenatal and neonatal approach to genetic screening would allow for optimal effectiveness and safety. After carrier identification occurs, the patients with an increased risk of fetal conditions with a higher morbidity and no effective neonatal therapy would be offered prenatal diagnosis and possible fetal therapy (if available) or termination. Certain fetal outcomes such as hydrops could also add to the maternal pregnancy risk. The genetic conditions that are screened and/or diagnosed neonatally have demonstrated options for treatment with early neonatal detection of the condition. This combined pre-conception/prenatal and neonatal screening and diagnostic approach can be used for counselling and family centered choice. One example, for the support of this combined approach, is to use the neonatal screening for CF for the at risk fetus, as prenatal testing for CF has had very limited uptake by carrier couples,62,63 thereby removing the risk of invasive testing but allowing early neonatal diagnosis for management and therapy. Prenatal CF diagnostic testing for the carrier couple would be used when pregnancy termination of an affected fetus is a parental consideration.

Expanded Carrier Testing through DTC or Self Pay Physician Ordered Carrier Testing

A number of academic societies and health care groups have recently published opinion statements related to expanded carrier testing DTC testing.64—70

The American College of Medical Genetics published a statement in June 2013.64 Their major concerns were centred around the choice of disorders selected to be on an expanded panel. Individuals need to understand concepts such as mild phenotypes, variable expression, low penetrance, and adult onset. Quality control for the testing and for the laboratory is necessary.

McGowan et al. used focus groups to examine these issues and concluded more research is indicated to anticipate the individual, professional, legal, and social implications of expanded carrier screening.65

Other carrier screening protocols are referenced with targeted sequencing for pan ethnic screening66 and for personalized medicine.67

A joint statement by the American College of Medical Genetics, ACOG, National Society of Genetic Counsellors, and Society of Maternal-Fetal Medicine was published in March 2015.68 In their summary, certain points related to expanded carrier screening are emphasized, including:

- Expanded screening can provide information about carrier status beyond population estimates and eliminates the need for ethnicity-based screening. This introduces complexities that require special consideration.
- Health care providers are reminded that the focus of carrier screening is to identify the at-risk fetus.
- Health care providers are urged to increase their knowledge of genetic screening technology and remember that residual risk is always present, although not always quantifiable.
- There are unique research opportunities that are important to pursue to further our understanding of the full effect of expanded carrier screening on all stakeholders.
An excellent Canadian resource for genetic counselling information is available at www.geneticseducation.ca. This resource states that, “Currently, DTC-GT (genetic testing) is not regulated or accountable to an approved governing body. Numerous professional societies express concern about how DTC-GT is marketed to consumers, what and how information is provided and the lack of genetic counselling. Family health history-based risk assessment is still the gold standard in initial assessment for heritable conditions.”

The CCMG has a statement on DTC testing that is available on their website.

The NEW Educational and Counselling Approach is related to the addition of the neonatal screening information (Table 2) to the established pre-conception or prenatal information (three-generation genetic history with the risk for the transmission of a clinically significant genetic condition to their offspring by their primary care provider should be referred in the pre-conception period to a reproductive medical genetic provider for education and discussion of the implications for the couple and their offspring. (III-A) (GRADE moderate/moderate).

The NEW Discussion related to CF screening and diagnosis with the information that neonatal CF screening is routinely undertaken in certain provinces for all newborns.

Personal choice to use an expanded reproductive carrier testing panel usually occurs in the pre-conception period.

An SOGC Reproductive Genetic Carrier Screening Checklist is provided as a counselling and educational tool to assist the maternity provider in combining the pre-conception/prenatal (routine and directed testing) and the neonatal (routine and selected population testing) information (Appendix 1).

The Appendix 2 Glossary provides carrier screening definitions and the Hardy-Weinberg carrier frequency equation. Appendix 3 defines the Quebec Health Regions for better understanding of the regional ‘founder effect’ geography.

CONCLUSION

The reproductive genetic at risk carrier screening process is complex and ethically charged. It requires a collaborative inquiry, with informed care and ultimately, if required, directed carrier testing through the MRHP and other colleagues with reproductive genetic medicine expertise to identify if the women/families have a genetic at risk status and then requires the appropriate prospective education, counselling, and planning.

Committees Comment: There was a strong observational/expert opinion (quality and grade) for the genetic carrier literature with randomized controlled trial evidence being available only for the invasive testing. Both the Canadian Task Force on Preventive Health Care quality and classification and GRADE evidence quality and grade is provided.

REFERENCES


## APPENDIX 1

### SOGC ROUTINE AND DIRECTED REPRODUCTIVE GENETIC CARRIER SCREENING CHECKLIST (2016)

**Background:** A reproductive carrier screening discussion, to determine the patient’s a priori at-risk status, should be offered by the maternity care provider. If the carrier evaluation is accepted, prior to the laboratory testing either pre-conception or prenatally, a personal reproductive genetic history for the patient and her partner with the creation of a three-generation family pedigree for the couple should be undertaken. Maternal or couple routine or individual risk directed (based on identified probability of an increased carrier risk) screening and the provincial neonatal routine or directed screened/diagnosed conditions are considered in this guideline’s reproductive genetic screening checklist. Expanded next generation sequencing screening panels should be discussed with the patient for a complete informed consent process. Routine reproductive pre-conception/prenatal carrier screening is offered for:

- **AJ panel** (offered routinely for couples with AJ heritage)
  - Tay-Sachs (carrier frequency 1/28)
  - Canavan disease (carrier frequency 1/37–1/57)
  - Familial dysautonomia (carrier frequency 1/32)
- **AJ heritage associated with only one member of the couple:** offered routine Tay-Sachs only
- **French Canadian heritage from Quebec Saguenay Lac-St-Jean (CF carrier frequency 1/15) and Charlevoix (CF carrier frequency 1/20) regions — CF (medical genetic referral is recommended/offered routinely in medical genetics centres in Quebec)**
- **French Canadian heritage from Quebec Bas-St-Laurent (Rimouski) and Gaspesie regions (Tay-Sachs carrier frequency 1/14) — Tay-Sachs (medical genetic referral is recommended/offered routinely in medical genetics centres in Quebec)**
- **Family or geographic or emigration history of an association/connection to the Amish, Mennonite, or Hutterite religious groups.**

Directed pre-conception/reproductive prenatal carrier screening is offered to the patient, based on an increased a priori risk, with some conditions having selected neonatal (routine or directed) testing (consider reproductive or medical genetic referral) for:

- **CF (carrier frequency 1/23–1/25)/neonatal CF screening in certain provinces**
- **Thalassemia/hemoglobinopathy:** four severe disease conditions (involving either B-beta or A-alpha) with family history or ethnic considerations; or selected population testing neonatal testing for SC anemia (S/S), SC disease (S/C), and S-Beta thalassemia (S/B) in certain provinces
  - Thalassemia major (variant carrier of B globin synthesis/gamma B/Hb Lepore)
  - SC disease Hb S (B globin point mutation; carrier frequency 1/8 Africa)
  - Hb E (variant carrier B globin or Hb E)
  - Hb Bart’s hydrops fetalis syndrome (deletion carrier A globin 1 or 2 genes)
- **AJ (usual single condition with additional screening related to a positive personal/family history)**
  - Gaucher disease type 1 (carrier frequency 1/15–1/18)
  - CF (carrier frequency 1/28)/routine CF neonatal testing
  - Bloom syndrome (1/104)
  - Fanconi anemia group C (1/89)
  - Niemann-Pick (type A) (1/90)
  - Mucolipidosis IV (1/100–1/127)
  - Glycogen storage disease type 1a (1/71)
  - Familial hyperinsulinism (1/68)
  - Maple syrup urine disease type 1B (1/97)/MSUD neonatal testing in certain provinces
  - Dihydrolipoamide dehydrogenase deficiency (1/107)
  - Usher syndrome type 3 (1/120)
  - Nemaline myopathy type 2 (1/168)
  - Joubert syndrome type II (1/92; consult laboratory re carrier testing)
  - Walker-Warburg (1/150; consult laboratory re carrier testing)
- **FXS (XL dominant; positive family history of affected males or premature ovarian dysfunction)**
- **XL carrier (positive family history for male related bleeding disorder or muscular dystrophy)**
  - Hemophilia A (factor VIII) or B (factor IX)
  - Positive family history for muscular dystrophy (Duchenne or Becker)
- **Spinal muscular atrophy (carrier frequency 1/35–1/117) and a prevalence of 1/10 000 live births:** positive family history
Glossary is provided for additional supporting information: Definitions, added support for screening decisions/rationale, and the Hardy-Weinberg Equation/Law for carrier frequency calculation and understanding.

**Carrier screening:** Carrier genetic testing is performed on individuals for an inherited disorder who may be at risk of passing it on to their children. A carrier of a genetic disorder has one variant allele for a particular condition. When associated with an AR or XL disorder, carriers of the causative mutation are typically unaffected. When associated with an AD disorder, the individual may be affected or unaffected but at high risk of developing symptoms later in life, or may remain unaffected.

**Compound heterozygous:** The presence of two different mutant alleles at a particular gene locus, one on each chromosome of a pair.

**Expressivity/Expression:** The degree to which a penetrant genetic variant is clinically detectable within an individual.

**Genetic testing:** Genetic testing involves the analysis of chromosomes, DNA, RNA, genes or gene products to detect inherited (germline) or non-inherited (somatic) genetic variants related to disease or health.

**Homozygous:** Having the same alleles at a particular gene locus on homologous chromosomes (chromosome pair).

**Penetrance:** The proportion of individuals with a specific variant causing a particular disorder who exhibit clinical symptoms of that disorder.

**Residual risk:** The risk that an individual is a carrier of a particular condition but for whom genetic testing for carrier status of the condition is negative (for example, if the individual is a carrier a disease-causing mutation that was not included in the test assay).

Using Hardy-Weinberg equation: 3 genotypes determined from \((p + q)^2\) with \(p + q = 1\)

\[(p = \text{normal allele} / q = \text{disease allele frequencies}) \text{so } p^2 + 2pq + q^2 = 1\]

Frequency of \(NN = \text{normal} = p^2; Nn = \text{carrier} = 2pq; nn = \text{affected} = q^2\)

Carrier rate = \(2pq = 2(1-q)q = 2q - 2q^2\) but if disease is rare (1/1000 or less) then \(2q^2\) is very small

So approximated Carrier rate = \(2q\)

<table>
<thead>
<tr>
<th>Disease Frequency (q^2)</th>
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<th>Carrier frequency (2pq)</th>
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<tr>
<td>1/100</td>
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Appendix 3. Quebec map related to the designated health regions with an increased French Canadian genetic carrier risk (regional founder effect) as identified in the recommendations for CF and Tay-Sachs disease carrier screening.

(https://www.statcan.gc.ca/pub/82-221-x/01103/images/jpg/que_qc.jpg)