Rapid Genetic Testing for Critically Ill Patients

Genetic Testing Recommendations

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Introduction

Ontario Health is building a comprehensive and integrated system for clinical genetic services across the province. Through collaboration with health system partners, the Provincial Genetics Program (PGP) provides evidence-based guidance for genetic diagnostic testing and counselling services in key areas. PGP Expert Groups work with health care professionals, laboratory scientists, administrators, and patient and family advisors to establish standardized practices for collecting, using, and reporting clinical genetics data. These efforts ensure that people in Ontario can access high-quality genetic testing services when needed.

The PGP identified genetic testing in critical care settings as a domain for development in Ontario, resulting in the formation of the Rapid Genetic Testing in Critically Ill Patients Working Group (Working Group). The role of the Working Group was to develop evidence-based guidance for the provision of rapid genetic testing and counselling services for critically ill individuals in the province of Ontario.

Guidance Document Scope

This document focuses on the recommended approach for rapid genetic assessment and testing for critically ill individuals, recognizing that there are other indications for rapid testing outside of this setting. It includes recommendations on:

- Which patients in critical care settings should be offered rapid genetic testing
- What genetic testing strategy should be employed, and
- Considerations for the implementation of this test in Ontario

The recommendations within are intended for use by all physicians with relevant expertise, who are involved in the care of critically ill patients (e.g., clinical geneticists, neonatologists, intensivists, neurologists, metabolic specialists, and/or multidisciplinary teams).

Background

Rapid and accurate genetic diagnosis for critically ill patients can inform medical decision-making and allow for timely interventions, better outcomes, and reduced costs[1–5]. While genome-wide sequencing (GWS), including exome and genome sequencing, are available for a variety of clinical indications, rapid (<3 weeks) and ultra-rapid (≤7-14 days) turnaround testing have emerged as an optimal first-tier test in this setting. Results delivered in days rather than months can shorten the diagnostic period, and have treatment and management implications, including initiating tailored therapies or having meaningful discussions regarding prognosis or goals of care.

It is estimated that around 5-20% of children admitted into an Intensive Care Unit (ICU) have an underlying genetic condition, with emerging evidence of utility for critically ill adults [5–9]. These patients may exhibit a wide range of clinical features, some of which can be indicative of underlying genetic conditions, with high diagnostic yields of 30% to over 50% after genetic evaluation[1–3,7–12].

Despite this, ordering practices in Ontario for rapid GWS in the ICU setting are variable, with limited standardization on which patients are eligible for testing and with differences in the uptake of this test. At the time of this report, the standard in many centres in Ontario is to order GWS with a 7-14 day turnaround of results, with testing typically being sent to out-of-country commercial genetics laboratories. Requests require approval from the Ministry of Health's Ministry of Health's Out-of-Country (OOC) & Out-of-Province (OOP) Prior Approval (PA) Program for Laboratory Services which may further delay turnaround of results. This highlights the critical need for Ontario to integrate genetic testing early and equitably into clinical care in ICU settings[i].

In an effort to offer this testing in-province and address equity in access, the Rapid Genetic Testing in Critically Ill Patients Working Group was created to develop recommendations for critically ill patients in Ontario. The Working Group includes representation from paediatric intensivists, neonatologists, neurologists, genetic counsellors, clinical and metabolic geneticists, laboratory geneticists, clinicians with bioethics expertise, patients, and experts in provincial genetic testing and systems. Decisions were made based on currently available evidence and group consensus, and with the best interest of patients in mind.

[i] For the purposes of this document, the term "ICU" is inclusive of specialized ICUs including neonatal, paediatric, adult, neuro, cardiac, etc.

Eligibility Criteria

Rapid GWS (21 day in-province turnaround time) is indicated for:

Patients in an ICU setting with a suspected underlying genetic condition.

Ultra-rapid GWS (7-14[ii] day in-province turnaround time) is indicated for:

Patients in a hospital setting with a suspected underlying genetic condition who are:

- Dependent on mechanical ventilation or other organ support (e.g., dialysis, etc.) **AND**
- For whom the results of genetic testing will lead to immediate changes in clinical management (e.g., eligible for a certain treatment or surgical intervention based on the results, in the ongoing pregnancy in a family member, etc.) or will inform decisions regarding continuation of life-sustaining treatment.

Rapid/Ultra-rapid GWS testing is NOT recommended for individuals in the following situations:

- Patients in whom a genetic or other (e.g., infectious) diagnosis that explains the clinical phenotype has been established.
- A more appropriate specialized test is available for the suspected genetic disorder [e.g., repeat expansion testing for Myotonic Dystrophy type 1 (DM1), copy number variant analysis for Spinal Muscular Atrophy (SMA), etc.].
- Patients for whom exome or genome testing has been previously performed (e.g., prenatally), without subsequent re-involvement of a clinical geneticist.

Non-geneticist physicians are encouraged to consult with clinical genetics. The role for virtual consultation with genetics teams, if not available locally, can help ensure counselling, interpretation and ultimately, patient care, is delivered equitably across the province.

[ii] These numbers are based on existing, but heterogenous testing options for rapid and ultra-rapid GWS that are currently available at OOC labs. The 21 day and 7–14 day targets were chosen to reflect achievable turnaround times in Ontario.

Testing Approach

The Working Group recommends that to expedite diagnosis and treatment planning, a broad, non-tiered testing approach should be used for these patients when possible. **Rapid GWS, as opposed to specific panels for acute presentations (e.g., neonatal crisis panels), is recommended as the first-line test in the majority of cases**[11].

If there is a high(er) degree of diagnostic certainty for a condition, particularly in conditions that are not traditionally identified via short-read next-generation sequencing, then targeted genetic tests may be considered. A list of additional tests to consider, either together with or in lieu of GWS, are listed below in Table 1.

The decision on whether to opt for GWS upfront or pursue parallel or sequential comprehensive testing (e.g., testing to capture structural variants that may be missed due to limitations in GWS technology, etc.) should be made based on the physician's judgment, taking into consideration factors such as the patient's clinical presentation, family history, and the likelihood of identifying the genetic cause[11].

Table 1. Additional Genetic Tests to Consider Alongside Rapid/Ultra-rapid GWS.

Additional Tests to Consider	Examples
Copy number variant analysis	Chromosomal microarray, MLPA for SMA
Repeat expansion disorders	Myotonic dystrophy, Congenital central hypoventilation syndrome
Imprinting disorders	Prader-Willi/Angelman syndrome

MLPA, multiplex ligation-dependent probe amplification
Note: This is not an exhaustive list.

Parental Testing

Parallel testing of the proband's sample alongside parental samples (i.e., trio testing) **should always be pursued when possible and when it will not cause a clinically significant delay in testing**. Access to parental data helps with the prioritization of variants to report, facilitates the identification of *de novo* variants, and/or enables phasing of compound heterozygous variants. This test strategy offers a significantly higher diagnostic yield, reduces the number of uncertain findings reported which may cause undue stress, and eliminates the need for stepwise parental segregation testing which may be needed to clarify uncertain findings; this provides the additional benefit of reducing overall turnaround time.

Implementation Considerations

Given the acute nature under which rapid/ultra-rapid GWS may be ordered, additional factors must be considered to help ensure testing is ordered appropriately and to ultimately facilitate reaching a timely diagnosis.

Patient Access

Efforts to plan, implement, and continually improve rapid GWS into ICU care should consider its multidisciplinary nature. Clinical pathways should be developed collaboratively within institutions and should involve representation from all relevant health care professionals to ensure role clarity, the identification of improvement opportunities, and the prioritization of a person/family-centred approach.

The Working Group agreed that all physicians in the ICU with relevant expertise (e.g., clinical geneticists, neonatologists, intensivists, neurologists, metabolic specialists, and/or multidisciplinary teams) should be able to order genetic testing for individuals in ICUs with a suspected genetic condition. Further training and/or capacity building will be needed.

Genetics Consultation

The presence of on-site or available clinical genetics service personnel including clinical geneticists and genetic counsellors, can provide critical support to non-geneticist clinicians when rapid GWS is being considered, and should be consulted as needed. This can include (but is not limited to): providing consultation on the appropriateness of the test on a per-case basis, discussions with patients and substitute decision-makers about the risks and benefits of rapid GWS, providing support to those experiencing decisional conflict, helping interpret or communicate test results, and/or ensuring appropriate follow-up. While consultation is not a prerequisite for ordering the test, local practices where medical teams work collaboratively are encouraged. This will change current workloads and will require additional health human resources including genetic counsellors and clinical geneticists to support optimal patient care in this setting.

Psychosocial Considerations

Due to the time-sensitive nature of rapid GWS in the ICU setting, consideration must be given to the complex ethical and moral challenges related to the results of testing and how they can shape care decisions. Importantly, the high stress environment associated with the timing of this test may lead to substantial distress for patients and substitution decision-makers, potentially impeding their ability to fully understand the implications of genetic testing[14–18]. Secondary findings can also present challenges when deciding to learn about additional health risks[19–22]. The Working Group therefore recommends that patients and substitute decision-makers are offered adequate genetic counselling and support in navigating this testing. This should occur in the setting of informed consent with the return of childhood-onset secondary findings and the option to return adult-onset secondary findings[23]. This should be done with appropriate interpretation services, when needed.

Genome-wide Sequencing Technology

While rapid exome sequencing is currently the most comprehensive routinely available genetic test in Ontario, the Working Group recommends that rapid genome sequencing be the preferred testing method for this population. Relative to exome sequencing which often requires microarrays or additional tests to ensure comprehensive testing was completed, genome sequencing provides greater sensitivity and accuracy for detecting copy number and structural variants, and an overall faster turnaround time. As more comprehensive technologies become accessible and are shown to be cost effective (i.e., long-read genome sequencing, which has the potential to detect imprinting, repeat expansions, structural variants, etc.), ongoing re-evaluation of the technologies used for rapid-testing will be warranted. Laboratories should be appropriately resourced to ensure they are able to complete reanalysis of previous non-diagnostic GWS testing with the appearance of new disease features, or when sufficient time has elapsed for enhancements in diagnostic sensitivity to have occurred.

Turnaround Times

The Working Group currently recommends that rapid and ultra-rapid GWS be completed in 21 days and 7-14 days, respectively. It is anticipated however, that as technology improves and provincial laboratory capacity grows, turnaround times can and should be continually improved.

Summary of Recommendations

The Working Group recommends:

- The routine use of rapid GWS for all critically ill patients in an ICU setting with a suspected underlying genetic condition, with tests run in-province, and results returned in a maximum of 21 days. An additional subset of very sick patients will be eligible for ultra-rapid GWS with an in-province turnaround time of 7-14 days. To expedite diagnosis and treatment planning, rapid GWS is recommended as the first-line genetic test for critically ill patients.
  - Targeted genetic tests may be sent concurrently with GWS if there is a high(er) degree of diagnostic certainty, particularly in conditions that are not traditionally identified via short-read next-generation sequencing (e.g., congenital Myotonic dystrophy [repeat expansion of *DMPK*], Prader-Willi/Angelman syndrome [deletion and methylation status of *SNRPN*], etc.).
  - The working group advocated for a broad GWS approach rather than specific smaller panels for acute presentations (e.g., Neonatal crisis panels).
- All physicians with relevant expertise and who are involved in the care of patients admitted to the ICU (e.g., clinical geneticists, neonatologists, intensivists, neurologists, metabolic specialists, and/or multidisciplinary teams) should be able to order genetic testing for individuals in the ICU with a suspected genetic condition without restrictions.
- Clinical genetics teams, including clinical geneticists and genetic counsellors, can provide critical support to other clinicians and patient/families when rapid GWS is being considered. Clinicians are encouraged to consult genetics as needed; however, this is not a prerequisite to order the test.
- As trio testing offers the highest diagnostic yield, this should always be pursued when possible and when it will not cause a clinically significant delay in testing.
- It is recommended that individuals undergoing genetic testing receive adequate pre- and post-test counselling and support to navigate the psychosocial challenges of rapid testing in high-stress environments. Testing decisions should be undertaken with informed consent.

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Appendix

Acronyms

CNV	Copy number variant
DM1	Myotonic dystrophy 1
GWS	Genome-wide sequencing
ICU	Intensive care unit
MLPA	Multiplex ligation-dependent probe amplification
OOC	Out-of-country
OOP	Out-of-province
PGP	Provincial Genetics Program
SMA	Spinal muscular atrophy