Ordering Guidance: Genome-wide Sequencing for Neurodevelopmental Disorders

Genome-wide sequencing (GWS) is a genetic test that looks at genes across the entire genome. It can refer to either exome sequencing (ES) or genome sequencing (GS). The difference between ES and GS is that ES focuses only on sequence variants in coding regions or exons, while GS also analyzes non-coding segments of the genome and can detect copy number variants more reliably. As of fall 2025, the province of Ontario has the capacity for clinical ES for neurodevelopmental disorders and is actively working towards a transition to GS. Therefore, the term GWS has been chosen to refer to either test (ES or GS), anticipating an upcoming changeover from ES to GS.

Identifying Eligible Patients

GWS is recommended for individuals with a clinical diagnosis of unexplained global developmental delay (GDD), intellectual disability (ID), or autism spectrum disorder (autism) as follows:

- Global developmental delay **and** currently less than 5 years
- Intellectual disability (moderate, severe, or profound)[1]
- Autism or mild intellectual disability, **and** one or more clinical features suggestive of a genetic syndrome[2]

GWS can be offered to eligible individuals by specialist physicians who diagnose, treat and/or follow individuals with neurodevelopmental disorders (NDD), have sufficient genetics expertise to provide pre- and post-test counselling, and are prepared to manage results, including subspecialist referral when needed. This expertise may come from their practice area, additional self-study, or formal training experiences. For additional guidance visit the Neurodevelopmental Disorders Genetic Testing Recommendations.

Ordering GWS

1. Ordering Documents

- **GWS Requisitions:** GWS is processed at the following two laboratories: Children's Hospital of Eastern Ontario (CHEO) and The Hospital for Sick Children (SickKids). Blood draws from across Ontario are shipped to one of these two laboratories. Provincial catchment area for each laboratory is listed here. Requisition forms include a face sheet, a clinical data sheet, the eligibility criteria, provider attestation, and a consent form. Requisition documents are

[1] For individuals for whom there is a strong clinical suspicion of ID but who have not yet received a formal assessment/diagnosis, a clinician may use clinical judgment to order genetic testing in consultation with a genetics and/or neurodevelopmental specialist.

[2] Abnormal head size (e.g., ±2SDs), congenital anomalies, medical complexity, distinct physical features, unexplained growth abnormalities. For more details refer to the Neurodevelopmental Disorders Genetic Testing Recommendations.

available here. A GWS requisition must be completed for each individual undergoing testing (including family members).

- **Other required documents:** To aid in GWS variant analysis and interpretation, it is important to send detailed clinical information about the patient and family history to the genomics laboratory. Please send clinical notes or investigations (e.g., consult notes, imaging) directly to the laboratory, including information on physical exam, past medical history and family history, to support the phenotype indicated on the requisition.

2. **Trio Testing:** All efforts should be made to order GWS as a **trio** (i.e., samples from the patient and biological parents). Including samples from biological parents for co-analysis increases the chances of identifying a clear diagnosis from GWS and reduces the chances of an uncertain test result. Currently in Ontario, GWS does not analyze the genomes of all individual samples independently, family samples are used to help interpret patient findings.

   While ordering as a trio is preferred, other testing strategies will be accepted, including singleton (patient only), duo (patient and one biological parent), or quad (patient, both biological parents and one other biological relative, such as an affected sibling, in some circumstances). If you have questions about the best strategy for your patient and their family, contact the GWS laboratory directly for support.

   Ensure the appropriate documentation is completed for **each individual** for testing. Please check local protocols for your institution for how to manage medical records for family members.

3. **Chromosomal Microarray (CMA):** CMA is **not** a prerequisite for GWS. CMA can be considered for patients that have not previously had CMA testing, or can be considered following an uninformative ES result, as ES can miss small copy number variants. Concurrent ordering of CMA with ES or DNA banking/storage may be considered in cases with challenging sample collection.

4. **Informed Consent:** The GWS Acknowledgment and Consent Form is part of the GWS requisition. Consent can be written or verbal. Consent must be obtained from all capable adults or parents/legal guardians of individuals not capable of providing consent. Consent must be obtained from every individual submitting a sample (including family members) regarding:

   - **Secondary Findings:** Consent to receive information about gene change(s) identified that do not explain the patient's neurodevelopmental condition but that could impact the patient's health and are *medically actionable* (i.e., contribute to health issues that can be prevented, screened for, reduced, or treated). For example, a gene change that shows an increased risk of heart disease or certain inherited cancers (breast, colon, ovarian, etc.).
     - **In children,** variants that are **medically actionable during childhood will be reported** to parents/caregivers (no opt-out option). Parents/caregivers can choose whether to receive information about adult-onset medically actionable conditions for their children.
     - **Adults can choose not to learn about secondary findings** and still get the other results from the test (all family members can decide independently). However, some secondary findings have a high degree of inheritance, so may suggest the status of that finding in a relative.
   - **Incidental Findings:** Patients and families should be aware it is possible to get a test result including an unexpected result not related to the reason for the test (e.g., non-paternity/non-maternity). In cases of incidental findings, the lab will contact the physician to discuss and plan next steps. For support with incidental findings consider connecting with a genetic counsellor (see resources below).

- **Research:** Consent to be contacted by testing laboratory for future research opportunities. This is optional.
- **Clinical Data Sharing:** Consent to share coded data (i.e., personal identifiers removed) through the Genomics Knowledge Network(s) approved by testing laboratory for quality improvement. This is optional.

  For more details refer to the consent form and info sheet, included in the requisition.

5. **Sample Collection:** Blood samples are the preferred sample type (EDTA/purple tube), unless the patient has had a recent heterologous bone marrow transplant. DNA previously extracted from a blood sample will also be accepted. To submit other sample types, please contact the testing laboratory for further instruction. For individuals where blood draws are challenging/require sedation, consider options for DNA banking/storage by connecting with your local hospital laboratory for information and instructions.

   Families can have their blood drawn for GWS by visiting a community laboratory (e.g., Dynacare, LifeLabs) with their genetics requisition. The blood will be drawn and shipped to a testing laboratory, and there is no cost to individuals with OHIP coverage. Note that some community laboratories only draw blood for genetic testing on certain days of the week to facilitate shipping.

   Families do not need to travel to the genetics laboratory for blood draws; some hospitals do not allow blood draws to be collected for external patients, or adults.

6. **Results:** Test results will be available in approximately 12 weeks and returned to the ordering provider directly, either through fax or, in some instances, local Electronic Medical Records (EMR). As of fall 2025, GWS reports do not flow into the province-wide electronic health record viewable through Connecting Ontario. Local institutions may have procedures to prevent reports from flowing directly into MyChart without clinician review first.

Interpreting Results

No pathogenic/likely pathogenic variants detected: No genetic cause was identified that accounts for the reported phenotype. Negative results do not exclude the possibility of an underlying genetic condition but significantly reduces the likelihood in most cases.

Next actions:

- Refer to a genetics clinic if an underlying genetic cause is still highly suspected.
- Consider other diagnostic testing in consultation with a genetic specialist through direct referral or eConsult.
- Advise families to reconnect in around 5 years for reinterpretation or reanalysis, as more information may be available in the future. Reconnect sooner if there is a change in phenotype.

Pathogenic/Likely Pathogenic: The variant identified supports a genetic cause for the neurodevelopmental condition in the patient.

Next actions:

- Inform family or patient that there was a finding on genetic report. Give the patient or caregiver a copy of their report, if appropriate.

- Refer to a genetics clinic for genetic counselling, care planning, and cascade testing (testing other family members). Additional urgency may be required in some situations including pregnancy-related management decisions in a family member.

Variant of Uncertain Significance (VUS): A VUS does not confirm a genetic diagnosis. The variant may or may not be the cause of the patient's neurodevelopmental condition(s). Some genes and variants have emerging evidence of pathogenicity, which may also be reported.

Next actions:

- Inform family or patient that there was a finding on genetic report. Give the patient or caregiver a copy of their report.
- Counsel the patient/family about the uncertain result.
- Refer to a genetics clinic, as a VUS result may require additional genetic expertise to clarify.

Additional Support

Innovative care approaches and collaborative models are emerging to support non-geneticist providers. At present, for further assistance, please consider the following options as needed:

- Consult gcConnect (1-844-564-4363, gcconnect@ontariohealth.ca) for genetic counsellor support of health care teams in navigating genetic services for their patients.
- Submit an eConsult request to connect with a genetics specialist through OTNhub.
- Visit Genome-wide Sequencing Ontario for requisitions and test information.
- Send a referral to your local genetics clinic (Genetics Clinics in Ontario).
- Visit the Ontario Genetic Test Directory to find genetic tests available in Ontario.