APPLICABILITY

The below criteria apply to requests for clinical whole exome sequencing (WES) for Alberta patients funded through the Genetic Resource Centre (GRC).

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

WES is available for postnatal patients (infants, children, and adults), as well as for pregnancy loss, stillborn, and post-mortem patients provided the below criteria are met. Prenatal WES for ongoing pregnancies is not available at this time.

Trio WES, 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 uncertain findings and increase diagnostic yield of WES. If duo or singleton WES is requested, the reason must be clearly outlined in the application (ex. patient adopted, parents unavailable, etc.).

PURPOSE

This policy provides information regarding when the GRC will fund clinical Whole Exome Sequencing for Alberta patients.

POLICY

Section 1: Indications for Clinical Whole Exome Sequencing

An application for clinical WES will be considered eligible for 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.

1.2 The results of WES 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 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.
- 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

AND/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

Section 2: Exclusions to Whole Exome Sequencing

An application for clinical WES will be considered *ineligible* for 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 patient's phenotype 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 given priority over WES.

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, WES would be considered experimental/investigational, and would not fall within the scope of clinical testing funded by the GRC.

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

Application Review Process:

The above criteria in Sections 1 and 2 will be used to evaluate applications for clinical WES. In order to be considered eligible for funding, applications must clearly demonstrate that a) all criteria in Section 1 have been met, and b) that none of the exclusions outlined in Section 2 apply. The GRC may request the input of the Clinical Director or the GRC Medical Scientific Director or designate to adjudicate difficult cases. The GRC appeal process remains available to ordering physicians who wish to contest a decision made by the GRC to not fund a WES request.

RESPONSIBILITY

Ordering healthcare providers and the GRC personnel are responsible for implementing this policy.

Contact Information

Genetic Resource Centre Phone: 403-955-5400, Fax: 403-592-4238 Email: grc@albertahealthservices.ca

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
Patient-centered Laboratory Utilization Guidance Services (PLUGS) Exome Sequencing Coverage Policy. (n.d.). Retrieved January 2, 2020, from http://www.schplugs.org/wp-content/uploads/Whole-Exome-Sequencing-Policy_10.2019-FINAL.pdf