APPLICABILITY

This document applies to all healthcare providers who are coordinating publicly funded carrier testing for patients with Alberta health care coverage. This includes requests for molecular testing through the Genetics and Genomics Laboratories as well as requests for out-of-province genetic testing.

Carrier testing in the context of this guideline refers to any genetic analysis which is performed for the purpose of identifying an unaffected heterozygous carrier of an autosomal recessive (AR) disorder, usually for the purpose of reproductive planning. Carrier testing scenarios may include, but are not limited to, the following:

a) Targeted sequence analysis for an individual after an AR pathogenic variant has been identified in their family member.
b) Full gene sequencing for an individual whose partner is known to be a carrier of (or affected by) an AR condition.
c) Targeted testing, full gene sequencing, or NGS panel testing for one or both members of a couple known to be at an increased risk for a recessive condition, based on ethnicity or family history.

This guideline does not apply to genetic testing for autosomal dominant disorders or X-linked disorders, nor does it apply when testing for an AR condition is requested for the purpose of confirming a diagnosis in a symptomatic individual.

In some instances, carrier testing recommendations from an established clinical practice guideline may supersede this guideline if they are considered to be standard of care in Alberta (e.g. carrier testing guidelines for individuals of Ashkenazi Jewish descent[1]).

In general, expanded carrier screening is not currently publicly funded. Expanded carrier screening refers to panels which look at several conditions simultaneously and are aimed at screening a pan-ethnic population not known to be at any increased risk based on race or ethnicity.[2]

PURPOSE

This guideline provides information regarding when carrier testing will be publicly funded for patients with Alberta health care coverage. This document should not be used to determine when carrier testing should be offered by clinicians. For patients who are not eligible for publicly funded testing, it is the responsibility of the clinician to discuss the option of private-pay testing if deemed appropriate.

BACKGROUND

This guideline was developed based on feedback gathered in stakeholder engagement meetings with Clinical Geneticists, Genetic Counsellors, and Molecular Geneticists in Alberta, as well as benchmarking with other Canadian provinces, and review of relevant literature including guidelines surrounding carrier screening panel development[2-4] and North American insurance company policies.

During the development of this guideline, it was noted that there is no standardization of carrier testing funding guidelines across Canadian provinces. There is limited information available in the literature regarding when carrier testing should be publicly funded in Canada.

DEFINITIONS

For the purpose of this guideline, the following definitions apply:

Reproductive risk	The chance for a couple to have a pregnancy or child affected with a specific AR disorder.
Well-defined population	An ethnic or ancestral group in which a reliable prevalence of disease has been established based on multiple studies.[4]
Well-defined phenotype	The natural history of the condition (including typical age of onset, signs and symptoms, diagnostic options, available treatments, etc.)[5] has been documented in the literature and is generally well-understood.

GUIDELINE

In order for an individual or couple to be considered for publicly funded carrier testing, ALL of the following conditions must be met:

1. The individual being tested must meet one of the following criteria:
    a. Individuals with a family history of a known pathogenic or likely pathogenic variant (as defined by the ACMG variant interpretation guidelines[6]) in a gene that causes an AR condition are eligible for funded targeted variant testing, irrespective of their reproductive risk, provided that the other conditions in this guideline have been met. Testing should ideally be completed in a cascade manner within the family, and a copy of the index report must be provided.
    b. For individuals with no known family history of an AR condition, carrier testing will only be funded if the reproductive risk for the couple for a given condition is greater than or equal to 1 in 600. If one individual in a couple is known to be a carrier for an AR condition, this would correspond to a minimum carrier frequency of 1 in 150 for the individual with no family history.
    c. Individuals with a family history that is highly suggestive of a known recessive disorder, but it is not possible to test an affected relative, or results from the affected relative cannot be obtained after reasonable attempts are made. In this scenario, a single gene test or multigene panel may be funded for the individual to determine carrier status. This may include couples with two or more prenatal or postnatal losses where existing records (including any previous investigations or biochemical testing) are suggestive of a recessive disorder.
    d. Couples with an ongoing pregnancy in which the fetus is presenting with clinical features highly suggestive of a known recessive disorder. In this scenario, single gene or multigene panel testing may be funded for the parents of the pregnancy, provided that:
        i. An invasive diagnostic procedure is medically contraindicated, AND
        ii. Parental carrier results will impact the decision to pursue invasive testing and/or termination or will impact immediate prenatal or neonatal medical management for the mother and/or fetus.
2. The carrier frequency of the condition must be known in at least one well-defined population*.[3,4] Given that patients might not be aware of their ancestry information, the individual being tested does not need to be from the specific population that has an established carrier frequency.
3. The clinical sensitivity of the carrier screen must be 70% or greater in at least one well-defined population*.[4]
4. The condition must have a well-defined phenotype and complete penetrance.[2-4]

5. The condition must be medically significant in the sense that it is associated with physical or cognitive impairment, a detrimental impact on quality of life, or the requirement for medical or surgical intervention.[2,4]
6. The condition must have a prenatal or childhood onset.[2-4] Adult-onset conditions do not qualify unless the information would be used for reproductive decision-making (i.e. prenatal diagnosis or preimplantation genetic diagnosis).

*Exceptions may be made for individuals who come from an isolated population, or who belong to an ethnic group where information about carrier frequencies and detection rate are not available. Additionally, exceptions may be made for consanguineous couples.

For routine (non-urgent) requests that meet the above criteria, stepwise testing of a couple should be coordinated unless there are extenuating circumstances that necessitate simultaneous testing of both members of the couple. For urgent requests where the above criteria are met, testing can be performed simultaneously for a couple if results are needed to inform decision making in an ongoing pregnancy.

If a request is received that does not meet all of the above criteria, the request will be cancelled, and the ordering clinician will be notified. The clinician has the option to re-submit their request with additional information, if the aforementioned criteria can be met. In instances where the above criteria are not met but the clinician feels there is a strong clinical indication to offer publicly funded carrier testing, the request may be sent to the laboratory genetic counsellors who will forward all relevant information to the appropriate individual for review. Requests for molecular testing through the Genetics & Genomics laboratories will be reviewed by the Molecular Genetics Laboratory Director(s) and requests for out-of-province genetic testing will be reviewed by the Genetics & Genomics Medical Scientific Director.

RESPONSIBILITY

Ordering healthcare providers and the Genetics & Genomics laboratory personnel are responsible for implementing this guideline.

REFERENCES

1. Langlois, S., Wilson, R. D., Allen, V. M., Blight, C., Désilets, V. A., Gagnon, A., ... & Chudley, A. E. (2006). Carrier screening for genetic disorders in individuals of Ashkenazi Jewish descent. Journal of Obstetrics and Gynaecology Canada, 28(4), 324-332.
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3. Grody, W. W., Thompson, B. H., Gregg, A. R., Bean, L. H., Monaghan, K. G., Schneider, A., & Lebo, R. V. (2013). ACMG position statement on prenatal/preconception expanded carrier screening. Genetics in Medicine, 15(6), 482-483.
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5. Hall J. G. (1988). The value of the study of natural history in genetic disorders and congenital anomaly syndromes. Journal of medical genetics, 25(7), 434–444.
6. Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., & Voelkerding, K. (2015). Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in medicine, 17(5), 405.