Canada's path forward for rare diseases: 

*Discovery to translation*

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In Canada

~250,000 Canadian children have a rare genetic disease
~7000 Rare Diseases

gene known
~4200

At least 3000 diseases below the surface

![Image of an iceberg with a chart showing the increase in the number of novel genes identified by NGS and WES over time.](image-url)
Unmet Medical Need: Diagnosis is Care

250,000 Canadian children

Diagnostic odyssey

25% wait 5 to 30 years

40% wrong diagnosis

50% no diagnosis
Unmet Medical Need: Therapies

~ 400 therapies available for rare diseases
Addressing the ‘grand challenge’

1. Discover genomic causes of rare diseases
2. Determining how these genes cause disease
3. Use this information to configure therapies

Canada’s path forward
1. Orchestrated RD pipeline

Rare Disease Gene Discovery

4200 Genes Known

Gene Unknown

Patient Samples
21 Sites
80 Physicians
50 Scientists
21 Sites
80 Physicians
50 Scientists
What diseases do we study?

>700 Diseases Proposed

>400 Diseases Selected for Study

- Disorder is likely monogenic and gene unknown
- At least one Canadian patient with condition available for study
- Appropriate investigations have been performed to exclude known causes
Deep Phenotyping

Phenotips

Dr. Mike Brudno
U of Toronto
Strategies for gene discovery

1. Unrelated multiple affected with same disorder

2. Mapped Disorders

3. Affected Siblings: Compound heterozygous

4. Single affected: de novo trio or recessive with gene filters
365 disorders out of pipeline ...  

![Bar chart showing 55% solved disorders.](chart.png)

- Novel: 78
- Known: 125
- Disorder Solved: 203
- Disorders Unsolved: 138

55% Solved

Am J Hum Genet 2014; 94:809-817

FORGE Canada Consortium: Outcomes of a 2-Year National Rare-Disease Gene-Discovery Project

Chandree L. Beaulieu,1 Jacek Majewski,2 Jeremy Schwartzentruber,2 Mark E. Samuels,4 Bridget C. Fernandez,5 Francois P. Bernier,6 Michael Budnoff,7-12 Bartha Knoppers,13 Janet Marcadier,4 David Dyment,1 Shefin Adam,7 Dennis E. Bulman,1 Steve J.M. Jones,10 Denise Averdi,8 Minh Thu Nguyen,8 Francois Rousseau,11 Christian Marshall,12 Richard F. Wintle,12 Yaoqing Shen,10 Stephen W. Scherer,10,11 FORGE Canada Consortium,1 Jan M. Friedman,9 Jacques L. Michaud,4 and Kym M. Boycott1,4
Solving the unsolved

- Novel: 78
- Known: 125

203 Disorder Solved
138 Disorders Unsolved

45% unsolved
National Data Coordination

PhenomeCentral
An integrated portal for sharing and searching patient phenotype data for rare genetic disorders

www.phenomecentral.org

Share phenotypic and genotypic information with partners

Deep phenotypes

Exome and genome datasets

Dr. Mike Brudno
U of Toronto
Multiple disconnected solutions

Matchmaker Exchange

ClinVar & ClinGenDB

PhenoDB Gene Matcher

DECIPHER

LOVD

GEM.app

Undiag. Diseases Program

Café Variome

CARE for RARE

ClinVar and ClinGenDB

Phenome Central

Courtesy of Heidi Rehm
When there is a diagnosis...

- Natural history
- Accurate genetic counselling
- Prevention of complications
- Tailored therapy
First therapeutic opportunity

95 known disease genes revealed by NGS

Therapy adjusted
- Primary adrenal insufficiency
- Infantile myofibromatosis
- Intractable epilepsy

Therapy initiated
- Hunter syndrome
- Riboflavin transporter defect
- Cerebral Folate Transport deficiency
Glucocorticoid deficiency

- Diagnosed with Primary adrenal insufficiency
  - Presented with hyopglycemia, comma, N electrolytes, low serum morning cortisol, high serum ACTH level, red hair, mild obesity
  - Combined cortisol and aldosterone replacement therapy (15 years)

- WES trio: compound het mutations in POMC

- Withdrawal Florinef

therapy adjusted

Mark Samuels, J Clin Endocrinol Metab 98: 736, 2013
Riboflavin transporter defect

- Childhood onset sensory neuropathy, hearing loss, optic atrophy
- WES identified homozygous mutation in SLC52A2 consistent with Brown-Vialetto-VanLaere type 2
- Riboflavin supplementation

therapy initiated

Bernard Brais, Montreal
2. Orchestrated RD pipeline

Disease phenotyping and mechanism

Mutation
Gene
Protein
Pathway
Disease expertise

Cell Models
Yeast Models
Zebra fish Models
Mouse Models

Triaging

‘Omics Profiling
High-content imaging
RD Models and Mechanisms Network
RD Models and Mechanisms Network

$2.3 M Catalyst Grant
RD Models and Mechanisms Network

GeneX

$25K

$2.3 M Catalyst Grant
RD Models and Mechanisms Network

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$25K$
RD Models and Mechanisms Network

$25K

$2.3 M Catalyst Grant

$25K
Canada’s ‘Omic Platforms

Molecular Basis for the Disease Determines Lead Platform for Analysis

- Replication / Transcription: RNAseq
- Signaling / Ubiquitination: Proteomics
- Intermediary metabolism: Metabolomics
- Lipid storage / metabolism: Lipidomics
Diverse opportunities

Optic Farber atrophy type 1
Glut 1 type 1
Fronto-temporal dementia Loeys-Dietz syndrome
MAPT CMT1B Spondyloepiphyseal dysplasia tarda
HSP Type 4 Benign chronic pemphigus
Cerebellar Hemiplegic ARSACs
atrophy Migraine type 2
short stature POLR3A Leuko
stature Dysferlinopathies
HSP54 D-bifunctional protein deficiency

Benign chronic pemphigus
Creatine transporter deficiency
3. Orchestrated RD pipeline

Therapeutic Discovery and Validation

- Screening FDA-approved pharmacopeia
- Pharma’s shelved Phase II assets
- Druggable target identification
- Yeast RNAi
- Protein-Drug Interactions
- Drug lead validation in model systems

Discovery  Validation
Repurposing clinically approved agents

Rare Disease

No transcript

Dr. Alex MacKenzie
Repurposing clinically approved agents

Rare Disease

- No transcript

FDA Approved Drug Treatment

Known Biological Effect
Repurposing clinically approved agents

Rare Disease

Known Biological Effect

Off-Target Biological Effect

FDA Approved Drug Treatment

Unanticipated Action for Rare Disease = Repurposed Drug
FDA “hit” – Loeys-Dietz syndrome

SMAD3 haploinsufficiency associated with Loeys-Dietz syndrome (familial thoracic aneurysms)

Identification of inducing drug(s) in pool

#592 = Isotretinoin (Accutane™)
Isotretinoin induction of SMAD3

SMAD3 Protein in 3031 cells after 13-CRA treatment 8h

![Graph showing SMAD3 protein expression after 13-CRA treatment with different doses.]

![Images of cell staining for DAPI and SMAD3 under different conditions (WT, DMSO, 100 nM, 200 nM, 500 nM).]
Target to trial

Congenital sideroblastic Anemia; *SLC25A38*; 2009

Transfusion-dependent $58,500/pt/yr

SLC25A38 is a mitochondrial glycine importer

Exogenous glycine plus folate ameliorate a zebrafish model

Phase 2 clinical trial as an innovative therapy for CSA patients at IWK
Trans-Canadian pipeline

Rare Pediatric Disease Gene Discovery → Disease Phenotyping and Mechanism → Therapeutic Discovery and Validation

- CHU Sainte-Justine
- Centre for Pediatric Clinical Genomics
- RDMM
- CIHR IRSC
- cdrd
- IGNITE
- CARE for RARE
- Personalized Medicine for Epilepsy

Building on previous $30M investment in operating funds
Trans-Canadian RD pipeline

Rare Pediatric Disease Gene Discovery

>4000 rare disease samples

Disease Phenotyping and Mechanism

90 mechanism projects

Therapeutic Discovery and Validation

>200 rare diseases to enter pipeline
Benefits to Canadian Families

Changing healthcare through cost effective diagnosis tests for rare diseases

Identification and advancement of therapeutic opportunities