

MOHLTC Process for Approval Clinical Whole-Exome Sequencing (WES)

The Ministry of Health and Long-Term Care requires that all applications for Out-of-Country/Out-of-Province (OOC/OOP) Prior Approval Program funding for clinical Whole-exome sequencing (WES) are accompanied by the attached completed checklist; an incomplete application may delay review and adjudication of the funding request. In alignment with the Genetic Testing Advisory Committee report entitled, "Use of Genome-Wide Sequencing for Undiagnosed Rare Genetic Disease in Ontario (Dec 2016)", and as recommended by Ontario experts in the field of clinical and molecular genetics, the checklist outlines specific clinical criteria for WES testing and attestations that state that the most appropriate clinical approach is being undertaken. Note that checklist criteria will evolve as more data is generated and should be considered *provisional* at this time.

Laboratory and Analysis Approach:

*Testing should be completed on the affected individual. Additional affected relatives or unaffected parents, if available, may be analyzed concurrently to facilitate and improve variant interpretation. The following approaches are suggested:

- Trios are the preferred WES strategy for undiagnosed patients with no family history of similarly affected individuals
- In the context of recessive inheritance, one affected individual and an unaffected parent OR two affected individuals is preferred
- If X-linked inheritance is clear, a singleton approach with filtering for X-linked variants is preferred.
- If a mitochondrial genome mutation is suspected, the mitochondrial genome should be analyzed directly using alternate and more sensitive approaches

Currently, WES is not funded as a reflex test when the appropriate genetic panel fails to yield a molecular diagnosis. If a comprehensive gene panel (ie. > 100 genes or where all known disease gene relationships are assessed) has been completed in the past 3 years and did not identify a causative pathogenic gene variant but there is a strong argument to be made for WES, please attach a letter justifying the need for WES.

This checklist cannot be used with prior approval applications for WES where the sample is from a fetus or stillbirth, or prior approval applications for WES with rapid/express turn-around-times.

Options if WES is Unrevealing:

If the clinical presentation of your patient is not explained after clinical WES you can consider the following:

- Request re-analysis (no less than 1 year after initial analysis)
- With appropriate consent, share your patient's phenotypic data, candidate gene and/or WES data with one of the many global sharing initiatives for unsolved rare diseases (e.g. www.phenomecentral.org)

Note that Whole Genome Sequencing (WGS), transcriptomes, proteomes, and metabolomes are NOT currently eligible for prior approval funding as a primary or reflex test.

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Laboratories and Genetics Branch
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CLINICAL WHOLE EXOME SEQUENCING (WES) CHECKLIST

PRIVATE & CONFIDENTIAL

Please complete this eligibility form and return it by fax with the prior approval application for funding of clinical WES to 416-326-2211 or 1-844-642-0202.

SECTION 1:

Patient Name: _____

SECTION 2: Analysis and Approach

*See "Laboratory Analysis and Approach" for guidance

I am requesting a:

Singleton

Duo

Trio

SECTION 3: Criteria

Clinical Presentation (must meet ≥ 2 items):

YES NO

- Moderate to severe developmental or functional impairment
- Multisystem involvement
- Progressive clinical course
- Differential diagnosis includes ≥ 2 well defined conditions requiring evaluation by multiple targeted gene panels
- Suspected severe genetic syndrome NYD for which multiple family members are also affected, or where parents are consanguineous

Management Impact (must meet ≥ 1 item):

YES NO

- Will limit further invasive diagnostic investigations
- Results allow for specific and informed reproductive decision making (for patient or parents)
- Will enable identification of at risk family members and facilitate early intervention

SECTION 4: Attestation (must meet all items):

YES NO

- I **confirm** that all the following conditions have been met:
- Detailed phenotypic characterization (physical examination, investigations) is documented
 - Pretest genetic counseling and consent has been completed
 - Chromosomal microarray has been completed and does NOT explain the patient's phenotype (applicable to patients with developmental delay, intellectual disability, multiple congenital anomalies, and dysmorphic features)
 - Other causative circumstances (e.g. environmental exposures, injury, and infection) do NOT explain the patient's clinical presentation, based on the most complete clinical history
 - Previous targeted testing was unrevealing where appropriate (eg. specific monogenetic disorder suspected)
 - Previous comprehensive panel testing has NOT been completed in the last 3 years (the panel contained virtually all known genes for the clinical indication)

YES NO

I **confirm** that the patient does NOT have:

- Isolated mild intellectual disability or learning disabilities
- Isolated non-syndromic autism
- Isolated neurobehavioural disabilities (e.g. attention deficit disorder)
- A phenotype highly specific to a known genetic condition for which an optimized genetic panel exists, or for which all known gene-disease associations could be assessed. If so, then the targeted gene panel should be given priority assuming it is more sensitive (e.g. Noonan spectrum disorders)

YES NO

I **confirm** that I:

- Practice in the area of genetics (as a geneticist/genetics consultant or in a clinic where a genetic counsellor has been integral to the care of the patient)
- Have expertise in performing a clinical genetics evaluation including family history, genetic-focused medical history and physical examination, and have a critical understanding of the prior genetic evaluations undertaken in the patient
- Have expertise in determining whether clinical WES is the test of choice for the specific clinical indication, prioritizing other available tests as appropriate
- Have expertise in providing adequate pre-test counseling, including informed consent for primary and incidental findings
- Have the ability to interpret the results of the clinical WES and provide adequate post-test counseling

YES NO

I **confirm** that:

- I understand that prior approval applications for WES may be audited and will provide clinical history to confirm the WES checklist attestations
- I understand that if recurrent inappropriate orders are identified, future prior approval applications for WES may be precluded from utilizing the WES checklist

Physician Signature: _____ Date: _____

If the required information is not received by the ministry **within 15 business days**, the prior approval funding application will be considered abandoned and the file will be closed.

Services rendered without written prior approval from the ministry are not eligible for reimbursement.

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