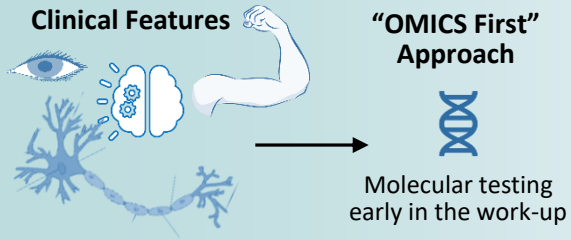
Diagnostic yield of whole exome sequencing for suspected inherited metabolic disorders (IMDs) stratified by clinical features

Angela Krutish[1,2], James Elmore[2], Aneal Khan[3,4], Marina Kerr[3], Leo Dimnik[3], Kiersten Johnston[3], Aizeddin Mhanni[1,2,5], Cheryl Rockman-Greenberg[1,2,5]

[1] Department of Biochemistry & Medical Genetics, University of Manitoba, Winnipeg, MB; [2] Children's Hospital Research Institute of Manitoba, Winnipeg, MB; [3] Discovery DNA, Inc., Calgary, AB; [4] M.A.G.I.C. Clinic Ltd. (**M**etabolics **a**nd **G**enetics **i**n **C**anada), Calgary, AB; [5]Department of Pediatrics & Child Health, University of Manitoba, Winnipeg, MB

Introduction



- Traditionally, diagnostic yield of WES: ~20-40%
- An "OMICS First" approach (i.e., whole exome sequencing [WES] early in the diagnostic work-up) for suspected IMDs can lead to quicker diagnosis and access to therapies
- Assessing the diagnostic yield by phenotype will help determine where an "OMICS First" approach is most beneficial

Objectives

- Evaluate diagnostic yield based on clinical features suggestive of an IMD using data from year 1 of the Canadian Prairie Metabolic Network (CPMN)

Acknowledgements

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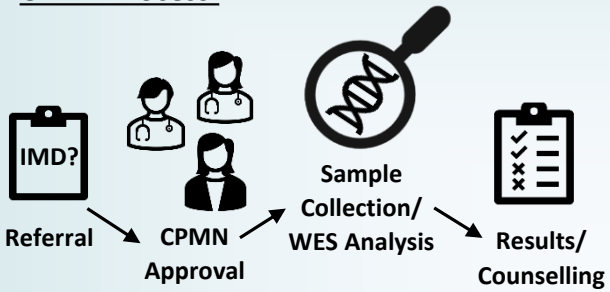
Methods

CPMN Process:



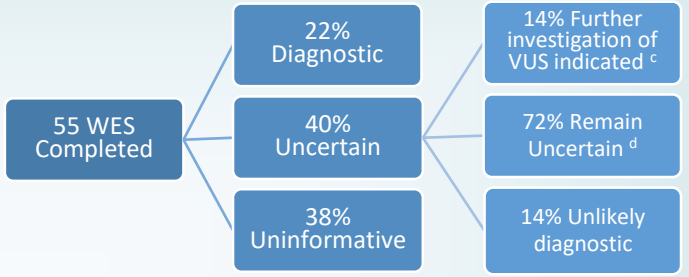
- Eligible participants provided an oral sponge sample for WES
- Participants were assigned to groups based on their major clinical features [a]
- Diagnostic yield was calculated as:

$$\frac{\text{\# LP/P variants explaining phenotype [b]}}{\text{\# WES completed for clinical feature}}$$

[a] Participants could be included in >1 group; groups with a sample size >1 were included

[b] **LP** = Likely Pathogenic and **P** = Pathogenic variants that explain the participant's clinical presentation

Results



[c] Follow-up studies recommended (e.g. parental or functional studies)

[d] Further interrogation not possible/unlikely to change classification

Table 1. Diagnostic yield by clinical feature

Clinical feature	Yield
Brain anomaly (n=2)	100%
Seizures (n=11)	46%
Ophthalmologic features (n=11)	46%
Rhabdomyolysis (n=3)	33%
Encephalopathy/neurodegenerative (n=7)	29%
Movement Disorder (n=10)	20%
Episodic (n=5)	20%
Muscular/Neuromuscular (n=24)	17%
Neuropathy (n=2)	0%
Hypoglycemia (n=4)	0%

Discussion

- Consistent with our findings, other studies reported high diagnostic yields for structural brain anomalies, seizures, ophthalmologic features[1-3]
- Further information is needed on how to best integrate the "OMICS First approach" into clinical practice

Future Directions:

- Further investigate diagnostic yield for specific phenotypes
- Health economic assessment of WES
- Functional studies for select variants in Drosophila, mice and other biological organisms to elucidate molecular and biological significance

References

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