# Psychosocial benefits of whole exome sequencing for patients with suspected inherited metabolic disorders

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### INTRODUCTION

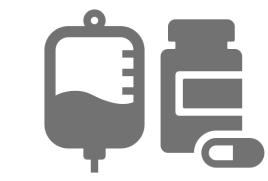
- 1 in 12 Canadians has a rare disorder, many of which are genetic and remain undiagnosed
- Diagnosis allows clinicians to provide support and anticipatory guidance to families
- Additionally, treatment options are becoming increasingly available for Inherited Metabolic Disorders (IMDs)
- Whole exome sequencing (WES) is increasingly used to establish a diagnosis for rare disease patients, with a diagnostic yield of 20-40%
- However, WES is not typically used as a first-line test for IMDs

#### **HYPOTHESIS**

Offering WES early in the diagnostic evaluation of patients suspected to have an IMD will lead to:



**Earlier** diagnosis

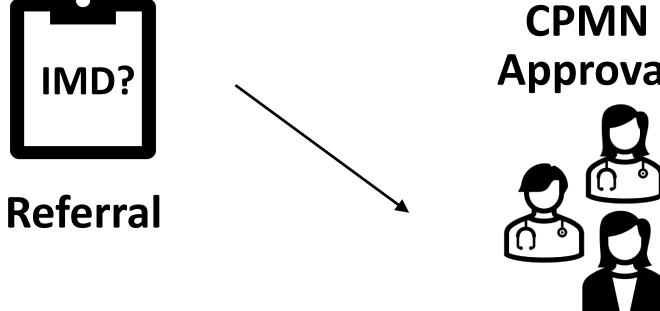


Timely initiation of treatment/ management



Higher patient satisfaction and quality of care

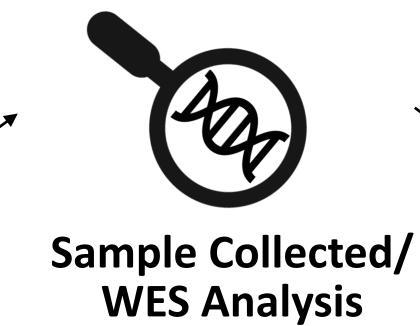
#### **METHODS**



Patients (any age) suspected to have an IMD are referred to the CPMN research study by any health care provider



Cases are reviewed by a multidisciplinary team for eligibility for WES



Eligible participants provide an oral sponge sample for WES at Discovery DNA, Inc. (Calgary, AB)

Results are reviewed by the team and/or referring provider and disclosed to the patient

Results/

Counselling

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#### ACKNOWLEDGEMENTS

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## Participant 1



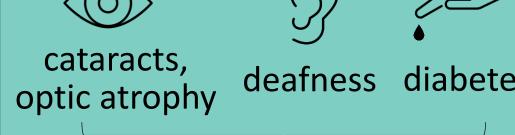
Congenital cataracts Muscle weakness

#### Genomic results:

1. Heterozygous likely pathogenic variant in WFS1 (c.1243G>T, p.Val415Phe)

- De novo (not inherited)
- Gene associated with:

cataracts,



deafness diabetes Wolfram-like syndrome

- 2. Heterozygous variant of uncertain significance in FLNC (c.4970G>A, p.Arg1657Gln)
- Inherited from healthy dad



cardiomyopathy

 No objective evidence of muscle weakness

- > WFS1 variant is likely the cause of his congenital cataracts
- Other associated features unlikely given his age

## Participant 3



#### Genomic results:

1. Heterozygous likely pathogenic variant in SYNGAP1

(c.987\_988delTG, p.Asp330Feufs\*88)

- Inheritance unknown (parentals pending)
- Gene associated with SYNGAP1-related intellectual disability:







- ➤ Diagnosis of SYNGAP1-related disorder
- Ruled-out previous working diagnosis, which required significant monitoring
- Not expected to develop any additional medical issues with this condition

## Shared health Soins communs





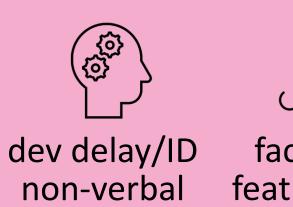
## **RESULTS: 3 CASE VIGNETTES**

### Participant 2

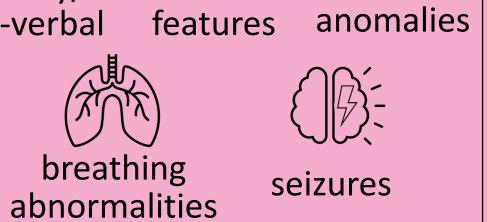
Developmental delay Agenesis of corpus callosum

#### Genomic results:

- 1. Heterozygous likely pathogenic variant in TCF4 (c.655G>C, p.Asp219His)
- De novo (not inherited)
- Gene associated with Pitt-Hopkins syndrome:



features



- 2. Heterozygous variant of uncertain significance in TRIO (c.4388G>A, p.Arg1463Gln)
- Inheritance unknown
- Gene associated with TRIOrelated intellectual disability:







- Diagnosis of Pitt-Hopkins syndrome, giving the family a name for her symptoms
- > Seizures unlikely given her age

brain

#### **DISCUSSION**

- Given that some features of IMDs are non-specific, this study is expected to identify both metabolic and non-metabolic disorders
- While the diagnoses in these 3 patients did not lead to changes in clinical management, the team was able to provide anticipatory guidance and reassurance that new manifestations are unlikely for each patient
- Anticipatory guidance is known to be an important component of genetic counselling
- Future Directions: Qualitative interviews with patients/families and analysis of quality of life data to gain a better understanding of the psychosocial impact of diagnosis through WES







