Course Information

Learning Objectives

As a result of completing this module, I am able to:

1. List common indications for rapid genome-wide sequencing (rGWS) testing in the NICU.
2. Describe the process of rGWS testing from identification of need to obtaining results.
3. Classify result types from rGWS and the implications of each for the patient and family.
4. Propose appropriate responses to common family concerns going through rGWS.

Inclusivity Statement

We acknowledge that experiences of health, illness, and care are shaped by individual identities, family structures, cultures, and languages, including personal or intergenerational experiences of trauma, colonization, or marginalization. Genetic testing can raise deeply personal and emotional questions for families. We encourage all health-care professionals to approach these conversations with cultural humility, empathy, and respect, recognizing that every family's experience is unique.

We have aimed to use inclusive language throughout. As terminology continues to evolve, we remain committed to continuous learning and person- and family-centred care.

Course Structure and Features

The course is divided into 4 modules and Take-Home Resources. The 4 modules are divided into the following topics:

1. Foundations of Rapid Genome-Wide Sequencing (rGWS) in the NICU
2. Indications for Testing and Testing Process
3. Types of Results and Their Implications
4. Family-centred Care and Resources

Modules
Each module is divided into individual separate multi-page interactive lessons. Pre- and post-survey questions are not graded and do not impact your completion.

Take Home Resources
This course includes a PDF summary of all content, resources, and optional additional reading.

Acknowledgements

Planning Committee
Alison M. Elliott, PhD, MS, CGC
Grace Garvey, BSc Hons
Lauren Piers, MSc, CGC
Horacio Osiovich, MD, FRCP
Tasha Wainstein, PhD, MSc (Med), CCGC

Instructional Design and Illustration
Kate Campbell, MSc, BSc (Hons)
Katherine Co, MArch, BEnds (Hons)
Natalia Kayda

THE UNIVERSITY OF BRITISH COLUMBIA Continuing Professional Development Faculty of Medicine
BC Children's Hospital
Genome BritishColumbia
Michael Smith Health Research BC

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Lesson 1: Foundations of Rapid Genome-Wide Sequencing (rGWS) in the NICU

Why Genetics Matter in the NICU

Genetic conditions are a significant contributor to infant hospitalizations and mortality and are highly represented in neonatal intensive care units (NICUs).

- Prevalence of genetic conditions in patients admitted to the NICU range from 9-16%[1,2]
- Of patients who pass away in the NICU, 15-32% will be due to recognized syndromes, metabolic disorders or genetic conditions , making these the leading cause of death in NICUs[3]

Traditionally, genetic testing for critically ill infants in the NICU has involved:

- chromosome testing (karyotype and microarray analysis) to detect structural and numerical chromosome abnormalities;
- single-gene testing based on the most likely clinical diagnosis; or
- testing small to medium sized groups of genes (panel gene testing) which are associated with overlapping clinical phenotypes.[4,5]

But this approach is not optimized. It is:

- **Time-consuming,** often requiring multiple rounds of sequential testing
- **Difficult to target,** especially in infants who have non-specific or evolving clinical features (particularly if they are premature)
- **Prolonging the diagnostic odyssey,** delaying answers that are critical for clinical decision-making and family support

Identifying a genetic diagnosis early can provide clarity during a highly stressful time. It may guide treatment, support decisions about palliative care, and offer important information about prognosis and recurrence risk. As testing becomes faster and more accessible, genetics is playing an important role in how we care for infants and families in the NICU.

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The Shift to Rapid Genome-Wide Sequencing (rGWS)

Recent advances in genetic testing technologies have resulted in enhanced diagnostic capabilities, price reductions, and much quicker turnaround times. Specifically, rapid genome-wide sequencing (rGWS) has resulted in a transformation of genetics service provision for critically ill infants in the NICU.[1]

What is rGWS?
rGWS is a type of genomic test that examines either the entire protein-coding regions (whole exome sequencing; WES) or the entire genome (whole genome sequencing; WGS) of the infant and their biological parents to determine whether there is an underlying genetic or genomic cause that explains their clinical picture.

- **Results from rGWS** received in as little as **3 to 23 days**[2-8]
- **Identifies** a genetic change in **30-60% of patients** thought to have a genetic condition
- Uses **trio analysis** (infant + both biological parents) to improve interpretation accuracy

Why it matters:
rGWS has been shown to influence clinical management, including commencement of targeted treatments, redirecting care towards palliation when indicated, and other benefits.

Implementing rGWS clinically requires a considered approach, including timely identification of patients, optimal referral pathways, consenting, pre- and post- test (results) genetic counselling, and result interpretation, alongside operational and logistical considerations (e.g. organizing blood draws and funding approval).

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Role of the NICU Team in Supporting rGWS

Families who have a child in the neonatal intensive care unit and undergoing rGWS testing that will potentially inform their clinical management, are frequently and understandably very anxious and overwhelmed.[1,2] While this advanced diagnostic tool has the capacity to identify underlying genetic conditions, the absence of immediate access to genetics health-care professionals can leave families seeking guidance from the NICU staff they rely on for support and comfort.

Even when rGWS testing is facilitated by genetics specialists, there is still benefit to NICU staff having this knowledge in helping families to adapt to the outcomes of rGWS testing as a routine part of care in the NICU. Parents establish close relationships with one or more healthcare professionals involved in their child's care, but who these individuals are for different families will vary.[1] Therefore, it is important that all members of the team have the necessary information about rGWS.

This education module has been designed to equip NICU staff (physicians (neonatologists), nurses, social workers, allied health professionals, and trainees) with the necessary knowledge and resources to support families through the rGWS process.

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Genetics 101 — Key Concepts for NICU Staff

Before discussing rGWS, here are some important refreshers on genetics and genomics and their relationship to health and illness.

DNA, Genes and Genomes

- **DNA (Deoxyribonucleic Acid):** A long molecule made of repeating units called bases (A, T, C, and G). These bases form coded instructions that tell the body how to make proteins.
- **Gene**: A segment of DNA that contains instructions to make a specific protein. Genes are made of exons and introns.
    - **Exons**: the coding regions (1–2% of the genome); are parts of the genes that provide the code to make functional proteins in the body.

    - **Introns and promoters**: the regulatory (non-coding) regions (~98% of the genome); they switch genes on or off, controlling the amount of protein produced depending on the body's needs.
- **Genome**: The complete set of DNA in an organism. In humans, this is about 3 billion base pairs of DNA. The genome is a blueprint, providing information about how our bodies should grow, function, and look.
- **Chromosomes:** Tightly packed structures of DNA in the cell nucleus. Human DNA is typically arranged into 23 pairs of chromosomes (46 in total), with one set from each biological parent.

Genetic and genomic testing

Genetic and genomic testing refers to diagnostic investigations which use a sample of DNA (typically blood but can also be saliva or buccal (cheek) samples) to compare a patient's genetic makeup with a reference and determine whether there is **variation** associated with their clinical phenotype. This information can be used to guide and inform diagnosis, prognosis, clinical management, and family planning. Genomic testing may or may not include evaluation of mitochondrial disorders. Mitochondrial disorders are a group of genetic conditions that affect how mitochondria in your cells produce energy.

Different test types will be discussed in more detail in "Lesson 2: Indications for Testing and Testing Process".

What Is Genetic Variation?

- DNA sequences vary between individuals. These differences (called variants) are classified by whether they impact the function of the gene[1]:
    - **Benign**: No effect on gene function; considered part of the normal variation that makes each human unique.
    - **Likely benign**: Very unlikely to affect gene function or cause disease based on strong evidence.
    - **Variant of uncertain significance (VUS)**: Impact on gene function unknown; current evidence is unclear or is conflicting.
    - **Likely pathogenic:** Likely to impact gene function and cause disease; strong evidence suggests this causes disease.
    - **Pathogenic**: Known to impact gene function and cause disease (previously called mutations).

Note: Classifications of a variant may change over time as research evolves.

- Genetic variation can also occur at the **chromosomal level**:
    - **Numerical abnormalities** (**aneuploidies)**: Extra or missing chromosomes
        - *e.g., Trisomy 21 (Down syndrome), Monosomy X (Turner syndrome)*
    - **Structural abnormalities**: Parts of chromosomes are rearranged, deleted, or duplicated.
        - *E.g., Deletions, duplications, inversions, and translocations*

Understanding How Genetic Conditions Arise

- A **genetic condition** is caused by pathogenic changes in one or more genes or in chromosome structure or number.
- They may be:
  - **Inherited** from one or both biological parents
  - ***De novo*** (new) due to a pathogenic variant in a parent's egg or sperm or early embryogenesis

Genetic counsellors are allied health professionals who have specialized training in both medical genetics and counselling. Given this combination of skills, genetic counsellors can help individuals and families:

- understand the nature, inheritance, and implications of genetic conditions; and
- provide psychotherapeutic support in adapting to their conditions and other concerns[2].

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Lesson 2: Indications for Testing and Testing Process

Indications for rGWS Testing in the NICU

In Lesson 1, we explored why rapid genome-wide sequencing (rGWS) is transforming care for acutely ill neonates in the NICU. rGWS can reveal underlying genetic diagnoses that directly inform treatment, prognosis, and family counselling. In this lesson, we focus on when to consider rGWS for a newborn in your care.

A **key indication** for rGWS testing is an **acutely ill neonate** with an **unlikely environmental or external cause** for their condition. Infants with multiple congenital abnormalities should also be considered for rGWS testing as described in further detail below:

Clinical Indications

1. **Multiple congenital anomalies and/or dysmorphic features**
   This includes infants who present with anomalies affecting multiple organ systems (e.g., Smith-Lemli-Opitz syndrome), especially when the pattern does not correspond to a well-known syndrome like trisomy 21 (Down syndrome).

2. **Suspected errors of metabolism (IEMs; also referred to as biochemical disorders)**
   These disorders disrupt how the body metabolizes or transports fats, proteins, or carbohydrates (e.g., congenital disorders of glycosylation). Presentations are often non-specific in neonates.

Note: Standard newborn screening does not detect all IEMs or other genetic disorders.

3. **Neurologic presentations**
   E.g., neonatal seizures can be caused by pathogenic variants in many different genes.

4. **Congenital cardiac defects**
   Particularly if accompanied by other anomalies (e.g., as seen in CHARGE syndrome).

5. **Undiagnosed critical illness despite standard evaluations**
   E.g., after negative results from chromosomal microarray (CMA), imaging, and metabolic studies.

Family History
Family history can provide additional clues but may not be considered indicators for rGWS in isolation

- Parental consanguinity (i.e., biological relatedness between parents)
- Siblings or relatives with similar or unexplained conditions
- Multiple affected individuals across generations

Clinical Tip
However, **an unremarkable family history does not exclude a genetic condition**. Many genetic conditions are caused by ***de novo*** (new) variants that arise spontaneously.
In these cases, the recurrence risk for future pregnancies is typically low (estimated at 1–2%).

The Testing Process

Rapid genome-wide sequencing (rGWS) involves multiple coordinated steps, from clinical assessment to communicating results. The process is collaborative and time-sensitive, often unfolding over several days.

A typical workflow for rGWS in the NICU may look something like this (video transcript):

(0:14) Rapid genome-wide sequencing is becoming an important tool in the neonatal intensive care unit. The workflow typically follows five key steps, from clinical assessment to family follow-up.

(0:53) Step one begins at the bedside. A critically ill infant **presents with symptoms suggestive of a genetic condition**, such as multiple congenital abnormalities, unexplained seizures, or metabolic disturbances.
The NICU team, often in consultation with a specialist team, **evaluates whether rapid sequencing is appropriate**. If so, the family is referred to a pediatric specialist—such as a medical geneticist, neurologist, or biochemical disease physician—and a genetic counsellor. **Together, they review the purpose of the test, its benefits, limitations, and possible outcomes**.

(1:13) In step two, **informed consent is obtained**. The family is supported in understanding the implications of testing, including potential secondary and incidental findings.
Once consent is secured, the **referring team submits a request for provincial funding** to move the testing forward.

(1:45) Step three involves **sample collection and laboratory testing**. A small blood sample is collected from the infant, and for trio analysis, samples are also obtained from both parents—using blood, saliva, or buccal swabs.

If the infant has recently undergone a transfusion, sample collection may need to be delayed. Once collected, **samples are sent to the sequencing laboratory for processing and bioinformatic analysis**. **Preliminary results are typically available within seven days.**

(2:12) Step four is **result interpretation**. Genetic variants of interest are categorized as pathogenic, likely pathogenic, or of uncertain significance.
A multidisciplinary team then reviews the findings, which may be classified as:
• **Positive**, meaning diagnostic,
• **Uninformative**, sometimes referred to as negative, or
• **Uncertain**, when results remain inconclusive.

(2:47) The final step is **communication and follow-up**. Results are shared with the family by the referring specialist, ideally with the NICU team present. If a diagnosis is made, the clinical team considers next steps, including **targeted treatments, further testing, or palliative approaches**.
Families should receive ongoing support—covering **prognosis, care planning, future pregnancies, and possible testing for at-risk relatives**. This stage may also involve referrals for additional psychological or financial resources.

(3:09) In summary, the workflow for rapid genome-wide sequencing in the NICU follows five steps: clinical assessment, consent, sample collection, result interpretation, and follow-up. Each step ensures that critically ill infants and their families receive timely, informed, and supportive care.

The Importance of Trio Analysis

Trio analysis (i.e., genetic or genomic testing for the neonate and both biological parents) can significantly improve the diagnostic yield of rGWS[1,2]. Everyone has hundreds of thousands of genetic variants. Being able to sift through those and identify which are likely contributing to or are causative of the genetic condition can be very challenging and time consuming. Having the parents available for comparison at the same time allows for the identification of variants that are new (*de novo*) in the child. The parental samples serve as controls. Many critically ill infants and children who are hospitalized due to a suspected genetic condition are likely to have a *de novo* variant, making these variants a top priority to identify. Also, testing both biological parents at the same time as the infant can help confirm the diagnosis of a recessive condition.

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Different types of genetic testing in the NICU

Test	Detects	Pros	Cons
Karyotyping (Chromosome analysis)	Large numerical and structural chromosomal abnormalities (like aneuploidies, translocations, inversions).	Detects balanced chromosomal rearrangements and mosaicism. Mosaicism is the presence of two or more genetically distinct cell populations within an individual that arise from a single fertilized egg.	Low resolution: cannot detect small deletions or duplications. Rapid Aneuploidy Detection (RAD) can identify common chromosome aneuploidies within a few days but there is a longer turnaround time for comprehensive karyotyping.
Chromosomal Microarray analysis (CMA)	Submicroscopic chromosomal deletions and duplications (copy number variants).	Higher resolution than karyotyping. Faster results. Can detect regions of homozygosity, and uniparental disomy.	Cannot detect balanced rearrangements (e.g. translocations). May identify variants of uncertain significance.
Multigene Panel	Specific pathogenic variants in a set of genes associated with a particular condition or phenotype.	Targeted approach when there is some clarity about the diagnosis. Higher coverage of relevant genes.	Limited to selected genes. Will miss pathogenic variants in genes not included in the panel. Less useful if the clinical diagnosis is uncertain.
Whole Exome Sequencing (WES)	Single nucleotide variants and small insertions/deletions in the coding regions (exons) of genes.	Covers all coding regions of the genome which are most frequently associated with disease. Useful when the clinical diagnosis does not point to a specific causative gene.	Does not assess non-coding regions. May miss non-coding (intronic) variants. May identify variants of uncertain significance, incidental findings, and secondary findings.
Whole Genome Sequencing (WGS)	Comprehensive detection of genetic variants, including single nucleotide variants, insertions/deletions,	Most comprehensive. Detects variants in both coding and non-coding regions. Sensitive for trinucleotide repeats.	Increased complexity of bioinformatics analysis. May identify variants of uncertain significance, incidental findings,

Test	Detects	Pros	Cons
	copy number variants, and structural variants across the entire genome.	Equivalent to CMA and WES in one test.	and secondary findings.
Rapid Genome Wide Sequencing (rGWS)	Either WES or WGS but with optimized laboratory and analysis procedures to ensure speed and efficiency of results in the critical care setting.	Significantly faster turnaround times essential for the NICU. Streamlines diagnostic process by reducing the need for multiple tests.	Requires specialized infrastructure and expertise.

Lesson 3: Types of Results and Their Implications

Understanding the Value of rGWS Results

Before diving into the different result types, it's important to re-centre on *why* rapid genome-wide sequencing (rGWS) matters in the NICU. The impact of receiving a diagnosis (or not receiving one) shapes clinical decisions, family expectations, and care planning in profound ways[1-7].

Why Diagnosis Matters in the NICU

- Genetic conditions are often individually rare and present with a variety of clinical features
- Neonatal presentations can be atypical, incomplete, or obscured by prematurity
- There is clinical urgency to establish an accurate diagnosis
- Some conditions are very effectively managed if identified early but can be catastrophic if missed

Clinical benefits

rGWS has benefits from a clinical perspective for health-care professionals and for families.

- Provide information on the condition itself, including potential associated health concerns, learning and development concerns
- Helps guide prognosis and future care planning
- Can enable redirection of care when appropriate, especially in life-limiting conditions

Emotional benefits for families

rGWS also has benefits from an emotional perspective, particularly for families.

- Brings a sense of clarity in an uncertain and unfamiliar environment
- Reduce the length of time to diagnosis (prior to rGWS, it often took months or years for families to attain a genetic diagnosis for their child's condition)
- Can reduce the number of unnecessary tests and procedures
- Supports reproductive planning by clarifying recurrence risk (which may be relevant for members of the extended family too)
- May connect families to:
    - Condition specific support groups
    - Financial or community-based supports

When No Diagnosis is Found

Note: **A negative rGWS result does not rule out a genetic condition**

- It may provide a degree of relief if no known severe genetic condition is identified
- Genetic counselling is essential both before and after testing to support families
- Reanalysis of the genomic data in a few years can be helpful for some families

Advantages of rGWS

- Accelerates time to diagnosis and shortens the diagnostic odyssey for patients and families
- Improves diagnostic yield over conventional genetic testing, which is particularly beneficial when clinical symptoms are non-specific
- Guides treatment and management, including clarifying prognosis, avoiding unnecessary interventions, and/or redirecting care
- Reduces feelings of uncertainty
- Helps direct families to additional sources of psychological and financial support

Complications of rGWS

No test is perfect however, and it is important to be aware of the following complications with rGWS:

- May identify **variants of uncertain significance** that can complicate clinical decision-making and lead to uncertainty and anxiety
- May detect **incidental findings** unrelated to the indication for testing
- A non-diagnostic result may mean **continued testing** which can prolong uncertainty and stress.

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Types of rGWS Results

Result Type	Explanation	Clinical Actions and Family Implications
Positive	Genetic variant/s identified that are known or strongly suspected to cause the patient's condition.	Confirm diagnosis. Initiate targeted treatment or management. Provide genetic counselling to family. Consider testing at-risk relatives.
Uninformative (sometimes referred to as Negative)	No pathogenic variants detected related to the patient's condition. This does not rule out a genetic condition. We have not yet discovered the cause of all genetic conditions, and not all gene changes are detectable, even with this detailed testing.	Continue clinical evaluation for non-genetic causes. Consider reanalysis in the future .
Inconclusive / Variants of Uncertain Significance (VUS)	A genetic variant is identified, but its association with the condition is unclear. We all have a lot of variation in our genes, and it can be difficult to decide whether a gene change is just part of normal variation or whether it could be the cause of the child's condition.	Do not use for clinical decision-making. Extra discussion and sometimes extra tests may be required to help make a decision.
Incidental Finding*	A pathogenic variant unrelated to the patient's current condition and detected **unexpectedly** during the analysis.	Evaluate clinical relevance. Discuss implications with the family. Consider further testing or referrals as needed.
Secondary Finding*	A pathogenic variant in a gene unrelated to the patient's current condition but **deliberately** analyzed as part of rGWS and having established clinical actionability.	Inform family if they opted to receive such findings. Initiate preventive measures or surveillance.

Result Type	Explanation	Clinical Actions and Family Implications
		Offer genetic counselling and consider testing for at-risk relatives.

*When a trio analysis is performed, these types of results may be relevant for both the neonatal patient AND their biological parents.

Lesson 4: Family-centred Care and Resources

Common family concerns with rGWS and example responses

Conversations about genetic and genomic testing can be complicated and caregivers may have important concerns they would like to address with you. In this lesson, we look at some common examples and consider possible answers to alleviate parental concerns.

Rani and Ari are the parents of a critically ill infant named Kai. Kai's illness has features suggestive of a genetic condition. Rani and Ari have been offered rGWS with trio analysis to determine the cause of Kai's illness. Click through the key moments below to follow them on their journey as they bring their questions and concerns to you and your team.

1. **Withdrawal of a blood sample from the baby**

Concern:
Rani tells you they are worried that drawing blood could cause additional stress or harm to their already ill infant.

What not to say:
"This is standard procedure, you don't need to worry; it's a tiny amount anyway. It won't hurt."

Instead try:
"I understand seeing your baby go through anything extra can be very difficult, especially when they are already unwell. For this test, we only need a small amount of blood, about 1 teaspoon. We can often coordinate it with other blood draws to avoid additional pokes."

Explanation:
Addressing caregivers' concerns is important. Reassuring them that for rGWS, only a small sample of blood (approximately one teaspoon) is required, like routine tests being performed, can also be helpful. The blood test can be coordinated with other bloodwork, so the baby is not repeatedly poked.

2. **Discussing complicated results with families**

Concern:
The couple describe that they feel overwhelmed by the complexity of the genetic information and fear they will not understand or forget the implications.

What not to say:
"Don't worry, it's not that complicated and you probably won't need to remember most of it anyway".

Instead try:
"A lot of people find genetic information complicated. We can go through this at your pace, and I can give you some other resources you can refer to later. We can also arrange for you to talk with the genetic counsellor again, if more questions come up for either of you."

Explanation:
Normalizing the complicated nature of genetic information might be helpful in this situation. If there are questions that are possible to answer at the time, then doing so would be beneficial. Additionally, organizing for the genetic counsellor who was involved in the family's genetic testing experience to follow up with them can be arranged. Providing written resources that allow for periodic revisiting of the genetic information can also be arranged (see resources at the end of this module or through facilitation by a genetic counsellor).

3. **Insurance and data privacy implications**

Concern:
Ari is concerned that genetic information could impact their insurance coverage and that their privacy could be compromised.

What not to say:
"It's very unlikely anything will happen with your data or insurance company."

Instead try:
"This is a valid concern. In Canada we have laws like the Genetic Non-Discrimination Act that protect people from being required to share genetic test results with insurers and employers. We also work diligently to ensure strong privacy protections are in place to make sure your information is kept confidential. We can talk more about how your data are stored and used if that would help?"

Explanation:
In Canada, the Genetic Non-Discrimination Act protects individuals from being required to undergo genetic testing or disclose genetic test results to obtain insurance or other services. Also, there are strict policies in place to ensure that genetic information is confidential and cannot be used by insurers without explicit consent.

4. **Processing the meaning and implications of negative (uninformative) results**

Concern:
Ari and Rani decide to pursue rGWS testing and one week later, they are informed that the results are negative/uninformative (i.e., no definitive genetic diagnosis). They describe feeling confused and disappointed. They were eager to find clarity about a path forward.

What not to say:
"Well, at least nothing was found – that's good news!"

Instead try:
"It's completely valid to feel disappointed. When families go through this testing, they're hoping to find clear answers, and it's difficult not to get them. It's important to note that a negative result doesn't mean there is no genetic explanation for Kai's symptoms. It could mean that we can't find the answer with the tools we currently have at our disposal. Sometimes answers become available later as we do more research and technology improves. Future testing is a possibility."

Explanation:
Reminding families that a negative result means that a genetic cause for their infant's condition was not found at this time, but that this may not rule out all genetic factors could be helpful. Our understanding of genetics is still evolving, and so we may find answers in the future. It is also important not to be falsely reassuring about negative results and to detect this false reassurance in the family's reaction to a negative result.

Summary

Here is a summary of the key points from each lesson in this course.

Lesson 1: Foundations of Rapid Genome-Wise Sequencing (rGWS) in the NICU
Rapid Genome Wide Sequencing (rGWS) is a recent advancement in genomic testing which examines either the entire genome (WGS) or the exome (WES) in a reduced time frame compared to traditional genetic testing options. rGWS:

- Results in accelerated time to diagnosis and a shortened diagnostic odyssey
- Has improved diagnostic yield over conventional genetic testing
- Guides treatment and management (i.e., clarifying prognosis, avoiding unnecessary interventions, and/or redirecting care)
- Helps direct families to additional sources of psychological and financial support

Lesson 2: Indications for Testing and Testing Process
rGWS testing is indicated for acutely ill neonates who have an unlikely external or environmental cause for their condition. This includes infants with multiple congenital abnormalities and/or dysmorphic features, suspected errors of metabolism, neurologic presentations, congenital cardiac defects, and undiagnosed critical illness despite standard evaluations. A substantial proportion of critically ill newborns are likely to have *de novo* (new) variants as the cause of their condition.

A typical workflow for rGWS testing:

- Clinical assessment and a decision that rGWS is indicated
- Referral to a pediatric specialist and/or genetic counsellor to discuss the option of genetic testing. Should the family decide to pursue testing, written consent is obtained, and the specialists apply for funding approval.
- Samples (blood, saliva, or buccal swabs) are collected (preferably) from both biological parents and the infant to perform a trio analysis
- The laboratory issues a preliminary report typically within 7 days which is evaluated by the multidisciplinary care team
- A result of either positive, uninformative, or inconclusive is relayed to the family. Discussions and decisions about clinical and management options are also conveyed to the family.

Lesson 3: Types of Results and Their Implications

There are 3 main types of results from rGWS testing for the infant:

- The result could be **positive** which indicates that pathogenic variant/s have been identified that explain the clinical features and a diagnosis can be confirmed. Treatment options and clinical management may be directed based on these results.
- The result could be **uninformative** (sometimes referred to as negative) which indicates that variants that explain the clinical features could not be identified. This may not rule out a genetic condition and future re-analysis of the patient's DNA may be warranted.
- The result could be **inconclusive** (VUS) which indicates that variants were detected but there is insufficient evidence to determine if they explain the infant's clinical features. These results would be assessed with the patient's clinical presentation to determine their clinical relevance and may result in additional follow up testing being ordered.

There are 2 extra types of results from rGWS testing for the infant and the biological parents if trio analysis is performed:

- **Incidental findings** are pathogenic variants with clinical implications unrelated to the current condition and detected unexpectedly during the analysis.
- **Secondary findings** are pathogenic variants in a gene unrelated to the current condition but deliberately analyzed as part of rGWS and having established clinical actionability.

Lesson 4: Family-centered Care and Resources

rGWS testing can be a complex discussion between healthcare professionals and families. Through empathic communication, normalization of uncertainty, and support for informed decision-making, healthcare professionals can respond to parental concerns on the following frequently raised topics:

- **Blood sample collection**: parents may worry about causing further distress to their ill infant. A compassionate and informative response helps alleviates anxiety by explaining the minimal requirements of the blood draw and efforts to reduce discomfort.
- **Understanding complex results**: families may feel overwhelmed by genetic information. Acknowledging this and offering ongoing support, written resources, and follow up opportunities with a genetic counsellor can help improve understanding and reduce anxiety.
- **Insurance and privacy concerns**: parents may worry about the implications of genetic results on insurance and data privacy. Explaining legal protections, such as Canada's Genetic Non-Discrimination Act, can provide reassurance.
- **Coping with negative results**: families may feel disappointed when testing does not provide answers. Validating these emotions and explaining that genetic understanding may evolve over time with additional testing can help families remain hopeful and informed.

Resources

For NGHPs

Genomics Education Programme:

- The Consent Conversation for Genomic Testing – guidance on how to approach consent discussions in genomic testing: https://www.genomicseducation.hee.nhs.uk/genotes/knowledge-hub/the-consent-conversation-for-genomic-testing/
- Genomic Testing Infographic – A visual overview of genetic test results and their implications: https://www.genomicseducation.hee.nhs.uk/wp-content/uploads/2021/06/Genomic-Testing-Infographic_w-title.pdf

Canadian Association of Genetic Counsellors

- GNA Fact Sheet – Information about the Genetic Non-Discrimination Act (GNA): https://www.cagc-accg.ca/doc/Resources%20for%20Practice/2018_06%20revised%20GNA%20fact%20sheet%20ENGLISH.pdf

For Families

Exeter Clinical Laboratory

- Patient Information Leaflet – Information about rGWS that is sutiable for use with patients and families: https://www.exeterlaboratory.com/wp-content/uploads/R14-Patient-Information-Leaflet-v1.pdf