# Neurodevelopmental Disorders

## Recommendations for the Delivery of Genetic Testing in Ontario

PROVINCIAL GENETICS PROGRAM
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# Introduction

Ontario Health has been mandated by the Ministry of Health (MOH) to "*ensure the successful implementation of genetic testing and establishment of a comprehensive provincial program for all genetics with robust provincial oversight to deliver these services to drive better outcomes for Ontarians and improved value.*" To fulfill this mandate, the Provincial Genetics Program (PGP) was launched in April 2021. The PGP and Provincial Genetics Advisory Committee (PGAC) identified neurodevelopmental disorders (NDDs) as a priority domain for development in Ontario, resulting in the formation of the Neurodevelopmental Genetics Expert Group. The role of the Expert Group is to develop evidence-based guidance for the provision of genetic testing and counselling services.

The NDD patient journey and provision of genetic services through the healthcare system is multifaceted and complex. While the Expert Group has a plan to address the need for guidance throughout the patient pathway, genetic testing was prioritized as the initial focus for its ability to inform specific diagnoses and guide families towards evidence-based treatments and supports. This report was developed by the Expert Group in collaboration with health care professionals, laboratory scientists, administrators, and patient and family advisors, and outlines genetic testing recommendations for individuals with NDDs in Ontario.

## Guidance Document Scope

This document provides a set of general principles and recommendations for the delivery of standardized, coordinated, and evidence-based genetic services for individuals with NDDs in Ontario and their families. Multiple organizations have released recommendations to address genetic testing of individuals with NDDs (See Appendix A). In 2023, the Canadian College of Medical Geneticists (CCMG) published a position statement on genetic testing for patients with NDDs to promote standardization of Canadian clinicians. The CCMG document was intended to inform immediate clinical practice and considers the variability across the country in access to publicly funded genetic testing. This guidance document developed by Ontario Health is specifically intended to develop a stepwise plan towards an ideal future state in Ontario.

This document includes recommendations for evidence-based genetic testing for NDDs in pediatric settings but may also be applicable to adult populations. The NDDs covered by these recommendations include intellectual disability (ID), global developmental delay (GDD), and autism spectrum disorder (ASD or autism). Attention deficit hyperactivity disorder (ADHD), specific learning disabilities (LD), and communication and motor disorders are excluded at this time, as evidence for genetic investigations in these conditions is not yet established. Although this does not represent the full breadth of NDD diagnoses, these groups (autism, ID, GDD) are currently understood to have the highest likelihood of an underlying genetic diagnosis. For other NDD diagnoses, there is less evidence on which to base recommendations at this time.

This Expert Group acknowledges the evolving use of medical terminology, as well as the importance of language with respect to identity and neurodiversity. In this report, we have chosen to use identity-first language ("autistic child" as opposed to "child with autism") in line with the voiced preferences of many members of the autistic community[2].

This report will be reviewed by the Expert Group on a timeline of every 2 years to ensure it remains up to date. If emerging knowledge arises before then, the guideline and recommendations may be reviewed sooner to support patient care as needed.

# Background

Neurodevelopmental disorders (NDDs) are a group of early childhood-onset conditions that cause difficulties in the acquisition of specific intellectual, motor, language, or social skills or abilities[3]. According to the Diagnostic and Statistical Manual Of Mental Disorders, Fifth Edition (DSM-5), NDDs include intellectual developmental disorder (i.e., intellectual disability- ID), global developmental delay (GDD), autism spectrum disorder (ASD - here referred to as 'autism'), attention-deficit/hyperactivity disorder (ADHD), specific learning disorder (LD), and communication and motor disorders[4]. NDDs are among the most common childhood-onset disorders; they have a combined prevalence of ~17% in children aged 3-17 years[5]. For the purpose of this report, the NDDs that are in-scope include ID, GDD, and autism. The prevalence of ID is calculated at around 1%[5], GDD affects 1-3% of children under the age of 5[5,6], and autism is estimated between 1-3%[5,7,8], with a third of cases co-occurring between ID and autism[9].

Diagnosis of NDDs is typically the purview of childhood developmental specialists such as physicians (e.g., paediatricians, child psychiatrists, and child neurologists) and psychologists, with significant input from therapists (e.g., speech, occupational, and physiotherapists) and early childhood educators. Some NDDs can be diagnosed by taking a thorough developmental history and clinical examination (e.g., GDD, autism), whereas other NDDs require standardized psychological tests (e.g., ID, LD). Referral to genetics often occurs after a developmental diagnosis has been established, or if there are clinical features suggestive of an underlying genetic syndrome/condition (Appendix B)[10]. However, referral may precede a formal diagnosis in young children with obvious developmental delays and/or in adults who may face barriers to accessing a formal diagnosis.

While not every patient with a NDD has an identifiable underlying genetic condition, for those who do, the benefits of obtaining a genetic diagnosis are well documented[8]. A genetic diagnosis can inform genetic counselling for the individual and their family members. It may also guide medical care for the individual by helping to anticipate possible complications related to the specific diagnosis and allow for targeted surveillance for known co-morbidities[11]. In some cases, a genetic diagnosis may lead to tailored, disorder-specific therapies, which is an emerging area of medicine for this patient population[8,12]. Examples include a Food and Drug Administration (FDA) approved treatment indicated for individuals with Rett syndrome (cause by variants in the *MECP2* gene) and clinical trials are underway for multiple compounds to treat Fragile X syndrome[13,14]. Finally, a genetic diagnosis may improve the quality of life for families and facilitate a better understanding of a child's needs[15]. There are important psychological benefits of identifying the underlying cause of an NDD in a child, which can bring an end to an often long diagnostic odyssey and open the door to a more tailored plan of care[8,10,16].

Recent research suggests that using genome-wide sequencing (GWS) approaches, such as genome or exome sequencing with copy number variation (CNV) analysis, improves the diagnostic yield, is cost-effective, and reduces the time to achieve a genetic diagnosis[8,17–20]. The diagnostic yield of genetic testing in this patient population is estimated to be 31-53% in individuals with ID/GDD and 12-25% for autistic individuals[8,17–20]. The highest diagnostic yield is found in autistic individuals who have lower IQs, co-occurring neurological conditions (e.g., seizure disorders), specific physical or morphological features, and/or congenital anomalies[8]. For the purposes of this document, GWS refers to all the

possible alternatives to identify single nucleotide variants (SNVs) and CNVs (i.e., genome sequencing [GS], exome sequencing [ES] with chromosomal microarray analysis [CMA], or any other applicable technologies). ES and CMA are more widely used in current medical practice, but as costs decrease, GS is likely to be more widely implemented (see Appendix D for a comparison of laboratory genetic testing strategies)[21]. The decision between implementing ES or GS for this patient population in Ontario is beyond the scope of this document.

# Current State

## Genetic Testing in Ontario

In general, genetic testing for individuals with NDDs fall into 3 main categories:

- Syndrome-specific testing (e.g., testing for Fragile X and Angelman syndromes)
- Detection of CNVs (e.g., CMA)
- Detection of genetic variants in multiple genes simultaneously (e.g., multigene panels [MGP] and GWS)

The specific test options offered to the patient is dependent on the clinical presentation and the physician's comfort level with ordering genetic testing and interpreting the results. If genetic testing is offered, it is typically done in a stepwise fashion whereby 'first-tier' tests such as CMA are completed before MGP or GWS. Fragile X testing and CMA are available in multiple hospital-based genetics laboratories in Ontario. Multigene NDD panels and/or medically urgent GWS can be accessed through the Ministry of Health's Out-of-Country & Out-of-Province Prior Approval Program for eligible patients who are approved for funding (see Appendix E for in-province and out-of-country testing volumes), while 'routine' (non-urgent) clinical GWS has been available in Ontario since April 2021 for eligible patients through the Genome-wide Sequencing Ontario (GSO) pilot project.

In 2016, the Genetic Testing Advisory Committee (GTAC) published a report recommending GWS to be publicly funded for undiagnosed rare diseases, then in 2020, Ontario Health Technology Advisory Committee (OHTAC) and Ontario Genetic Advisory Committee (OGAC) released a recommendation for funding of ES as a second-tier test[22,23]. Subsequently, the GSO pilot was funded by the Ministry of Health (MOH) as a mechanism to evaluate the feasibility of implementation of ES in Ontario. GWS for rare disease diagnostics has been available as a clinical service in Ontario for eligible children and adults since April 1, 2023. This service has oversight and funding from Ontario Health.

The primary goal of the GSO pilot project was to demonstrate the feasibility of implementation of genome-wide sequencing in the province of Ontario. The diagnostic yield reported by GSO was 31% (1,238 patients sequenced) (pending publication). It is important to note that the patient eligibility criteria for this project specifically excluded those with isolated mild ID or isolated autism, and therefore only included a subset of individuals with NDD.

## Access to Clinical Genetics Services

There is considerable variability in the types of genetic testing that may be offered for patients with NDDs in Canada[24]. Genetic testing can often be logistically complicated to order and requires specialized knowledge to interpret the results in the context of the phenotype of the patient, which can be a significant barrier for clinicians without specialized training in genetics. Local resources, particularly in northern and rural Ontario, are lacking (e.g., community-based blood draw facilities are not equipped to ship samples to specialized labs or take blood samples from individuals, particularly children, with disabilities)[25]. In Ontario currently, second-tier tests (i.e., ES or MGP) can only be ordered by clinical geneticists or specialists working with a genetic counsellor. Given the limited availability of genetic clinicians who specialize in this area, wait times for clinical genetics consultation (and therefore access to second-tier testing) can range from 6 months to 2 years[26]. Genetics clinics in the province have locally developed referral criteria (Appendix F), and this can also mean that access to genetic consultations for patients with NDDs is highly variable depending on local resources and wait times.

# Recommendations

## Guiding Principles

The following principles were established to guide the development of the recommendations provided in this document.

- Genetic testing for individuals with NDDs should be initiated **as early as possible** to support clinical management and genetic counselling[27].
- Clinicians and patients should have **equitable access** to effective and appropriate genetic testing that maximizes personal and clinical utility.
- Genetic care should be efficient, person-centered, and enabled by **appropriate capacity** and access to genetic professionals and/or specialists with genetics expertise.
- Clinicians, patients, and families should have access to **educational tools and resources** to improve navigation through the system, guide eligibility for genetic testing and evidence-based management, and aid in the interpretation of test results.
- Provincial planning should support **coordination and standardization of services** across the province for all patients to optimize health care resources.

The recommendations in this document are intended to provide advice to the Ministry of Health on the following questions related to genetic testing and services for NDDs:

- Who should be eligible for genetic testing?
- What genetic tests should be available to patients and families with NDDs?
- How should genetic testing for patients with NDDs be implemented in the province of Ontario?

## Recommendation 1: Establish standardized clinical pathways to guide genetic testing and referral to genetic services for NDDs.

Based on the best available evidence of diagnostic yield and clinical utility of genetic testing in patients with NDDs and Expert Group consensus, genetic testing is indicated for all individuals diagnosed with unexplained GDD, ID and autism as follows[1,8,20]:

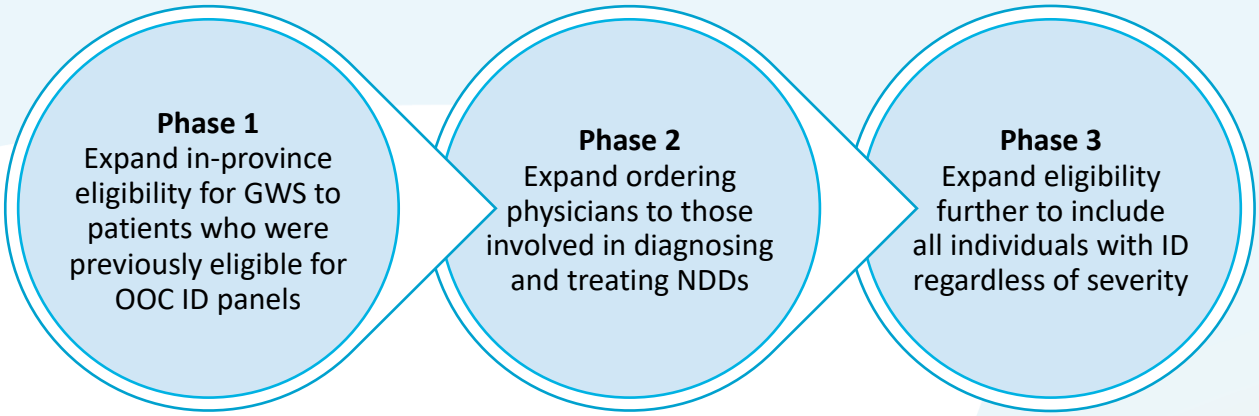
- GDD, ID[a], or autism with one or more clinical features suggestive of an underlying genetic syndrome:
  - GWS with concurrent CNV analysis
- Isolated autism[b]:
  - CMA
- GDD, ID, or autism:
  - Fragile X testing or other rare single gene tests when indicated (Appendix C)[1,28].
  - Metabolic screening when indicated (Appendix C)[1].

Given that the current eligibility criteria for GWS in Ontario will need to be broadened to accommodate for the proposed indications, the Expert Group supports a phased approach to implementing the recommendation (Figure 1). The anticipated decreasing costs and increasing availability of GWS will facilitate the adoption of these recommendations, however system level planning to initiate steps towards an ideal future state is needed now[21]. The proposed approach considers the collection of real-world data at every stage to measure the impact of the recommendations in Ontario and to revise and refine the implementation as required. Measurement will require linking the test results data to administrative health datasets. The Expert Group can assist with defining performance metrics related to health outcomes, health system value, patient satisfaction, and clinician experience. These metrics would be used to inform data collection, evaluation, and improvement initiatives. By defining a clear method for prospective assessment, a pathway to broader implementation (or disinvestment) could then be mapped.

[a] 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 judgement to order genetic testing in consultation with genetics and/or a neurodevelopmental specialist.

[b] For isolated autism (i.e., autism without intellectual disability and without additional clinical features suggestive of a genetic syndrome), evidence on the clinical utility of GWS sequencing is still emerging as of 2024. For this initial guidance document, we recommend adopting Canadian guidelines (i.e., CMA not GWS)[1] for this group, to first enable capacity building for GWS in Ontario; recommendations will be updated in 2 years incorporating new evidence on GWS in autism.

**Figure 1. Proposed Phases to Implement Genome-wide Sequencing for Neurodevelopmental Disorders**




## Phase 1: Redirect individuals currently tested via MGPs to GWS

As a first step, the Expert Group recommends **adopting the eligibility criteria outlined in Table 1 for GWS**, such that individuals currently being approved for out-of-country/out-of-province (OOC/OOP) ID MGPs would now be eligible for in-province GWS testing. Phase 1 aims to streamline the testing process for individuals with NDDs and ensure access to appropriate testing readily within Ontario. Neurodevelopmental specialists ordering genetic testing should work with genetics clinics to establish testing pathways and deliver appropriate genetic counselling for their patients. Implementation, evaluation, and measurement of outcomes of this phase is crucial to assess the system readiness for the next phase.

## Phase 2: Promote front-lining of GWS to be ordered by physicians who diagnose and/or treat patients with NDDs

In line with the priority of earlier access to genetic testing for patients and families, phase 2 would focus on moving to a model in which **genetic testing could be initiated at the "front-line" by the diagnosing and/or treating physician**[1]. In phase 2, the Expert Group recommends avoiding stepwise or tiered genetic testing, particularly when it creates additional access barriers for patients and families[20,29]. In this phase, consenting and sample collection could be facilitated at a single visit for the patient. Prior to entering phase 2, the genetics laboratories should assess the best testing pipeline (e.g., perform CMA and reflex to ES if CMA is uninformative, CMA and ES concurrently, or perform GS directly, if available) and physicians not previously trained to order and interpret GWS should have education and support available to allow for smooth transition to a new model of care.

## Phase 3: Expand funded indications for GWS.

In Phase 3, we **introduce an expansion to the funded indications for GWS**, initially allowing testing of individuals with ID, regardless of severity. The available evidence reviewed for the development of this report focused on individuals with GDD, ID, and autism. The evidence varies greatly in terms of the clinical phenotypes studied. Research evaluating the performance of GWS on individuals with mild ID or isolated autism is emerging[30–32], and more evidence is needed to definitively exclude milder cases of ID. The CCMG recommendation also recognized that there is insufficient evidence to exclude

individuals from genetic testing based on level of disability and recommended further studies to be conducted[1].

Before initiating phase 3, it would be crucial to focus on planning and ensuring capacity and funding for genetics laboratories to meet the expected increase in clinical need and volumes of an expanded patient population. Also, pathways for implementation and novels models of care should be considered to ensure adequate service provision at this stage[27], and primary care physicians should be supported with education, tools, and resources to order testing, particularly GWS.

This phase should be contingent upon further evidence building for testing of NDDs and system readiness (e.g., wait times, referral volumes, testing uptake).

## Guidance Regarding Ordering Genetic Testing

Genetic testing may be ordered by any clinician that is involved in diagnosing and/or treating a patient with an NDD who has the skills, knowledge, and expertise to provide the care described below. Evidence-based guidelines, expert opinions, and accrediting bodies have emphasized the importance of providing pre- and post-test genetic counselling to assist individuals in complex clinical decision-making[33–35]. Pre-test counselling should include information on why the test is being offered, how test results may impact medical management, benefits and limitations of the test, explanation of possible test results for the individual and family as well as technical aspects and accuracy of the test. Post-test counselling should include results disclosure, discussion of the results and the interpretation, a discussion of next steps in terms of medical management, discussion of potential psychosocial impacts, and provision of diagnosis-specific resources.

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

## Table 1. Phased Approach to Service Delivery of Genetic Testing for Individuals with Neurodevelopmental Disorders

| | Phase 1 | Phase 2 | Phase 3 |
|---|---|---|---|
| **Goal** | Expand in-province eligibility for GWS to patients who were previously eligible for OOC ID panels | Expand ordering physicians to those involved in diagnosing and treating NDDs | Expand eligibility further to include all individuals with ID regardless of severity |
| **Eligibility criteria for GWS** | Individuals with:<br>• GDD and age <5 years moderate, severe, or profound ID[a]<br>• Moderate, severe, or profound ID[a]<br>• Autism[b] or mild ID, and one or more clinical features suggestive of an underlying genetic syndrome. | Same as Phase 1 | Individuals with:<br>• GDD and age <5 years;<br>• ID (any severity);<br>• Autism with one or more clinical features suggestive of an underlying genetic syndrome. |
| **Recommended ordering physician** | Geneticists and neurodevelopmental specialists | All physicians involved in diagnosing and treating NDDs | Same as phase 2 |

[a.] 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 judgement to order genetic testing in consultation with genetics and/or a neurodevelopmental specialist.

[b.] For isolated autism (i.e., autism without intellectual disability and without additional clinical features suggestive of a genetic syndrome), evidence on the clinical utility of GWS sequencing is still emerging as of 2024. For this initial guidance document, we recommend adopting Canadian guidelines (i.e., CMA not GWS)[1] for this group, to first enable capacity building for GWS in Ontario; recommendations will be updated in 2 years incorporating new evidence on GWS in autism.

## Recommendation 2: Implement strategies to improve access to genetic testing and clinical services.

Successful implementation of updated, evidenced-based and comprehensive genetic testing strategies for patients with NDDs will require consideration and planning for a number of improvements within the system of care that supports these patients. While these testing strategies are not necessarily novel, they do require a culture shift within the system. In addition, many of the suggested improvements could span beyond NDD and be universally beneficial for the genetics system. A phased or incremental approach to system level changes is envisioned with both short- and long-term solutions. Success should be defined through the lens of health quality in that genetic

testing and interpretation of test results for patients and families with NDDs should be efficient, timely, safe, effective, patient-centered, and equitable.

The recommendations outlined below would support these goals:

- Testing should be initiated as early as possible in the diagnostic journey; barriers to test ordering by non-genetics physicians should be minimized.
- Increased capacity for timely access to genetics specialists for clinical advice and patient care is required. Development of wait time targets may be beneficial[36].
- Tools and resources should be developed for clinicians and patients/families regarding genetic and genomic testing for NDDs and the interpretation of results.
- Novel models of care delivery should be explored and developed to support equitable access in under-served and equity-deserving populations[27,37–39]. This includes models where non-genetics specialists are equipped to initiate and interpret testing enabling triage of the most clinically appropriate patients to genetics.
- Specimen collection and transport through saliva/buccal kits should be available to support access to testing and better enable the collection of parental/family samples for trio-based testing.
- Robust provincial oversight for both laboratory and clinical genetics services, including the measurement of key performance indicators, should be implemented to facilitate continuous quality improvement (see Key Performance Indicators for more information).

To advance the recommendations outlined above, the Expert Group considered several opportunities related to implementation:

## Improved Access to Genetic Testing and Services

Currently, the ability to order comprehensive genetic testing (i.e., large MGPs and GWS) for NDDs is largely restricted to medical geneticists, specialists with expertise and/or training in genetics, or in a clinic where a genetic counsellor has been integral to the care of the patient. This group of clinicians currently has the most well-defined skill set to provide high-quality genetics care and navigate the appropriate use of genetic testing for patients. However, given the size of this patient population, the limited number of trained genetics professionals, and associated wait time pressures in genetics clinics across the province, test ordering limitations are a significant barrier for access to genetic testing in most individuals presenting with NDDs.

The gap in the system of clinical genetics to appropriately meet demand for services has been previously evaluated in the 2018 report, “Recommendation Report for Ontario’s Clinical Genetic Services”[26]. In order to ensure genetic testing occurs as early as possible in the diagnostic pathway, systems to support the ability of non-genetics physicians to order testing need to be developed.

To improve the clarity and standardization of the process for ordering genetic testing, the Expert Group recommends:

- Clear guidelines for Ontario health care professionals regarding genetic testing eligibility for patients with NDDs (such as those proposed in this recommendation report) and regarding criteria

for referral to genetics clinics. The preferred format would be a brief, Ontario-focused, decision tree regarding what tests to order for which patients and when to consider a referral to a clinical genetics service.

- A comprehensive, centralized provincial genetic test directory that includes relevant information and clear instructions regarding sample requirements, collection, and transport for publicly funded testing available in Ontario.
- A directory of genetics clinics providing consultative care for patients with NDD, including current, detailed information related to referral requirements and catchment area.
- Establishment of new models of clinical service delivery, with the aim to support timely access to high-quality care, support collaboration between genetics professionals and other health care professionals, increase capacity, and optimize health system resource use as has been completed previously for cancer genetics services in Ontario[37,39,40].
- A provincially accessible electronic medical record (e.g., Ontario Laboratories Information System [OLIS]) in which genetic test results can be accessed at any time by all clinicians within the circle of care. This will help to prevent duplication of testing and delay in test result communication to patients.
- Increased capacity for virtual, asynchronous consultation with a medical geneticist or genetic counsellor, for timely support in complex and/or unique clinical situations, and creation/ adoption of a billing mechanism that would incentivize both referring and consulting providers to use it.
- Genetic lab reports that are standardized and provide clear, non-technical language to support interpretation of results for the non-expert clinician and patients. This could include customization of variant reporting based on the comfort level of the ordering provider. These guidelines would be designed in partnership with the laboratories, clinicians, and patients to meet all knowledge user needs[41,42].
- Additional strategies proposed by the Expert Group to support the transition to the proposed model include enabling rapid access to direct clinician-to-clinician consultation alternatives, and exploring alternatives for laboratory reporting (e.g., dual signing of reports, by a clinician and a laboratory scientist, or limiting the variants of uncertain significance [VUS] reported).

## Enhanced Education and Training for Healthcare Practitioners

The field of genetics and genomics is expanding and evolving rapidly, and non-genetics physicians often do not feel comfortable or knowledgeable about ordering genetic tests. On the other hand, some physicians with appropriate expertise may be restricted from ordering genetic testing (as is currently the case with GSO).

To improve the competency in ordering genetic testing by non-genetics physicians, the Expert Group recommends:

- Development of concise summaries of key steps to order genetic testing for patients with NDDs, accessible to clinicians without expertise in this area.
- Access to a provincial resource where clinicians can receive on-demand, patient-specific guidance regarding genetic testing eligibility, consent process, results interpretation, and counselling.

- Creation of resources to educate clinicians on the key components of pre-test counselling, results disclosure, interpretation, change in management, reproductive decision making, and prognosis. The development of educational resources and materials may be advanced through strategic partnerships.
- Development of continuing medical education content that could be delivered at clinical conferences and communities of practice. Specific partners for the delivery of such education around genetic testing for NDDs could include the Canadian Pediatric Society, College of Family Physicians of Canada, Canadian Nurses Association, Genetics Education Canada: Knowledge Organization (GECKO), and the Canadian Psychiatric Association.
- Increase genetics and genomics education in general in the curriculum of undergraduate and post-graduate medical programs.

## Increased Support for Patients, their Families, and Equity-Deserving Populations

There are several factors that need to be taken into consideration in developing an approach to genetic testing for patients with NDDs. Patients, family, and caregivers have diverse backgrounds with respect to genetics knowledge and health literacy, requiring personalization of the process of pre-test counselling. Mistrust regarding genetic testing based on patient experience/background also serves as a barrier to accessing genetic services[27]. The prevalence and impact of non-genetic factors (e.g., socio-economic factors) in the development of NDDs may also vary by population[43]. Finally, blood-derived DNA samples and trio samples may be difficult to obtain in some individuals with NDDs and their families and this is an important factor affecting access that requires consideration.

The development of strategies to support equitable access to genetic services should consider currently available resources (e.g., GECKO, locally developed materials, telehealth for group genetic counselling) and prompt a needs assessment to identify any gaps and unmet needs in Ontario.

To support a person-centred and equitable approach to genetic testing, the Expert Group recommends the development of:

- Patient education materials that help patients and families to understand:
  - The benefits of genetic testing and pre-test counselling information, which ultimately contribute to informed consent for testing.
  - Genetic test results and how to appropriately interpret them.
- Intake processes that limit barriers to test access for patients and families, including simplified methods of collecting family history information. Patients and caregivers should be involved in identifying barriers and providing input as to proposed improvements.
- Processes that promote shared decision-making between clinicians and patients, to build trust and honour individual preferences and goals.
- Engagement with equity-deserving, remote and under-served communities to promote awareness, understanding, and appropriate implementation of genetic testing that aligns with the needs and priorities of individual communities.

- Promote access to direct clinician-to-clinician consultation alternatives, including e-consult and telephone consultations.

### Key Performance Indicators

The PGP is in the process of developing a measurement plan to support ongoing measurement and evaluation of these recommendations, as well as to ensure continuous quality improvement in Ontario's genetics system. Specific goals for which metrics are being developed include:

- Providing timely and equitable access to genetic services.
- Improving the quality of life and health outcomes for patients and families with genetic conditions.
- Improving the patient and clinician experience.
- Improving efficiency at a system level.

Potential metrics for neurodevelopmental disorders genetic testing include volumes of in-province and OOC/OOP genetic testing, test turnaround times, and variant detection rates. Clinical metrics could include wait times, number of genetics clinics in each region, uptake in remote, underserved, and equity-deserving populations, and rates of care close to home.

Currently, the PGP is working to support the development of provincial wait time targets and implementation of a systematic approach to measurement, monitoring, and quality improvement for genetic services.

The Ontario Health Pathology and Laboratory Medicine Program provides oversight for funded genetic testing in Ontario. The current metrics that are collected from laboratories for funded tests include volumes, turnaround times, and diagnostic yield (variant detection rates). A broader strategy for the collection, storage, and use of all provincial genetic testing data is under development at Ontario Health. While the time-limited collection of real-world data may initially be feasible in a pilot setting without the larger data strategy in place, it is not a sustainable solution on a provincial scale. Ontario's genetics digital strategy must be implemented to support ongoing performance and quality measurement of all genetic testing performed in Ontario, including genetic testing of neurodevelopmental disorders.

## Recommendation 3: Invest in the resources and infrastructure required to fulfill the recommended NDD clinical pathway.

### Technical and Laboratory Considerations

The consensus of the Expert Group is that:

- In patients with NDDs who meet the criteria for genetic testing outlined in this document, a GWS approach that analyzes both SNVs and CNVs is recommended.
- A trio-based approach to GWS testing (sequencing of patient and both biological parents) is recommended to optimize variant interpretation whenever possible.

- Ordering clinicians should submit detailed information about the patient phenotype, medical and family history to optimize variant interpretation, however, efforts should be made to ensure streamlined processes for ordering genetic testing.
- An option to limit the information presented in a genetic test report to pathogenic/likely pathogenic variants related to the primary clinical indication should be available for the clinicians and/or patients, though personalized reporting exclusions may be operationally challenging[44].
- The option to order re-analysis and/or re-interpretation of genomic data over time should be available as evidence emerges about new gene-disease associations and when the phenotype or relevant family history of the patient changes[45–47].
- The decision to update or expand genetic testing to patients who have previously received uninformative results should be made in collaboration with local laboratory genetic services and should be associated with a reasonable likelihood of clinical benefit to the patient/family.
- Analysis and reporting by labs should be consistent and phenotype-driven to reduce the number of VUSs that are reported. The language and organization of lab reports should be designed to facilitate understanding by patients, caregivers, and non-genetics physicians. This could include synoptic, abbreviated versions provided to non-genetics physicians[41,42,44].

There is high genetic heterogeneity and prevalence of non-specific phenotypes in this patient population. Based on reliable gene curation resources (e.g., ClinGen and PanelApp England), there are hundreds to thousands of gene variants (both SNVs and CNVs) that have been associated with NDDs. There are also large-scale efforts to curate evidence-based gene lists for autism[48]. The process of gene curation for this patient population is ongoing and continually evolving. Given the number of genes involved, the ability to curate and maintain an MGP in Ontario would have significant carrying costs for the system as it would require regular review and updating by the Expert Group followed by ongoing resources to support validation and implementation of updated testing within genetics laboratories. Due to current reporting practices, MGPs will identify more VUSs than GWS as interpretation depends less on phenotypes provided by the clinician and more on the contents of the panel.

There are several technical considerations that will be important to consider in implementation of lab testing. ES is currently clinically available in Ontario, although eligibility is based on criteria that exclude patients with mild ID without additional features suggestive of a genetic syndrome. While ES is less costly than GS, GS is emerging to have several technical advantages over ES[47]. GS enables detection of variants in introns, promoter regions, and regulatory elements, has high sensitivity for CNVs down to exonic level deletions and duplications, can be optimized to detect variants in homologous genes and resolve variations in functional vs pseudogenes, can detect variants in mitochondrial genes, and can screen for large rearrangements and repeat expansions (with lower sensitivity and precision than traditional approaches at this time). A more detailed comparison of the pros and cons of different testing strategies are outlined in Appendix D.

All forms of genetic testing can produce VUSs, which can be clinically challenging to interpret. Generally, the more genes tested, the more VUSs will be reported back to the clinician. The issue of reported VUSs and their diagnostic uncertainty cannot be understated as it requires significant laboratory resources for variant interpretation and classification, time from clinicians in terms of

clinical correlation and follow-up, and ultimately, can result in additional distress and uncertainty for patients and families[49]. To reduce VUS reporting and its impact on the system, the laboratory analysis and reporting should be consistent across laboratories[49]. As is the current standard for ES and GS, VUSs should not be reported unless consistent with the clinical phenotype as provided by the clinician at the time of ordering.

## Volume Projections and Implementation Considerations

The prevalence of GDD and/or ID in a pediatric population has been estimated at 1-3%[5,6], where individuals with moderate, severe, and profound ID represent 0.5-1%. In Ontario, 141,699 children were born in 2022[50]. Based on this figure, in phase 1, up to 1,417 children might be eligible for testing yearly, and up to 4,250 children might be diagnosed with GDD/ID each year and be eligible for genetic testing once the expanded eligibility criteria are implemented in phase 3. The potential volumes of autistic individuals with additional clinical features are harder to predict, however, these patients may already be considered for genetic testing due to multisystemic involvement. Universal CMA testing for autism is part of current eligibility guidelines, although the rate of uptake in autistic individuals is not known.

To support implementation of expanded genetic testing options for NDDs, the Expert Group recommends:

- Updated cost effectiveness analysis of first-tier GS vs ES after CMA[22] to identify the optimal moment to transition from exomes to genomes[47].
- Capacity planning for GWS in laboratories should consider costs for capital equipment, test development, test validation, and long-term volume-based reimbursement of tests costs.
- Provincial planning for required laboratory capacity to support predicted volumes.
- Strategic planning related to the storage and sharing of variant interpretation and genomic data amongst provincial laboratories to support care planning, care provisioning, system planning, research, and innovation.
- Standardized sequencing and bioinformatic pipelines in laboratories performing GWS.
- Laboratories that perform GWS for this patient population must adhere to provincial guidance and/or evidence-based best-practice standards.

# Conclusions

This report provides a set of principles and recommendations for the delivery of standardized, coordinated, and evidence-based genetic services for patients and families in Ontario with NDDs (specifically ID, GDD, and autism).

The three recommendations made in this report are:

1) Establish standardized clinical pathways to guide genetic testing and referral to genetic services.
2) Implement strategies to improve access to genetic testing and services.
3) Invest in resources and infrastructure to fulfill the recommended NDD clinical pathway.

The current clinical pathway involves CMA and/or targeted testing for specific conditions such as Fragile X, followed by GWS as a second-tier test which can only be ordered by a small group of expert clinicians. This report recommends that in future, GWS with CNV analysis should be the first-tier test in patients with NDDs who are most likely to benefit from genomic testing based on current data, and that ultimately, this testing should be ordered as early as possible in the patient's diagnostic journey to maximize the benefits.

Additional supports should be provided to non-genetics physicians to enable them to confidently order genetic testing. This would include clear genetic testing eligibility criteria, rapid access to genetic services and expertise, ongoing education and training opportunities, and plain-language laboratory reports.

Recommendations provided on this document were selected using best available evidence at the time of writing this report and expert consensus. Clinical relevance and appropriateness to guide patient care were prioritized over resource limitations. The implementation and sustainability of these recommendations in Ontario require a robust workforce in laboratory and clinical genetics, and an effort should be made to overcome the current shortage of resources available to provide this expert clinical care.

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# Appendices

## Appendix A: Summary of North American Position Statements on Genetic Testing for Neurodevelopmental Disorders (2018-2023)

### Summary of North American Positions Statements on Genetic Testing for Neurodevelopmental Disorders (2018-2023)

**Canadian College of Medical Geneticists (CCMG)[1] (2023)**

Phenotype: GDD, ID, Autism

Recommendations:

- First tier:
  - CMA
  - If suggestive clinical features:
    - Fragile X testing
    - Biochemical screening
- Second tier: ES (or a comprehensive gene panel) for GDD, ID, and autism with syndromic features

**American College of Medical Genetics and Genomics (ACMG)[35] (2021)**

Phenotype: Developmental delay, ID

Recommendations:

- First or second tier: ES or GS

**American Academy of Child and Adolescent Psychiatry (AACAP)[51] (2020)**

Phenotype: ID

Recommendations:

- First tier: CMA and Fragile X testing
- Second tier: Consider additional testing, which could include ES.

**American Academy of Pediatrics (AAP)[52] (2020)**

Phenotype: Autism

Recommendations:

- First tier: CMA and Fragile X testing
- Second tier: Consultation with clinical geneticist or metabolic specialist

**Canadian Pediatric Society (CPS)[53] (2018)**

Phenotype: GDD, ID

Recommendations:

- First tier: CMA, Fragile X testing, biochemical screening
- Second tier: Consultation with clinical geneticist or metabolic specialist

# Appendix B: Clinical Features that May be Suggestive of a Genetic Syndrome for Individuals with Neurodevelopmental Disorders[1]

## Clinical Feature Definitions and/or Examples

**Abnormal head size:** Occipitofrontal circumference less than or greater than 2 standard deviations from the mean for age, sex, and ethnicity (e.g., microcephaly, macrocephaly).

**Additional medical comorbidities:** Coexisting or cooccurring health conditions (e.g., sensorineural hearing loss, vision impairment, renal disease, epilepsy, ataxia).

**Congenital anomalies:** A non-progressive morphological anomaly of a single organ or body part which is present at birth (e.g., cleft palate, polydactyly, congenital heart defect).

**Distinct physical features:** Visible morphologic findings that differ from those commonly seen in the general population or within the same ethnic background (e.g., hypertelorism, syndactyly).

**Family history of NDD with similar phenotype:** Suspected genetic syndrome NYD for which ≥ 1 close family member(s) is similarly affected, or where parents are consanguineous.

Sibling with similar phenotype may suggest autosomal recessive condition. Similarly affected male relatives related through maternal line may suggest an X-linked condition. Parent with a similar phenotype may suggest autosomal dominant condition.

**Unexplained growth abnormalities:** Growth parameters greater than or less than 2 standard deviations from the mean for age, sex, and ethnicity (e.g., prenatal growth restriction, postnatal failure to thrive, short stature, overgrowth).

NOTE: These definitions and examples are for educational and demonstration purposes only and should not be used as testing criteria in the context of patient care.

# Appendix C: Referral and Special Testing Considerations[1]

## Single Gene Tests for Rare Genetic Syndromes Associated with NDDs

Certain variant classes are not detected by sequencing-based technologies but may be required for appropriate diagnostics in some patients with NDDs. These include, for example, epigenetic/methylation changes for disorders such as Angelman syndrome (AS) and Prader-Willi syndrome (PWS).

## Fragile X Syndrome

Fragile X syndrome is an X-linked condition caused by an unstable expansion of a CGG repeat in the 5' UTR of the *FMR1* gene which can be identified via a widely available polymerase chain reaction (PCR) testing. High suspicion from a clinician, based on their clinical assessment for Fragile X is critical in determining the diagnostic yield of the test.

The CCMG recommendations for Fragile X testing in NDDs are as follows:

- Fragile X testing is recommended as a first-tier diagnostic test for individuals presenting with GDD, ID, or autism **AND** a clinical presentation or family history suggestive of Fragile X syndrome.
- All patients with an NDD who have a confirmed family history of Fragile X syndrome or other *FMR-1* related disorder.

## Inherited Metabolic Diseases

Inherited metabolic diseases may present with NDDs as part of the clinical spectrum, however, the diagnostic yield of metabolic testing in NDD populations is very low in the absence of additional clinical features of a metabolic disease. Nonetheless, these rare conditions are clinically important to diagnosis as early identification and treatment can improve outcomes.

The CCMG recommendations for metabolic screening in patients with NDDs are as follows:

- Metabolic testing is recommended as a first-tier diagnostic testing for individuals presenting with GDD, ID, or autism **AND** clinical features suggestive of an inherited metabolic disease (IMD). Metabolic testing should be tailored to the clinical presentation and a prompt referral made to a metabolic specialist.
- Metabolic testing for individuals presenting with GDD/ID/autism who were born outside of Canada, or who otherwise may not have had newborn screening in the neonatal period.

## Consideration of Non-genetic Etiologies

The etiology of GDD, ID, and autism is heterogeneous and may include multiple genetic and/or environmental factors[54]. Genetic testing may still be considered for individuals with GDD, ID, or autism, when a secondary and/or acquired non-genetic cause (e.g., congenital infections, fetal alcohol syndrome, prematurity, and hypoxic encephalopathy) is suspected but a clinical suspicion remains of a co-existing genetic diagnosis. Non-genetic investigations to exclude acquired causes should be considered and obtained in the appropriate setting.

## Referral to a Genetics Clinic is Indicated for:

- Patients who have abnormal genetic test results (including variants of uncertain significance [VUS]).
- Patients for whom genetic testing was normal, but the clinician still has high suspicion of an underlying genetic etiology (See Appendix A).
- Patients with a family history of a known or suspected genetic syndrome associated with NDD who are requesting genetic counselling about recurrence and/or inheritance.

# Appendix D: Comparison of Laboratory Genetic Testing Strategies[c]

## Comparison of Laboratory Genetic Testing Strategies

**Multigene panel test:** Testing and reporting on a defined set of genes that are clinically valid for a set of indications. Can vary from a small number of genes to >4,000 genes known to be involved in human disease. Can be proband only or trio sequencing for large panels.

Pros:

- Less capital investment.
- Simpler informatics.
- Easier to interpret and report than a genome-wide test.
- No secondary findings and lower chance of incidental findings.
- Most laboratories have existing infrastructure.
- Lower cost per test.
- Possible to report out on del/dup if sequenced to high depth of coverage.
- Possible to report out on a panel where exome or genome is sequenced (informatics *in silico* panel or genomic 'slice').

Cons:

- Lengthy laboratory development time.
- Need to continually update the panel when new discoveries are made (inflexible).
- Requires batching that can be difficult to work into laboratory flow.
- Cannot 'reflex' to broader testing if using targeted kits.
- Current practice often tests only the proband requiring familial follow-up when a variant is reported.
- Lower overall clinical sensitivity.
- More likely to report VUSs for large panels compared to exome and genome.

[c] Prepared by C. Marshall and A. Vaags on September 19, 2022

**Exome sequencing:** Sequencing of the coding portion of all known genes with reporting and interpretation of variants based on provided phenotype. Still a 'targeted' test since only looks at the coding portion of the genome but a broader approach to testing where multiple panels would otherwise be needed.

Pros:

- Higher clinical sensitivity and diagnostic yield compared to panels.
- Requires fewer computation resources than genomes and is easier to analyze.
- Less costly compared to genomes.
- Reporting only on variants related to phenotype.
- Can detect copy number variation but at a lower resolution, compared to panels or genomes.
- Possible to report out on a panel where exome or genome is sequenced (informatics *in silico* panel or genomic 'slice').

Cons:

- High capital and infrastructure costs.
- Complex and expensive informatics compared to panels.
- Higher cost per test (trios) compared to panels.
- Potential for secondary and incidental findings, so more genetic literacy is needed for ordering and return of results.
- Does not detect (most) deep intronic variants.
- Not designed to detect copy number changes unless coverage is increased to 200X-500X.
- Requires detailed phenotypic information for variant analysis and interpretation.
- Less likely to report VUSs

**Genome sequencing:** Sequencing of the entire genome (3 billion base pairs) with reporting and interpretation of variants based on provided phenotype.

Pros:

- Highest clinical sensitivity and diagnostic yield.
- Analytically sensitive to almost all classes of variation (CNVs, SVs, STRs, MT variants, etc.) so a more 'complete' single test.
- Can detect causative non-coding changes.
- Possible to report out on a panel where exome or genome is sequenced (informatics *in silico* panel or genomic 'slice'

Cons

- High capital and infrastructure costs.
- Complex and expensive informatics compared to panels.
- Highest capital and infrastructure cost.
- Complex and expensive informatics.
- Higher cost per test (trios) and currently higher cost compared to exomes.
- Inability to interpret much of the genomes (e.g., non-coding regions).
- Potential for secondary findings so more genetic literacy is needed for the return of results.
- Requires detailed phenotypic information for variant analysis and interpretation.
- Less likely to report VUSs

CNVs, copy number variants; SVs, structural variants; STRs, short tandem repeats; MT, mitochondrial; VUS, variant of uncertain significance.

# Appendix E: Testing Volumes for NDDs

## Table E1. In-Province Testing Volumes for NDDs Between 2020-2022

| Test | 2020 | 2021 | 2022 |
|---|---|---|---|
| **CMA**[d] | 11,491 | 9,432 | 11,455 |
| **Fragile X** | 5,237 | 3,364 | 4,661 |
| **ES with NDD indications** | Not applicable | 598[e] | Not available |

CMA, chromosomal microarray analysis; ES, exome sequencing; NDD, Neurodevelopmental Disorder.

## Table E2. OOC/OOP Testing Volumes for NDDs Between FY2019/20 and FY2022/23

| Test | FY2019/20 | FY2020/21 | FY2021/22 | FY2022/2023 |
|---|---|---|---|---|
| **Comprehensive panel testing** | 218 | 138 | 243 | 276 |
| **ES with NDD indications** | 235 | 136 | 15[f] | 15[d] |

ES, exome sequencing; FY, fiscal year; NDD, Neurodevelopmental Disorder; OOC/OOP, out-of-country/out-of-province.
Reported volumes do not include self-pay, research, or sponsored genetic testing.
Volumes reported on November 6, 2023 from April 2019 to June 2023.

[d] Total number of tests completed. CMA is considered first-tier testing for multiple indications, including NDDs.
[e] ES was implemented in Ontario through Genome-Wide Sequencing Ontario (GSO) in 2021.
[f] After implementation by GSO, OOC ES is now only available for urgent and/or prenatal cases.

# Appendix F: Ontario Neurodevelopmental Clinic List and Referral Information[g]

**Table F1. Ontario Neurodevelopmental Clinic List and Referral Information**

| Clinics | Referral Criteria | Pre-Referral Requirements | Exclusions |
|---|---|---|---|
| **Genetics Program, North York General Hospital** | • GDD/ID<br>• Autism with additional features or multisystem involvement | • CMA and Fragile X completed | • Autistic individuals with no findings on CMA and Fragile X<br>• ADHD/ADD with no additional features |
| **Medical Genetics Program, London Health Sciences Centre** | • GDD<br>• Autism with additional features or multisystem involvement | • CMA and Fragile X completed<br>• Family history questionnaire completed | • LD or ADHD or fetal alcohol spectrum disorder (FASD) with no additional features |
| **Neurodevelopmental Disorders Diagnostic Clinic (NDDC), Children's Hospital of Eastern Ontario** | • GDD/ID<br>• Autism<br>• Other NDD (LD/ADHD) with findings on test results | • CMA for individuals >2 years old | • ADHD or LD with no additional features |
| **Centenary Genetics Clinic, Scarborough Health Network** | • GDD<br>• Autism | • CMA and Fragile X completed | • ADHD/ADD with no additional features |
| **Northeastern Ontario Medical Genetics Program, Health Sciences North** | • GDD/ID<br>• Autism | • CMA and Fragile X preferred/ recommended | • ADHD/ADD, LD, behavioural issues, etc. with no additional features |
| **Genetics Program, Thunder Bay Regional Health Sciences Centre** | • GDD/ID<br>• Autism/NDD's referred by a pediatrician only | • CMA and Fragile X completed | • ADHD/ADD and FASD with no additional features |

[g] This list represents results of an informal survey of services available provincially collected at the time of the writing of this report and is not maintained or updated.

| Clinics | Referral Criteria | Pre-Referral Requirements | Exclusions |
|---|---|---|---|
| **Clinical Genetics Program, McMaster Children's Hospital** | • GDD, autism, ID, usually with additional features | • CMA completed | |
| **Neuromuscular and Neurometabolic Clinic at McMaster Children's Hospital** | • GDD/ID<br>• Autism with additional features or multisystem involvement | • No previous testing required | • ADHD, LD, or autistic patients with no additional features |
| **Clinical & Metabolic Genetics, Hospital for Sick Children** | • GDD, autism, ID, usually with additional features | • CMA and Fragile X completed | |
| **Genetics Clinic, Mackenzie Richmond Hill Hospital** | • GDD/ID<br>• Autism | • CMA and Fragile X completed<br>• Follow-up for parental testing with VUSs | • ADHD or LD with no additional features |
| **Clinical Genetics, Trillium Health Partners** | • GDD/ID<br>• Autism<br>• Other NDD (LD/ADHD) with findings on test results | • CMA and Fragile X completed or ordered at the time of the referral | • ADHD or LD with no additional features |
| **Medical Genetics Program, Kingston Health Sciences Centre** | • GDD/ID<br>• Autism | • CMA and Fragile X completed | • ADHD/ADD with no additional features |

ADD, attention deficit disorder; ADHD, attention-deficit/hyperactivity disorder; CMA, chromosomal microarray analysis; FASD, fetal alcohol spectrum disorder; GDD, global developmental delay; ID, intellectual disability; LD, learning disability; NDD, neurodevelopmental disorder.

## Appendix G: Acronyms

| | |
|---|---|
| **ADHD** | Attention deficit hyperactivity disorder |
| **AS** | Angelman syndrome |
| **ASD** | Autism spectrum disorder |
| **CCMG** | Canadian College of Medical Geneticists |
| **CMA** | Chromosomal microarray analysis |
| **CNV** | Copy number variant |
| **DSM** | Diagnostic and Statistical Manual of Mental Disorders |
| **ES** | Exome sequencing |
| **FASD** | Fetal alcohol spectrum disorder |
| **FY** | Fiscal year |
| **GDD** | Global developmental delay |
| **GECKO** | Genetics Education Canada: Knowledge Organization |
| **GS** | Genome sequencing |
| **GSO** | Genome-wide Sequencing Ontario |
| **GWS** | Genome-wide sequencing |
| **ID** | Intellectual disability |
| **IMD** | Inherited metabolic disease |
| **IQ** | Intelligence quotient |
| **LD** | Learning disability |
| **MGP** | Multigene panel |
| **NDD** | Neurodevelopmental disorder |
| **OLIS** | Ontario Laboratories Information System |
| **OOC/OOP** | Out-of-country/out-of-province |
| **PCR** | Polymerase chain reaction |
| **PGAC** | Provincial Genetics Advisory Committee |
| **PGP** | Provincial Genetics Program |
| **UTR** | Untranslated regions |
| **VUS** | Variants of uncertain significance |

## Appendix H: Glossary

**Exome sequencing:** Involves sequencing the protein-coding regions of the genome. The human exome represents less than 2% of the genome but contains ~85% of known disease-related variants, making this method an alternative to GS.

**Genetic counselling:** Genetic counselling is the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to health and development. This process integrates interpretation of family and medical histories to assess the chance of occurrence or recurrence of a particular condition(s), education about inheritance, testing, management, prevention, resources and research and counselling to promote informed choices and adaptation to the risk or condition[55].

**Genome sequencing:** Genome sequencing is a comprehensive method for analyzing entire genomes.

**Genome-wide sequencing:** Genome-wide sequencing (GWS) includes exome sequencing (ES) and genome sequencing (GS). This type of analysis provides broad detection and evaluation of genetic variants. ES and GS are currently the most comprehensive genetic tests available and are used to identify underlying genetic causes for conditions where traditional approaches have failed to find a diagnosis.

**Incidental findings:** Incidental findings are genetic findings unrelated to the patient's symptoms, i.e., unrelated to the original purpose of the test, that are discovered by chance during the analysis.

**Secondary Findings:** Secondary findings are genetic variants unrelated to the patient's symptoms, i.e., unrelated to the original purpose of the test, that are purposely analyzed as part of the test.
In May 2021, the American College of Medical Genetics and Genomics (ACMG) announced the list of 73 genes (formerly 52) of which variants are recommended to be reported as secondary findings[56].