ALBERTA PRECISION LABORATORIES
Leaders in Laboratory Medicine

Exome Analysis Guideline

APPLICABILITY

This document applies to all healthcare providers who are coordinating exome analysis, historically referred to as whole exome sequencing, for patients with Alberta health care coverage. This includes requests for testing through the Genetics & Genomics Laboratories as well as requests for out-of-province genetic testing. Exome analysis is available for postnatal patients (infants, children, and adults), prenatal cases (DNA from amniotic fluid or chorionic villi during an ongoing pregnancy), as well as for pregnancy loss, stillborn, and post-mortem patients provided the criteria below are met.

At this time, the ordering of clinical exome analysis is restricted to medical geneticists with a designation of Fellow of the Canadian College of Medical Geneticists (FCCMG) and/or a Royal College of Physicians of Canada certification in Medical Genetics and Genomics, OR specialist physicians working with a certified genetic counsellor.

Trio exome analysis, which includes the proband and both biological parents, is preferred whenever possible. The inclusion of the proband's biological parents has been demonstrated to reduce the number of variants of uncertain significance (VUS) and increase diagnostic yield of exome analysis.

PURPOSE

This guideline provides information regarding when clinical exome analysis will be publicly funded for patients with Alberta health care coverage and applies to testing performed in-house or by an external laboratory.

GUIDELINE

Section 1: Indications for Clinical Exome Analysis

A request for clinical exome analysis will be considered eligible for public funding only when **all three** of the following criteria are met:

1.1 A baseline evaluation has been completed by a Medical Geneticist or appropriate specialist, including a physical examination (or autopsy, if applicable), family history evaluation, and any relevant preliminary investigations such as chromosomal microarray (applicable to patients with developmental delay, intellectual disability, multiple congenital anomalies, and/or dysmorphic features), biochemical studies, and/or targeted molecular testing.

1.1.1 For prenatal cases, a detailed fetal ultrasound and additional fetal imaging (ex. fetal echocardiogram, fetal MRI) or biochemical studies should be completed when possible based on gestational age. Rapid aneuploidy detection (RAD) should be completed prior to prenatal exome analysis. Studies to determine maternal cell contamination, and chromosomal microarray should be completed in parallel with exome analysis, or prior to exome analysis if timing allows.

1.2 The results are anticipated to directly impact clinical decision making and care for the patient and/or their family members, beyond providing anticipatory guidance. Results must be anticipated to meet **at least one** of the following criteria:

1.2.1 Will impact the patient's medical management or management of the fetus and/or pregnant person by limiting further invasive diagnostic investigations, informing the application of specific treatments, withholding contraindicated treatments, changing ongoing surveillance, or initiating palliative care.

1.2.2 Will allow for specific and informed reproductive decision making for the patient and/or their family members, including plans for continuation or termination of an affected pregnancy, delivery and/or post-natal management, and plans for postnatal palliative care.

1.2.3 Will enable identification of at-risk family members and facilitate early intervention or will enable the ability to rule out risk to family members, thus avoiding long term monitoring.

1.3 A genetic etiology is the most likely explanation for the patient's phenotype, supported by a clinical presentation which includes:

1.3.1 Severe to profound intellectual disability in the absence of known risk factors

OR **at least two** of the following:

1.3.2 Moderate to severe developmental or functional impairment

1.3.3 Multisystem involvement

1.3.4 Progressive clinical course

1.3.5 Differential diagnosis which includes two or more well-defined conditions requiring evaluation by multiple targeted gene panels

1.3.6 Suspected severe undiagnosed genetic syndrome for which multiple family members are also affected, or where parents are consanguineous

OR **at least one** of the following for an ongoing pregnancy:

1.3.7 Multiple congenital anomalies in the fetus. Anomalies may include any system or organ abnormality, as well as unexplained IUGR (growth <3rd percentile), unexplained overgrowth (growth >97th percentile), increased nuchal translucency (≥ 3.5mm), and unexplained polyhydramnios or oligohydramnios.

1.3.8 A single complex fetal anomaly that is considered highly genetically heterogeneous or in which two or more panels would be needed to cover the differential diagnosis. Decision to offer testing for any single complex anomaly will be determined by the clinical context, at the discretion of the most responsible physician.

Section 2: Exclusions to Exome Analysis

A request for clinical exome analysis will be considered *ineligible* for public funding if **one or more** of the following circumstances apply:

2.1 The clinical indication for testing the affected proband is:

2.1.1 Isolated mild intellectual disability or learning disability

2.1.2 Non-syndromic autism

2.1.3 Isolated neurobehavioral disorder (ex. attention deficit disorder)

2.1.4 Isolated neuropsychiatric condition (ex. schizophrenia, Tourette syndrome)

2.2 The phenotype of the patient or fetus is highly specific to a known condition or appears to fit into a single clinical category for which a more cost-effective phenotype-driven panel is available. In this situation, the phenotype-driven panel should be ordered.

2.3 The patient had an uninformative comprehensive gene panel reported within the past 2 years which included virtually all known genes related to their clinical indication. In this situation, clinical exome analysis would be considered experimental/investigational and would not be publicly funded.

2.4 A likely non-genetic etiology has been identified to explain the clinical presentation, such as a teratogen, environmental exposure, injury, or infection.

2.5 The fetus is presenting with any of the following in isolation, which are not considered eligible anomalies for exome analysis: gastroschisis, amniotic bands, or soft markers.

Section 3: Exome Reanalysis

Exome reanalysis should be requested through the laboratory that performed the initial exome analysis. For cases where the original exome was ordered prior to December 2017, the patient may be eligible for a second publicly funded exome analysis. Contact Genetics & Genomics to discuss.

Requests for exome reanalysis will only be considered eligible for public funding if **one of the following** criteria are met:

3.1 For patients with an initial exome report date of *at least* 2 years ago and who missed the window for free exome reanalysis (if applicable).

3.2 For patients who had an initial exome reanalysis reported *at least* 2 years ago, a second exome reanalysis will be publicly funded if there has been a significant change in the patient's clinical presentation.

3.3 For patients who had an initial exome reanalysis reported *less than* 2 years ago, a second exome reanalysis will be publicly funded if there has been a significant change in the patient's clinical presentation AND results are needed on an urgent basis to inform treatment, management, or family planning decisions.

Clinical Review Process:

The above criteria in Sections 1 and 2 will be used to ensure clinical exome analysis is indicated. In order to be considered eligible for public funding, ensure all criteria in Section 1 have been met, and none of the exclusions outlined in Section 2 apply. In rare scenarios when the above criteria may not be met; exome analysis will be considered if additional justification is provided. The lab genetic counsellors may request the input of the Clinical Director or the GRC Medical Scientific Director or designate to adjudicate difficult cases.

RESPONSIBILITY

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

Contact Information

Genetic Counsellors, Genetics & Genomics
Edmonton: 780-407-1015
Calgary: 403-955-3097

REFERENCES

Adapted from the Ontario Ministry of Health and Long-Term Care Genetic Testing Advisory Committee: http://www.health.gov.on.ca/en/pro/programs/gtac/reports.aspx

Lazier, J., Hartley, T., Brock, J. A., Caluseriu, O., Chitayat, D., Laberge, A. M., ... & Armour, C. M. (2022). Clinical application of fetal genome-wide sequencing during pregnancy: position statement of the Canadian College of Medical Geneticists. *Journal of Medical Genetics*, *59*(10), 931-937.

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