Advancing rare disease diagnostics through research-clinical integration: a translational framework

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Introduction

- **Diagnosis matters in rare disease** - may guide management decisions, connects families to support
- **Genomic sequencing has helped** - exome and genome increased diagnostic yield, but many remain without answers due to unresolved variants or genes of uncertain significance (VUS, GUS) or negative results
- **Research bridges the gap** - rare disease patients and their health care providers need access to emerging tools (RNA-seq, long read WGS, methyl-omics) not yet in clinical care
- The Rare Disease Discovery Hub at BC Children's Hospital provides **patient-centred research investigations** with the aim of **answering diagnostic questions**

Enrolled Participants

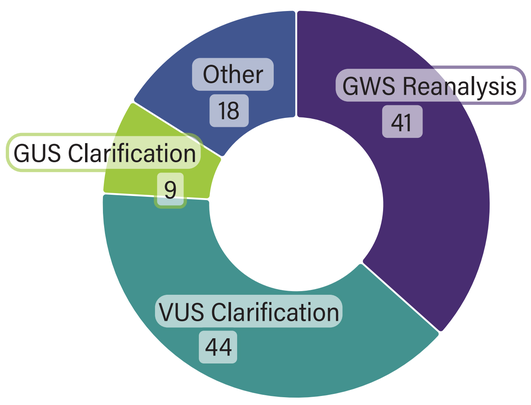


Figure 1. Patients with suspected rare diseases are referred by health care providers at different stages of the diagnostic odyssey, including those with negative GWS. VUS or GUS on prior testing, or other questions.

Global Collaborations

Figure 2. The broad research protocol of the RDDH has enabled the secure transfer of data and biological samples to collaborators all over the world to enable discovery and diagnosis.

Research Framework

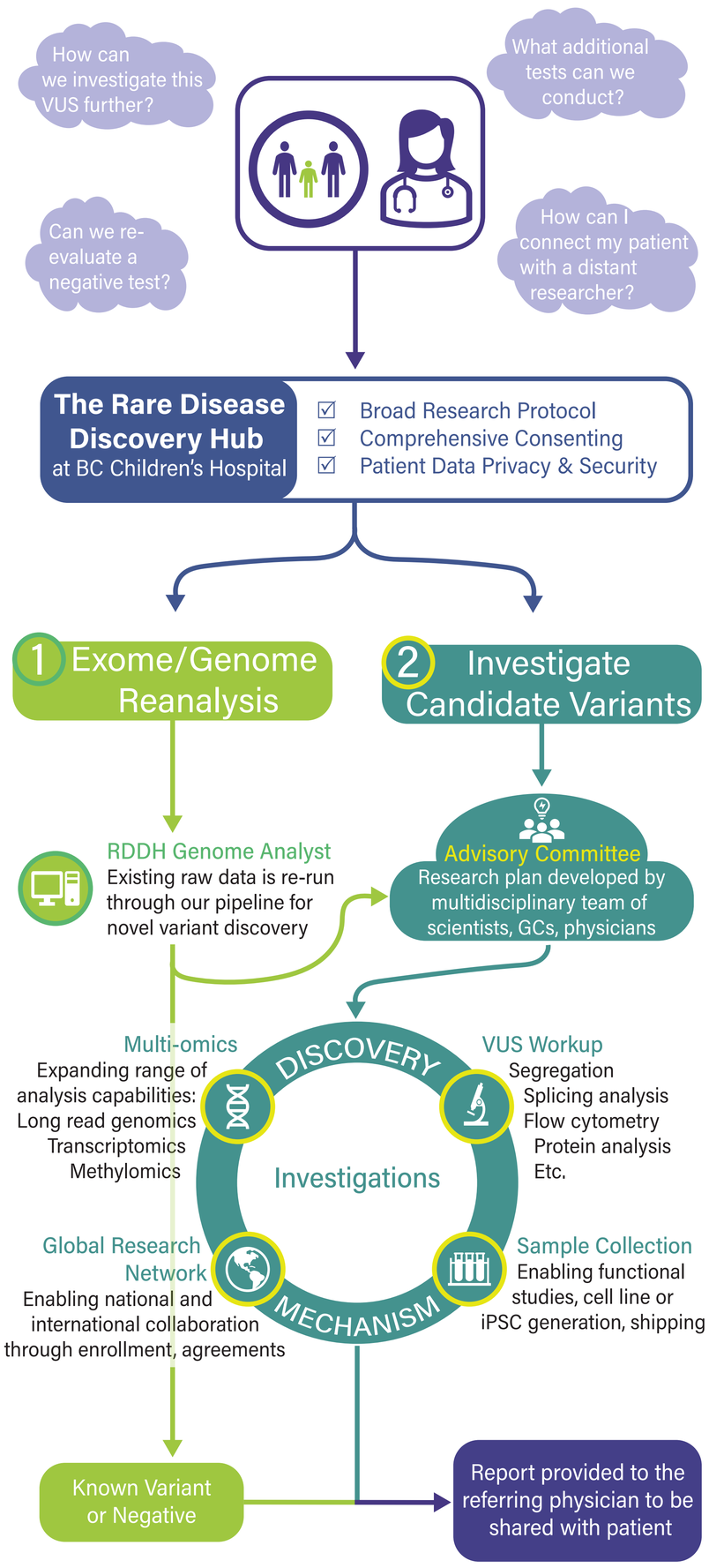


Figure 3. Overview of the Rare Disease Discovery Hub workflow. Undiagnosed patients with health care providers who are stuck are referred. Reanalysis of GWS data is initiated or an advisory committee decides on research approach. Results are shared with the patient by their referring provider.

Undiagnosed Case Outcomes

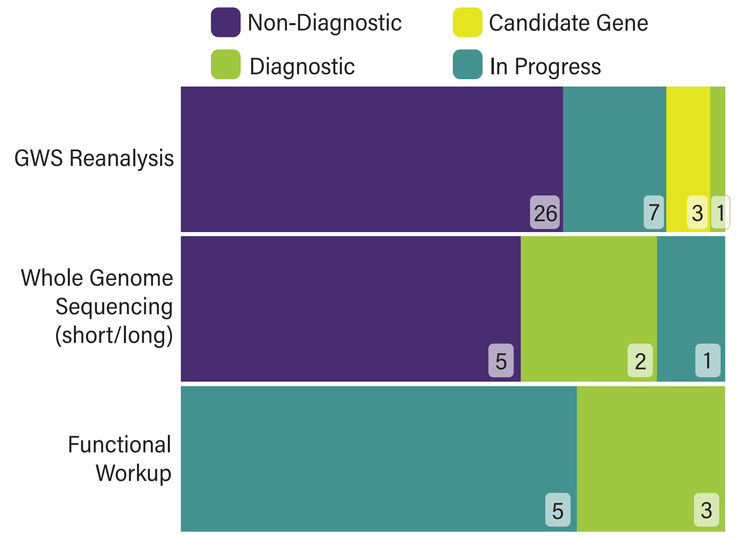
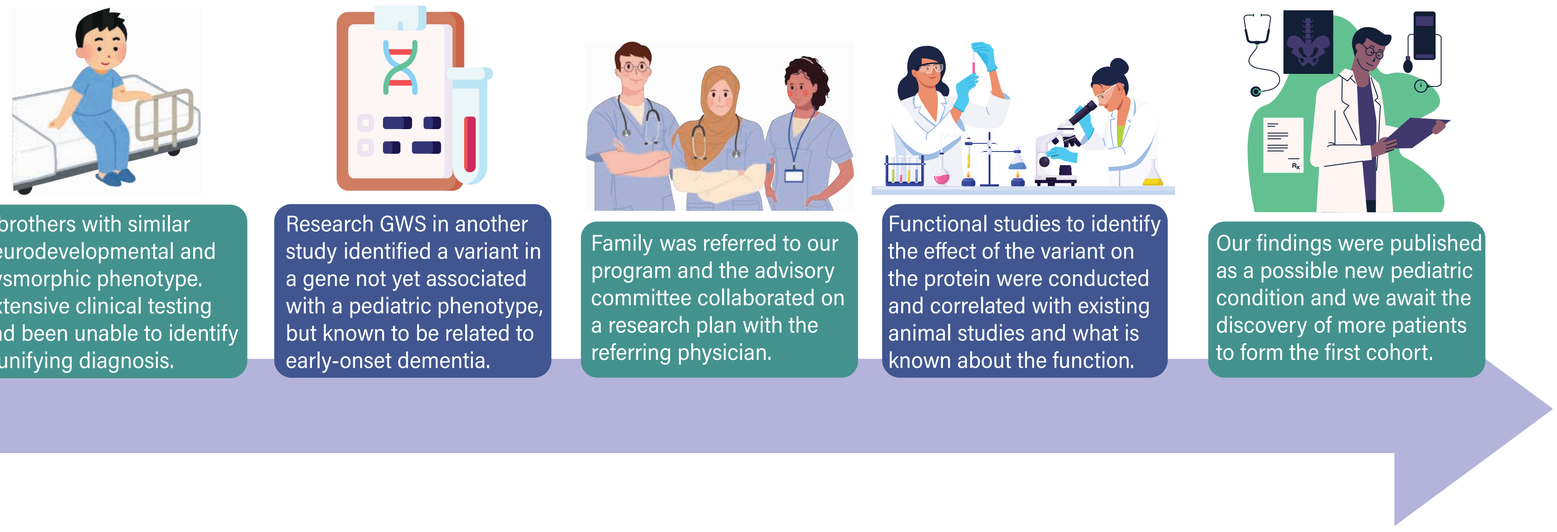


Figure 4. Overview of research analysis outcomes after clinical testing was reported as negative or GUS. In some cases, functional workup was pursued following identification of a candidate gene. Yield from GWS reanalysis was generally low compared with trio WGS.

VUS Resolution

Figure 5. Results from 34 VUS investigated in our program. Methods contributing to resolution included splicing analysis by RNA-seq (n=15), segregation analysis by Sanger (n=13), phasing or CNV analysis by long-read genome sequencing (LRS, n=5), and protein quantification by Western blot (WB, n=2). Of the resolved variants, 19 were supported as pathogenic and 15 as benign.

Example Case



Conclusions

Research programs embedded within clinical systems can help to bridge the diagnostic gap that exists due to limited clinical access to emerging technologies. Our protocols, consent forms, data, and experiences are freely available to teams who want to create similar programs in their jurisdictions.

Contact discoveryhub@bcchr.ca for more information.

Example Case

About Us

THE UNIVERSITY OF BRITISH COLUMBIA
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Faculty of Medicine

BC Children's Hospital Foundation
BC Children's Hospital Research Institute