MUSCULAR DYSTROPHY CANADA
DYSTROPHIE MUSCULAIRE CANADA

NMD4C

Webinar Report

RESEARCH Spotlight
#LetsTalkNMD

Genomics 101
09-01/2020

NMD4C (Neuromuscular Disease Network For Canada)

NMD4C launched in January 2020, is a Canadian network that is funded by Muscular Dystrophy Canada and the Canadian Institutes for Health Research.

NMD4C **brings together the country's leading clinical, scientific, technical, and patient expertise on neuromuscular disease.** The rarity and diversity of neuromuscular diseases make interdisciplinary collaboration and networking essential to future progress.

NMD4C strives to train and educate neuromuscular disease stakeholders

Muscular Dystrophy Canada (MDC) and the Neuromuscular Disease Network For Canada (NMD4C) have been working on a monthly webinar series to provide clinical and research updates by highlighting cutting-edge research, current state of clinical care and providing up-to-date information on interdisciplinary guidelines for a variety of neuromuscular disorders to clinicians, researchers, academics and medical/graduate trainees.

The Royal College of Physicians and Surgeons of Canada have accredited our webinars for Continuing Medical Education (CME) credits as part of the Maintenance of Certification Program (MOC).

In line with this new accreditation (CMA Policy; Guidelines for Physicians in Interactions with Industry; standard 22), the primary purpose o the “Neuromuscular Disease Rounds & Educational Webinars” is to address the educational needs of the clinical and research community in order to improve the health care of patients affected by neuromuscular disorders and improve health and quality of life. MDC shares a common interest with NMD4C in improving patient care, improving health outcomes and building clinical and research neuromuscular expertise.

WEBINAR DISCUSSION TOPICS

Genetic Counselling: What do families need to know and when
Lauren Brady

Testing Platforms:
Kim Amburgey

Non-genetic diagnostics in the genomics era:
Dr. Hernan Gonorazky

Variants of unknown significance:
Dr. James Dowling

Disclaimer: Please note the speakers in this webinar have involvement in the subject matter with real or perceived relationships

GENETIC COUNSELLING: WHAT DO FAMILIES NEED TO KNOW AND WHEN?

Lauren Brady, Master of Genetic Counselling, CCGC, CGC

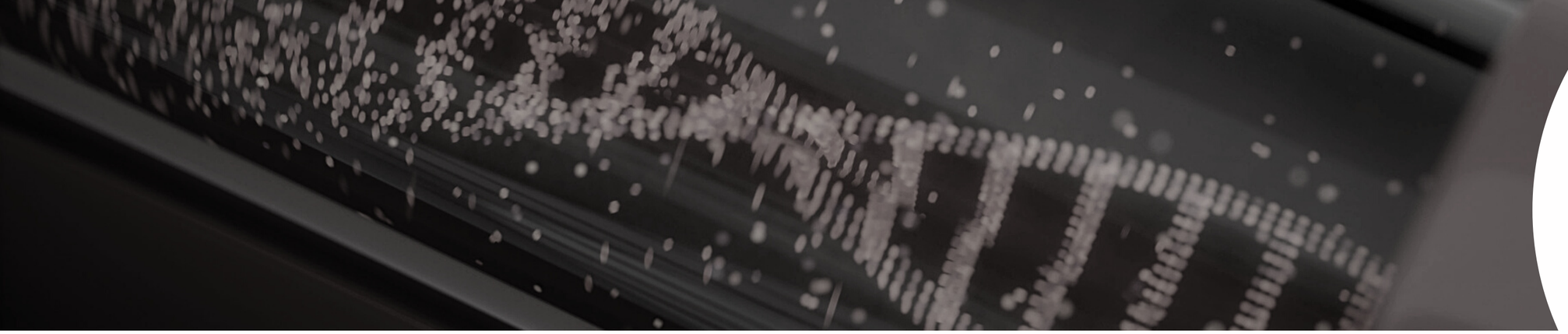
HAMILTON HEALTH SCIENCES
(HAMILTON, ONTARIO)

Genetic counselling involves an assessment of the risk of the condition occuring and re-occuring and discussions about inheritance patterns (how a gene is passed on), available testing options including interpretation of test results, prevention, medical management and options for prenatal diagnosis.

Genetic counsellors provide individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions.

A negative result means a mutated gene was not detected by the test, but it might be that not all genes were covered by that test. Variants of uncertain clinical significance (VUS) means there is a portion of the gene that looks different from the way it's normally expected to look. However, researchers haven't yet confirmed whether this variant is a harmless change or a risk factor for neuromuscular disorders.

If a genetic test result is positive, that means the genetic change that was being tested for was detected. This means a definitive diagnosis is identified and additional tests might be required.



Whole-exome sequencing and whole-genome sequencing are two major types of methods that are used to extensively identify genetic variants. Because most known mutations that cause disease occur in exons, whole exome sequencing is thought to be an efficient method to identify possible disease-causing mutations.

It has become possible to assess more of the genome (one's complete set of DNA) om in a cost-effective manner such as exome testing. Secondary findings are not related to the primary reason for ordering the test.

GENETIC TESTING PLATFORMS & RESULTS INTERPRETATION

Kim Amburgey, MSc, CGC

HOSPITAL FOR SICK CHILDREN
DIVISION OF NEUROLOGY
(TORONTO, ONTARIO)

Karyotype detects whole extra/missing chromosomes (aneuploidy), large structural rearrangements and marker chromosomes. This type of testing does not identify small deletions/duplications.

Cytogenetics involves the examination of chromosomes to identify structural abnormalities. Chromosomal microarray detects deletions/duplications of segments of chromosomes. It can't pick up on single gene disorders.

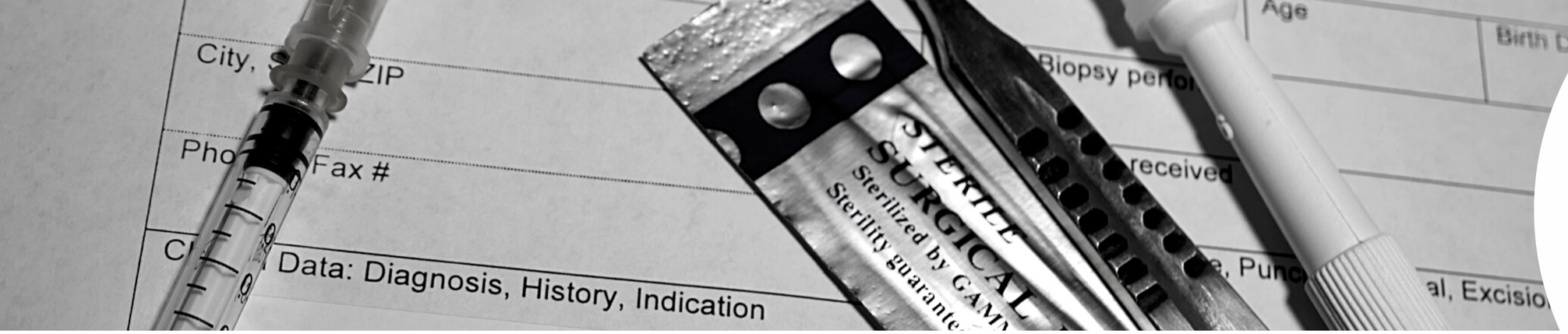
NGS serves as a second-tier test for individuals in whom previous targeted gene mutation analyses for specific neuromuscular disorder (NMD)-related genes were negative. This tests identifies mutations within genes known to be associated with inherited NMDs, allowing for predictive testing of at-risk family members.

Next-Generation Sequencing detects single base substitutions, small insertions/deletions. This type of test helps to establish a diagnosis of a neuromuscular disorder associated with known causal genes.

NON-GENETIC TESTING IN THE GENOMICS ERA

Hernan Gonorazky, MD

HOSPITAL FOR SICK CHILDREN
(TORONTO, ONTARIO)



A muscle biopsy is a procedure used to diagnose diseases involving muscle tissue. MRI scans of muscles may be helpful in selection of a site for muscle biopsy in patients with suspected inflammatory myopathy especially when a first muscle biopsy turns out to be negative.

Muscle biopsy is still an important tool for the evaluation and diagnosis of patients presenting with acute or progressive weakness who are suspected of having an underlying neuromuscular disorder.

CK results can help clinicians differentiate between various disorders that cause weakness, especially in neonates. Normal CK does not rule out neuromuscular disease.

Creatine phosphokinase (CK) is an enzyme found mainly in the skeletal muscle, but also in the heart and brain. Higher-than-expected serum CK indicates leakage of CK through the muscle membrane, and suggests muscle damage.

EMG is useful in infants only if for differential diagnosis in causes mimicking myopathies.

An electromyogram (EMG) is a test that measures the electrical activity of muscles both at rest and during contraction. Nerve conduction velocity studies (NCVs) measure how fast the nerves can send electrical signals.

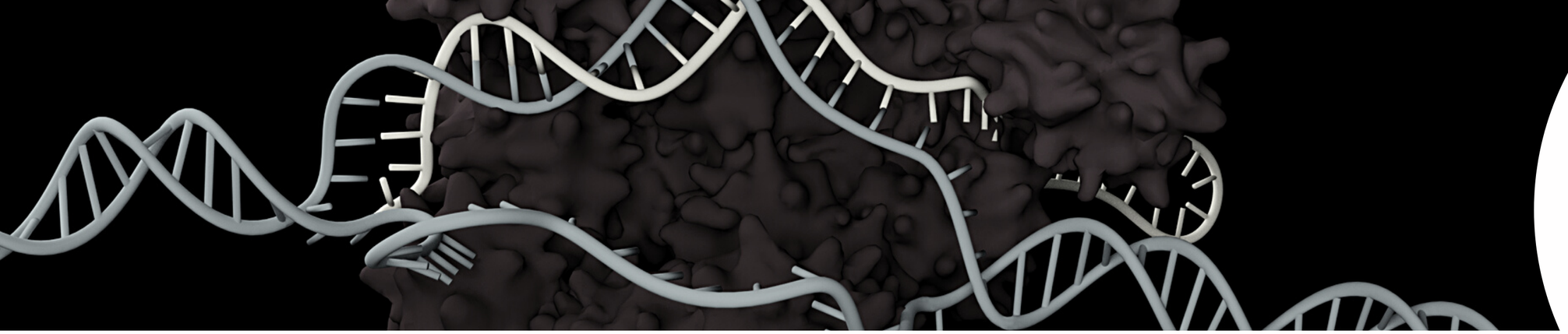
VARIANTS OF UNKNOWN SIGNIFICANCE

James Dowling, MD, PhD

HOSPITAL FOR SICK CHILDREN
(TORONTO, ONTARIO)

Around half of patients, whether children or adults, are considered 'unsolved' cases - leaving the genetic basis for disease unsolved in many individuals. This might be due to variant(s) of unknown significance in a known disease gene or candidate gene. These variants of unknown significance cause dilemmas for clinicians and uncertainty on how to advise patients.

Advances in DNA sequencing technologies and current standard genetic testing (gene panel and exome sequencing) have led to a solve rate of about 50%.



RNA-seq gets coverage of the entire tissue transcriptome (all of the RNA). It gets information about relative amount of expression for each gene and exon and also gets single base pair resolution. It helps to solve about 30-40% of the 'unsolved' cases.

RNA sequencing (RNA-seq) can be a powerful clinical diagnostic tool that can be applied to the large population of individuals with undiagnosed, rare neuromuscular diseases.

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QUESTIONS?

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