NSO Policy: Carrier Testing for Genetic Disorders

As per the position statement on reproductive carrier screening by the Canadian College of Medical Geneticists (CCMG)[1], Newborn Screening Ontario (NSO) is updating our policy on carrier testing, effective March 2026. This carrier policy has been developed with the aim of ensuring appropriate resource management in the context of Canada's publicly funded healthcare system. This policy may not be applicable to all cases, and healthcare providers seeking guidance on whether their patients may be eligible for genetic testing for carrier status are encouraged to reach out to the molecular team at NSO for guidance or to discuss exceptional cases.

Background Information

Individuals considered carriers for recessive conditions have pathogenic variants on one of their two copies of a gene and are typically clinically asymptomatic. For autosomal recessive genetic conditions, all individuals have 2 copies of the gene involved, and only those with pathogenic gene variants present on both copies of the gene will be clinically affected. If both partners are confirmed carriers of genetic variants in the same gene, their offspring have a 25% chance of inheriting both pathogenic gene variants and being affected by the genetic condition. Alternatively, X-linked recessive conditions are caused by pathogenic variants in a gene located on the X chromosome. XY individuals or individuals with a single X chromosome who carry a single pathogenic gene variant will be clinically affected. For autosomal recessive conditions, both XX and XY individuals are at risk of being carriers. For X-linked recessive conditions, XX individuals or individuals with two X chromosomes can be asymptomatic carriers. Their offspring risk is sex-dependent, with XX offspring having a 50% chance of being carriers, and offspring with a single X chromosome having a 50% chance of being affected by the condition. Transmission of X-linked recessive conditions typically occurs when a X-linked pathogenic variant is passed down from a carrier XX parent to a clinically affected XY child.

In Canada, publicly funded population-wide reproductive carrier testing for most genetic conditions is not currently available, however some provinces offer ethnicity-based carrier screening programs for specific subsets of conditions and populations. Individuals seeking carrier testing may be eligible for funded carrier testing based on increased reproductive risk. Outside of these programs, all have the option to pursue self-pay testing if desired. The goal of reproductive carrier testing includes identifying couples at risk of conceiving a pregnancy affected by a genetic condition, either prior to conception or in the

context of an ongoing pregnancy. Carrier testing enables accurate genetic counselling on reproductive risk and informed decision-making. Determining a pregnancy's risk for of a genetic condition gives families the options of planning, early diagnosis and in some cases, early intervention. At NSO, carrier testing has been available to any individual with a known increased risk of being carriers for a genetic condition based on their family history, and to those whose reproductive partners are known carriers. With this new policy, NSO seeks to specify eligibility for carrier testing and limit genetic testing for carrier status by stratifying the risk of the individual to ensure appropriate use of genetic testing resources in Ontario. This policy does not affect eligibility for diagnostic molecular testing, or segregation of variants of uncertain significance for the purposes of clarifying a molecular diagnosis.

Eligibility for Carrier Testing

At NSO, genetic testing is available for genes associated with diseases targeted by newborn screening, as well as for nuclear genes associated with mitochondrial diseases and inherited errors in immunity. Patients will be eligible for genetic testing with the goal of determining carrier status if they meet the listed eligibility criteria listed below. Carrier screening is restricted to genetic conditions with high penetrance and low variability of expressivity, for which a molecular diagnosis would have care management implications. For additional details and explanations, please see detailed descriptions and rational below.

If no partners are yet confirmed carriers for the genetic condition in question, one partner will be eligible for carrier testing if:

A. There is a known pathogenic gene variant in their family, AND/OR
B. There is an increased risk of being a carrier due to a family history

**Please see details below under 1 and 2*

If one partner is confirmed to carry at least one pathogenic variant in a gene associated with an autosomal recessive condition, their reproductive partner is eligible for carrier testing if:

A. Carrier frequency of the second partner is estimated to be ≥ 1/100, AND/OR
B. The overall risk of conceiving an affected pregnancy is ≥ 1/400

**Please see details below under 3 and 4*

Detailed Inclusion Criteria

1 – Familial Variant Testing

NSO continues to offer carrier testing in a patient for known pathogenic gene variant(s) identified in a patient's family. For targeted familial variant testing (FVT), NSO will conduct targeted sequencing for the specific variant(s), rather than sequencing the entire gene. Healthcare providers looking to order FVT should obtain genetic information from the relatives in question and provide the specific gene and variant information to NSO on the molecular requisition. The genetic testing report of the relative should be provided to ensure we are targeting the correct gene and variant. **To be eligible for FVT, the pathogenic gene variant must have been identified in a relative within 3 degrees of relatedness to your patient.**

For example, if considering a patient whose aunt is a confirmed carrier for cystic fibrosis (CF), an autosomal recessive condition, the patient would have a 25% chance of also being a carrier for CF. Another example could be a female patient whose brother has a molecular diagnosis of X-linked adrenoleukodystrophy (X-ALD), an X-linked recessive condition. The patient will have up to a 50% chance of being a carrier of for X-ALD. In these cases, if gene variant information is provided, NSO would agree to perform FVT in these patients.

2 – Increased Risk Due to Family History of Disease

Carrier testing remains available to individuals with a known increased risk of being carriers of pathogenic gene variant(s) due a family history of a monogenic condition. In the context of a family history of a genetic condition where no molecular testing was conducted, healthcare providers should consider referral to genetic services for assessment and genetic counselling. There is a wide array of contexts which may result in this situation, with some examples including a clinical diagnosis made in a child that has not yet been assessed by genetic professionals, or a clinical diagnosis in a deceased relative. There could also be a case of a molecular diagnosis in a relative where gene variant information is not available as testing was conducted out of country. In these cases, NSO may approve full gene sequencing for monogenic disorders **depending on the degree of relatedness to the patient in question, and the prevalence of the condition.** For example, a known affected uncle would be 2 degrees of relatedness and genetic testing in the patient may be indicated, whereas an affected second cousin would not be an appropriate indication for carrier testing. Genetic testing may often be most appropriate in another individual in the family first, such as a parent or grandparent, to determine the risk of the patient in question prior to pursuing carrier testing. Please contact the molecular team at NSO for clarification, as some exceptions can be made on a case-by-case basis.

For reproductive partners with consanguineous backgrounds who are at higher risk of both being carriers for the same autosomal recessive condition due to a shared family history, healthcare providers should consider referral to genetic services for assessment and genetic counselling. In this case, sequential testing starting with the partner at higher risk can be initially requested. The second partner will then be eligible for testing if carrier status is confirmed in the first partner. In the context of an ongoing pregnancy, concurrent testing of both partners may be considered based on background risk, as to expedite genetic testing results if carrier testing is being pursued for the purpose of prenatal genetic testing.

3 – Reproductive Partner of a Known Carrier of a Common Genetic Condition

If one partner is a known carrier for an autosomal recessive condition, the second partner may desire genetic testing to determine their children's risk of disease. Carrier testing remains available through NSO for reproductive partners of known carriers for common genetic conditions, even if the partner has no family history of the condition. Risk cut-offs for carrier testing have been selected to be in line with the practice guidelines reported in the CCMG position statement[1]. Healthcare providers should provide details on the gene and variant identified in the known carrier partner to ensure the correct test is performed on the reproductive partner. Full gene sequencing will be conducted by NSO.

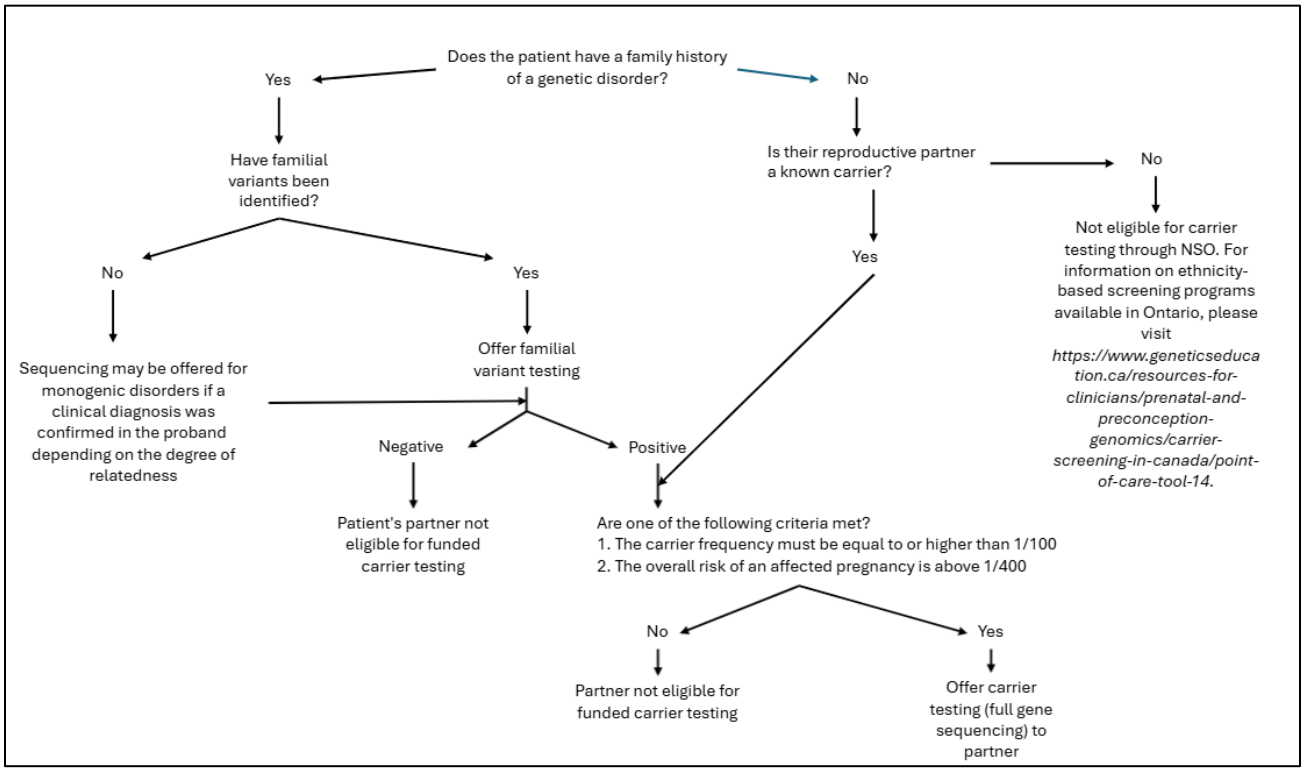
For a condition to be considered common, and therefore eligible for carrier testing through NSO, the carrier frequency must be equal to or higher than 1/100 (1%). As ascertaining exact carrier frequencies of gene variants can be difficult, clinicians should use their best judgement and may reach out to the molecular team at NSO to clarify eligibility. As an example, if a patient is confirmed to be a carrier of a pathogenic variant for spinal muscular atrophy (SMA), a recessive condition, the reproductive partner of this patient would be eligible for carrier testing as the overall population carrier frequency for SMA is approximately 1/60 in the general population. In contrast, if a patient was confirmed to be a carrier of a pathogenic gene variant in *CPT2*, the gene responsible for Carnitine Palmitoyltransferase Type II (CPT II) Deficiency, their partner would not be eligible for carrier testing as the population carrier frequency is estimated to be estimated to be 1/180, which is below the 1/100 cut off. In this case, the risk to the pregnancy is too low for publicly funded carrier testing, however the couple may choose to pursue self-pay direct to consumer carrier testing as an alternative.

Eligibility for carrier testing also includes reproductive partners whose overall risk of an affected pregnancy is above 1/400. This may be relevant if considering a case where one partner is affected by an autosomal recessive condition, rather than just a carrier. If considering the example above, if the patient was instead affected by CPT II Deficiency,

meaning they carry two gene variants, the reproductive partner still has a carrier risk of 1/180, but they would be eligible for carrier testing as the overall risk to the pregnancy would be 1/360, which is above the 1/400 cut off.

4 – Increased Risk of Reproductive Partner Due to Ancestral Background

Some recessive genetic conditions have carrier frequencies can vary greatly based on ancestral backgrounds. Carrier testing for both reproductive partners based on ancestral background alone is not currently offered through NSO. For information on ethnicity-based screening programs available in Canada, please visit GECKO: https://www.geneticseducation.ca/resources-for-clinicians/prenatal-and-preconception-genomics/carrier-screening-in-canada/point-of-care-tool-14. However, if a known carrier's reproductive partner has an ancestral background with a known increased carrier frequency, eligibility for carrier testing will be considered based on the evidence available. As examples, the general population carrier frequency of pathogenic variants in *CYP21A2* is approximately 1/55, whereas it is estimated to be as high as 1/10 in individuals of South Indian, Yugoslavian, and Cypriot ancestry. The carrier frequency for *CPT2* pathogenic variants is approximately 1/180 in the general population but estimated to be up to 1/45 in individuals of Ashkenazi Jewish ancestry. As carrier frequencies may alter eligibility testing, NSO encourages healthcare providers to include patient's ancestral backgrounds on molecular requisitions if there is a known or suspected increase in carrier frequency for their patient.



REFERENCES

1. Aul, R. B. *et al.* Reproductive carrier screening for genetic disorders: position statement of the Canadian College of Medical Geneticists. *J Med Genet* **62**, 758–766 (2025).