

Carrier Screening for Genetic Disorders in Individuals of Ashkenazi Jewish Descent

This guideline has been prepared by the Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC) and the Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists (CCMG) and approved by the Executive Council of the SOGC and the Board of Directors of the CCMG.

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Abstract

Objective: To give recommendations to physicians and midwives providing pre-conception or prenatal care about carrier screening for genetic disorders in individuals of Ashkenazi Jewish descent.

Options: To offer carrier screening for Tay-Sachs disease (TSD) only or to expand the screening to include other disorders known to occur with increased frequency in the Ashkenazi Jewish population.

Outcomes: To offer carrier screening to the Ashkenazi Jewish population for conditions in which the benefits to the couple outweigh the risks, which include psychological distress from screening and diagnostic interventions; to minimize practice variation across Canada with respect to carrier screening in individuals of Ashkenazi Jewish descent.

Evidence: The MEDLINE database was searched for relevant articles published from January 1966 to December 2004 related to carrier screening and genetic disorders in individuals of Ashkenazi Jewish descent. In addition, Canadian maternal-fetal medicine specialists and medical geneticists were surveyed to determine current practices and opinions.

Values: The results of the survey and evidence collected from the MEDLINE search were reviewed by the Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists (CCMG) and the Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC). Recommendations were quantified using the Evaluation of Evidence guidelines developed by the Canadian Task Force on the Periodic Health Examination.

Benefits, harms, and costs: Screening of couples of Ashkenazi Jewish descent will identify couples who have a 25% risk of having a child with a significant genetic disorder. However, the sensitivity of the tests being offered is not 100% in individuals of Ashkenazi Jewish descent and is significantly less or unknown in non-Ashkenazi Jewish individuals.

Screening might identify couples where one member is a carrier and the other member is negative. Given that such a couple would be at low risk but not zero risk of having an affected child, screening might result in psychological distress, unnecessary prenatal diagnostic procedures, and possibly termination of normal pregnancies. This guideline does not include a cost analysis.

This guideline reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed. Local institutions can dictate amendments to these opinions. They should be well documented if modified at the local level. None of these contents may be reproduced in any form without prior written permission of the SOGC.

Table 1. Criteria for quality of evidence assessment and classification of recommendations

Level of evidence*	Classification of recommendations†
I: Evidence obtained from at least one properly designed randomized controlled trial.	A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
II-1: Evidence from well-designed controlled trials without randomization.	B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.	C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination.
II-3: Evidence from comparisons between times or places with or without the intervention. Dramatic results from uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.	D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination.
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

*The quality of evidence reported in these guidelines has been adapted from the Evaluation of Evidence criteria described in the Canadian Task Force on the Periodic Health Exam.⁴⁴

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on the Periodic Health Exam.⁴⁴

Recommendations

- Carrier screening for Tay-Sachs disease (II-2A), Canavan disease, and familial dysautonomia should be offered to Ashkenazi Jewish couples. (III-A)
- Carrier screening for other disorders seen with increased frequency in Ashkenazi Jewish individuals (e.g., Bloom syndrome, Fanconi anemia, Gaucher disease, glycogen storage disease type 1a, mucopolidosis type IV, Niemann-Pick disease type 1A, cystic fibrosis) should be offered when there is a positive family history. (III-A)
- When only one member of a couple is of Ashkenazi Jewish ancestry, screening should be offered for TSD only. (II-2A)
- When only one member of a couple is of Ashkenazi Jewish ancestry, screening should not be offered for Canavan disease or familial dysautonomia (FD) because of a low carrier frequency and limitations of carrier screening (low detection rate in individuals of non-Ashkenazi Jewish ancestry). (III-D)
- When both partners are carriers of the same autosomal recessive condition, they have a 25% risk of having an affected child. They should be referred for genetic counselling, either before conception or prenatally. Prenatal diagnosis would be offered and performed according to the patient's informed decision. Prenatal diagnosis would consist of DNA analysis done on cells obtained by chorionic villus sampling or amniocentesis. (II-3A)

Validation: This guideline has been prepared by the Prenatal Diagnosis Committee of the CCMG and the Genetics Committee of the SOGC and approved by the Board of Directors of the CCMG and Executive Council of the SOGC.

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INTRODUCTION

The current Canadian Guidelines for Prenatal Diagnosis recommend carrier screening for individuals belonging to population groups known to have increased risk of certain genetic disorders.¹ This population-based genetic screening approach is recommended for reproductive

counselling of healthy couples during pregnancy when they are at risk of having an affected offspring. Through genetic counselling, and with the option of prenatal diagnosis, the birth of an affected child can be avoided. Population-based genetic screening for reproductive counselling for Tay-Sachs disease (TSD) has been offered to Ashkenazi Jewish individuals since 1970. More than 1.4 million individuals worldwide have been screened voluntarily. In the United States and Canada, the incidence of TSD in the Jewish population has been reduced by more than 90%.² Advances in molecular genetics have made it possible to determine the underlying mutations responsible for a number of other genetic conditions seen more commonly in the Ashkenazi Jewish population than in others. Furthermore, in the Ashkenazi Jewish population, it has been shown that for the common conditions studied, relatively few mutations account for more than 95% of disease causing mutations (Table 2).

Given the proven benefits of carrier screening for TSD and the progress made in our understanding and diagnostic capabilities of other disorders seen in the Ashkenazi Jewish population, the Genetics Committee of the SOGC and the Prenatal Diagnosis Committee of the CCMG have reviewed the literature for evidence for or against screening for genetic conditions other than TSD. Factors included in the analysis for each condition considered for screening were severity of the condition, carrier frequency, validity of the test currently available (including detection rate, false positive rate, and genotype/phenotype correlation), cost of screening, and availability of prenatal diagnosis (Table 3). In

Table 2. Most common childhood autosomal recessive disorders seen in the Ashkenazi Jewish population

Genetic conditions	Clinical description	Carrier frequency in AJ individuals	Common mutations	Detection rate of AJ carriers	Carrier frequency in NJC individuals	Detection rate of NJC carriers using AJ mutation panel
Autosomal recessive disorders of increased frequency in Ashkenazi Jewish individuals						
Tay-Sachs disease (HEX A) ^{3,4}	severe neurodegenerative disorder leading to death in the first few years of life	1/30	1277insTATC G269S IVS12+ 1G > C	98%	1/300*	98% by Hex-A biochemical assay
Canavan disease (ASPA) ⁵⁻¹⁰	severe neurodegenerative disorder leading to death in the first decade of life	1/37-1/57	693C > A 854A > C 914C > A	98%	unknown < 1/57	40%
Familial dysautonomia (IKBKAP) ^{11,12}	severe neurological disorder affecting the sensory and autonomic system with 50% of patients dying before age 30	1/32	IVS20+6T > C 2397G > C	> 99%	unknown very rare cases reported	0%
Bloom syndrome (BLM) ¹³⁻¹⁵	short stature, sun-sensitive facial erythema, immune deficiency, and high risk of cancer	1/104	2281del6< bp/ ins7 bp	97%	unknown << 1/104	rarely
Fanconi anemia group C (FANCC) ^{16,17}	congenital abnormalities, progressive pancytopenia, increased risk of cancer	1/89	IVS4+4A > T	> 99%	1/300	0%
Gaucher disease (GBA) ^{18-20,37,38}	variable clinical presentation from asymptomatic to severe morbidity from hepatosplenomegaly and bone involvement The neuropathic form is less common.	1/15	N370S R496H 84gg L444P IVS2+1	95-97%	~ 1/120	50-60%
Glycogen storage disease type 1a (G6Pase) ^{21,34}	enzymatic defect resulting in severe hypoglycemia	1/71	R83C Q347X	98%	1/158	48% (65% if test for 5 mutations)
Mucopolidosis type IV (MCOLN1) ²²⁻²⁴	severe neurodegenerative lysosomal storage disorder with visual impairment	1/100	IVS3-2A > G del (ex1-7)	95-97%	unknown << 1/100 > 50% of pts diagnosed are AJ	15%
Niemann-Pick disease type 1A (ASM) ^{25,26}	severe neurodegenerative lysosomal disorder associated with failure to thrive, hepatosplenomegaly and death by 2-3 years of age	1/90	905T > C 1487G > T fsP330	> 95%	unknown << 1/100 > 50% of pts diagnosed are AJ	0%
Cystic fibrosis (CFTR) ^{27,28}	disease is variable but most individuals have severe pulmonary and/or gastrointestinal disease	1/24	CFTR panel of 25 mutations	94%	1/25	88%

* Carrier frequency may be higher in individuals of French Canadian ancestry.

AJ: Ashkenazi Jewish; NJC: non-Jewish Caucasian.

addition, a survey of Canadian maternal-fetal medicine specialists and medical geneticists was carried out to gather information about current and desired screening practices for this ethnic group (Table 4).

Evidence and Opinion

Ashkenazi Jews, also known as Ashkenazic Jews or Ashkenazim, are descendants of the Jewish communities of Germany, Poland, Austria, and Eastern Europe.²⁹ In

contrast, Sephardi Jews, also called Sephardim, are descendants of the Jews who were expelled from Spain and Portugal during the Spanish Inquisition and settled mainly in Morocco, Turkey, Greece, North Africa, Southwest Asia, Southern France, Italy, Holland, Spanish North America, Spanish South America, and Brazil.³⁰ Approximately 80% of all Jews in the world are of Ashkenazi origin. According

to the 2001 Canadian Census, 329 995 Canadians identified themselves as Jewish.³¹

Certain autosomal recessive genetic disorders presenting in childhood are more prevalent in individuals of Ashkenazi Jewish ancestry (Eastern European Jewish descent) than in other populations. These disorders include Bloom syndrome, Canavan disease, FD, Gaucher disease, mucopolidosis type IV, Niemann-Pick disease type A, TSD,³² Fanconi anemia,³³ and glycogen storage disease type 1a.³⁴ Over the last 10 years, the molecular basis of these conditions has been delineated, providing a tool for carrier detection of these disorders in individuals of this ethnic background. Table 2 summarizes the clinical presentation of these disorders, their carrier frequency, common mutations, and carrier detection rates using currently available tests. Also included in Table 2 for comparison are carrier frequency and detection rates for these disorders in individuals of non-Jewish Caucasian descent.

In the Ashkenazi Jewish population, these disorders are the result of a limited number of causative mutations, which allows the easy development of a molecular screening test with a high detection rate. Carrier screening could also be considered for other autosomal recessive genetic conditions for which the molecular basis is well defined, even though the carrier frequency may not be increased in this population (e.g., cystic fibrosis [CF]).

Canadian maternal-fetal medicine specialists and medical geneticists were surveyed by email to obtain information about population screening for individuals of Ashkenazi Jewish descent. They were given background information regarding the carrier frequency of the disorders for which carrier testing is available and were asked:

1. For which of the following conditions is screening routinely offered at your centre to individuals of Ashkenazi Jewish ancestry?
2. In your opinion, for which of the following conditions should screening be routinely offered to individuals of Ashkenazi Jewish ancestry?

They were asked to comment on reasons for their choices. In addition, they were asked whether they would offer this population screening for CF, given that CF screening is not currently recommended in Canada for the non-Ashkenazi Jewish Caucasian population.³⁵ The results of this questionnaire survey are summarized in Table 4. Eighty-two percent of medical geneticists who responded believe that carrier screening of individuals of Ashkenazi Jewish descent should not be limited to TSD. Currently, 82% of medical geneticist respondents offer carrier screening for TSD and other disorders to individuals of Ashkenazi Jewish descent. Seventy-five percent offer screening for Canavan disease,

Table 3. Criteria for a carrier screening program

Serious recessive disorder
Intervention available and impacts outcome
High frequency of carriers expected
Availability of inexpensive, reliable test
high detection rate
low false positive rate
Access to genetic counselling
Voluntary participation
Informed consent process

and 64% offer screening for FD. Among the maternal-fetal medicine specialists who responded to the survey, only 45.5% offer screening for more than TSD, although 64% believe that screening should not be limited to TSD. Of the respondents, 64% indicated they believed screening should include Canavan disease, and 32% would include screening for FD. Finally, the majority of respondents in both groups would be concerned about offering screening for CF for this population group, given the current recommendation for Canadians.

Criteria judged by the survey respondents and committee members as most important in the decision making process for selecting conditions for carrier screening are disease severity, carrier frequency, and test validity. TSD meets all three criteria since it is a severe neurodegenerative disorder leading to death in the first few years of life; the carrier frequency is 1/30 and the carrier detection rate in the Ashkenazi Jewish population is 98%. Given the positive experience with carrier screening for TSD, it seems appropriate to expand the screening to include disorders that compare for these three criteria (Table 2). FD is characterized by a severe neurological disorder and has a 50% mortality rate by age 30. The carrier frequency is only minimally lower than that of TSD (1/32 compared with 1/30), and the screening test is associated with a carrier detection rate greater than 99%. Canavan disease is characterized by severe neurodegeneration with death in the first decade. The carrier frequency is lower than that of TSD (1/37–1/57 compared with 1/30), but the screening test is associated with a carrier detection rate of 98%. On this basis, screening for FD and Canavan disease should be offered. This recommendation is in keeping with the one proposed by the Committee on Genetics of the American College of Obstetricians and Gynecologists.³⁶

Any disease with a carrier frequency of 1/70 or less was excluded from screening for two reasons:

Table 4. Results of survey administered to members of the CCMG and MFM specialists of the SOGC

Survey Results	CCMG	MFM	Total
Number of respondents	28	22	50
Demographics			
Graduating years	1968–2003	1973–2003	1968–2003
Females	19	8	27
Males	9	14	23
Testing that is currently done (% of respondents)			
TSD only	18	2.5	30
TSD and others	82	45.5	66
Canavan	75	45.5	62
FD	64	18	44
CF	21	14	18
Gaucher	14	9	12
Fanconi anemia	11	4.5	8
Glycogen storage disease	3.5	0	2
Mucopolipidosis 4	0	4.5	2
Niemann-Pick disease	0	4.5	2
Bloom syndrome	0	4.5	2
None	0	9	4
Testing that should be done (% of respondents)			
TSD only	14	36	24
TSD and others	82	64	74
Canavan	75	64	70
FD	64	32	50
CF	36	23	30
Gaucher	25	23	24
Fanconi anemia	11	14	12
Glycogen storage disease	0.7	4.5	6
Mucopolipidosis 4	14	9	12
Niemann-Pick disease	0	9	4
Bloom syndrome	4	9	6
Unsure	4	0	2
Would have a problem offering CF carrier screening to Ashkenazi Jews and not Caucasians?			
Yes	78.5	68	74
No	18	23	20
No answer/uncertain	0.5	9	6

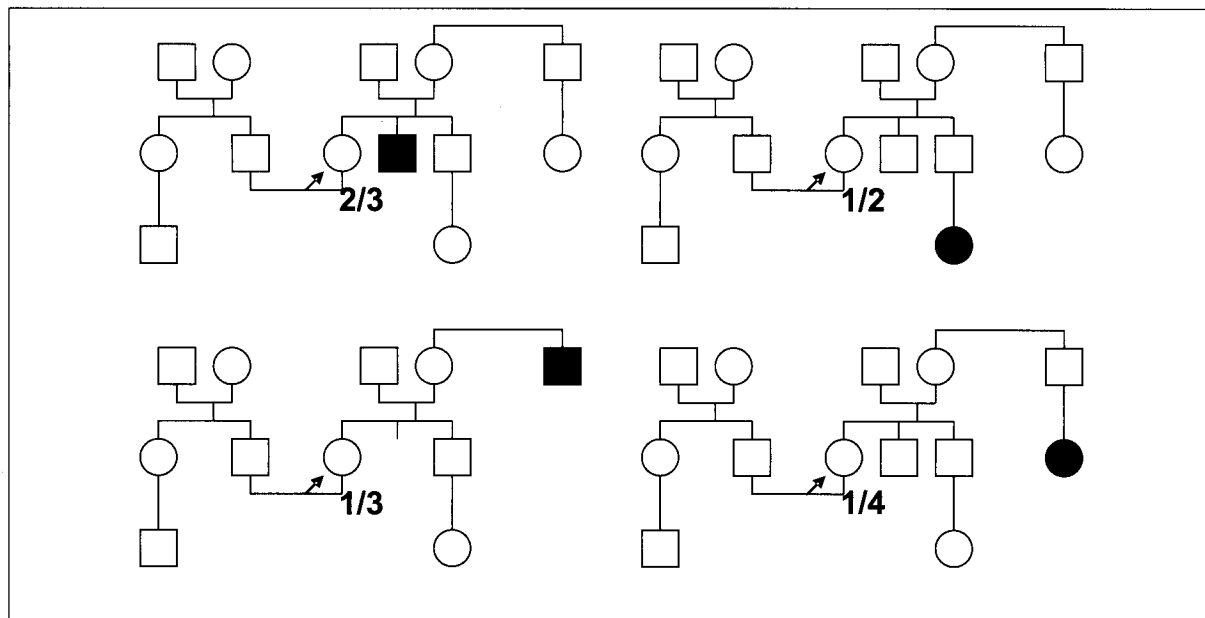
CCMG: Canadian College of Medical Geneticists; SOGC: Society of Obstetricians and Gynaecologists of Canada; MFM: maternal-fetal medicine; CF: cystic fibrosis; FD: familial dysautonomia; TSD: Tay-Sachs disease.

1. 4900 or more individuals would have to be screened to identify one couple at a 25% risk of having an affected child;
2. at least 69 carriers out of 70 (given a carrier frequency of 1/70 or less) will have a negative partner, giving them a

low risk but not zero risk of having an affected child. Knowing this might raise undue anxiety.

As for all patients, a three generation pedigree (Figure 1.) should be obtained to assess for the presence or absence of spontaneous abortions, stillbirths, congenital anomalies, and genetic disorders, including but not limited to those

Figure 1. Three generation pedigree and carrier risk based on family history of autosomal recessive condition



seen in increased frequency in the Ashkenazi Jewish population. Testing for genetic conditions with low carrier frequency should be offered if one of the partners has a positive family history for such a disorder. In this context, the individual who has a positive family history is at a significantly increased risk of being a carrier and should be offered screening. For example, having a sibling affected with an autosomal recessive condition increases an individual's risk of being a carrier to $2/3$; having a nephew or niece affected increases risk to $1/2$; having an uncle or aunt affected gives an individual a $1/3$ risk; and having a cousin affected, a $1/4$ risk of being a carrier. In the event that the family history is positive for a genetic disorder, referral of the couple for genetic counselling is recommended.

Two conditions, CF and Gaucher disease, were considered for screening on the basis of disease frequency and test validity (high detection rate). CF was excluded because the carrier frequency of CF in the Ashkenazi Jewish population is equivalent to the frequency in non-Ashkenazi Jewish Caucasians; in Canada, screening is not currently recommended for the latter population because of the validity and cost of the test.³⁵ Gaucher disease was excluded because there is poor genotype/phenotype correlation. Some individuals present in childhood with hepatosplenomegaly and bone disease, but other individuals with the same genotype will remain asymptomatic.^{37,38} In 1996, the NIH Technology Assessment Panel on Gaucher Disease also concluded that carrier screening was not appropriate.³⁹ Since then,

knowledge has not advanced enough to warrant a change in position.

The situation is not as clear for couples when one partner is of Ashkenazi Jewish descent and the other is not (mixed couples), as these couples have a much lower risk of having an affected child (Table 5).

In the case of TSD, biochemical testing, which has a high carrier detection rate, can be offered to the non-Ashkenazi Jewish partner. This justifies offering carrier testing for TSD to individuals of Ashkenazi Jewish ancestry even when the partner is not Ashkenazi Jewish. If the Ashkenazi Jewish partner is found to be a carrier of TSD, biochemical testing should be offered to the non-Ashkenazi Jewish partner. Regarding carrier testing for TSD, it should be noted that the carrier frequency may be higher than $1/300$ in French Canadian individuals. One study published in 1977 tested 119 individuals (spouses or very distant relatives of individuals with a positive family history) from the Bas-Saint-Laurent (Rimouski region) and Gaspésie region and found a carrier frequency of $1/14$.⁴⁰ The high carrier frequency was attributed to a founder effect. This figure is undoubtedly an overestimate as approximately 40% of enzymatically defined non-Ashkenazi Jewish carriers have a pseudodeficiency allele. Furthermore, with population migration, this risk estimate may no longer apply to the current population of those regions. No recent study assessing the carrier risk of French Canadians in different regions of Quebec has been published.

Table 5. Examples of risk of having an affected child prior to any carrier testing and after carrier testing results

Genetic Condition Carrier frequency	Risk prior to testing	AJ couple		Mixed AJ and NJC couple		
		1 partner carrier	Neither carrier	Risk prior to testing	AJ partner carrier NJC partner tested negative	AJ partner carrier NJC partner not tested
Tay-Sachs disease AJ: 1/30 NJC: 1/300	1/3600	~1/5800	1/8X10 ⁶	1/36000	~1/60000	1/1200
Canavan disease AJ: 1/40* NJC: 1/300*	1/16000	~ 1/7800	1/15X10 ⁶	1/48000	~ 1/12000	1 / 1200

AJ: Ashkenazi Jewish; NJC: Non-Jewish Caucasian.

* Estimate of carrier frequency for purpose of calculating risk.

Unlike carrier testing for TSD, carrier testing for FD and Canavan disease consists only of molecular analysis. Using this approach, there is a high carrier detection rate in Ashkenazi Jewish individuals because only a limited number of common mutations cause most of the disease. In contrast, molecular carrier testing is of limited value in the non-Ashkenazi Jewish populations because many different mutations are causative, resulting in a significantly lower carrier detection rate (Table 2). Furthermore, the carrier frequency of Canavan disease is unknown but thought to be lower in individuals of non-Ashkenazi Jewish ancestry. FD has only very rarely been seen in individuals of non-Ashkenazi Jewish descent. On the basis of the low carrier frequency and low detection rate using routinely available assays, carrier screening for Canavan disease and FD is not recommended for couples of mixed Ashkenazi Jewish and non-Ashkenazi Jewish descent.

The purpose of population-based carrier screening is to identify carrier couples who are at risk of having an affected child and offer them counselling and the option of prenatal diagnosis. Ideally, screening would be done for one member of the couple prior to conception. If the individual screens negative, there would be no need to screen the partner. However, if the woman is pregnant, the decision to test sequentially versus testing both partners together should be made with consideration given to gestational age and time to obtain results. It is paramount that screening be done in a timely manner to allow early prenatal diagnosis and all pregnancy management options.⁴¹ The laboratory should be made aware of the pregnancy and gestational age so that results can be made available quickly.

Our recommendations for screening of both Ashkenazi Jewish and mixed couples are summarized in Figure 2.

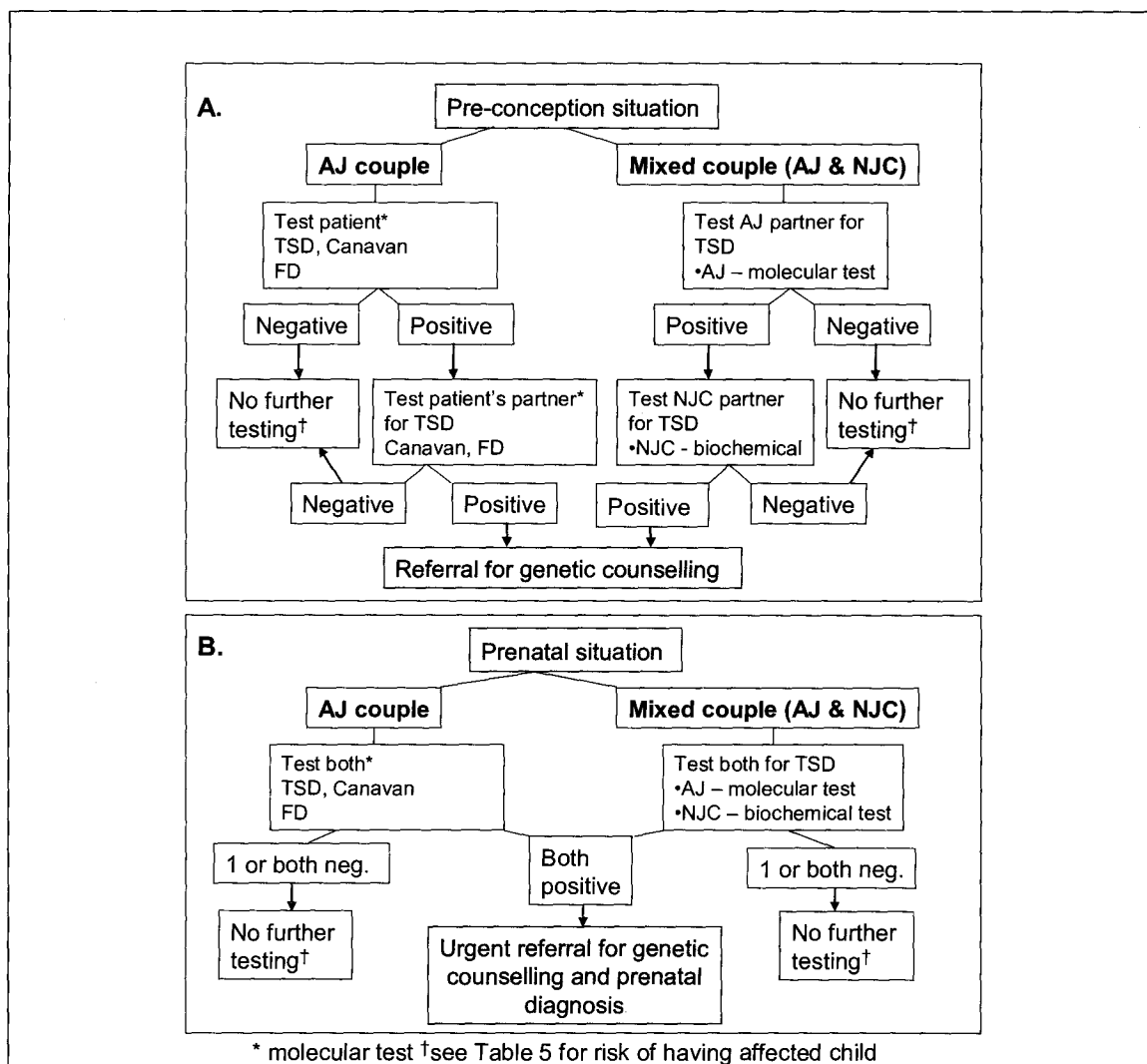
Other essential elements of population-based carrier screening include voluntary participation, informed

consent, and the availability of a public and professional educational program. Each province needs to develop its own brochures to include province-specific information on how to obtain testing, as well as general information for patients and health care professionals on TSD, Canavan disease, and FD. Examples of such information are available through a number of associations and institutions, such as the information website of the National Council of Jewish Women of Canada.⁴² Finally, physicians should be aware that some individuals of Ashkenazi Jewish ancestry may have been or will be screened through programs that follow the Dor Yeshorim approach to carrier testing. Carrier screening is offered to youth with parental consent. All testing is done confidentially and each person is given code numbers but not informed of the result of his or her tests. When marriage is contemplated, the couple provide their code numbers and birth dates. The program informs them if they are compatible (at low risk of disease) or incompatible (carriers of the same genetic condition). In the latter situation, couples are offered genetic counselling. This program was set up to meet the needs of the Orthodox Jewish community and has been highly successful.⁴³

Recommendations

1. Carrier screening for TSD (II-2A), Canavan disease and FD should be offered to Ashkenazi Jewish couples. (III-A)
2. Carrier screening for other disorders seen with increased frequency in Ashkenazi Jewish individuals (e.g., Bloom syndrome, Fanconi anemia, Gaucher disease, glycogen storage disease type 1a, mucopolidosis type IV, Niemann-Pick disease type 1A, and CF) should be offered when there is a positive family history. (III-A)

Figure 2. Approach to carrier screening with negative family history



AJ: Ashkenazi Jewish; NJC: Non-Jewish Caucasian; FD: familial dysautonomia; TSD: Tay-Sachs disease.

- When only one member of a couple is of Ashkenazi Jewish ancestry, screening should be offered for TSD only. (II-2A)
- When only one member of a couple is of Ashkenazi Jewish ancestry, screening should not be offered for Canavan disease or FD based on a low carrier frequency and limitations of carrier screening (low detection rate in individuals of non-Ashkenazi Jewish ancestry). (III-D)
- When both partners are carriers of the same autosomal recessive condition, they have a 25% risk of having an affected child. They should be referred for genetic counselling, either before conception or prenatally. Prenatal diagnosis would be offered and performed according to the patient's informed decision. Prenatal diagnosis would consist of DNA analysis done on cells obtained by chorionic villus sampling or amniocentesis. (II-3A)

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