Enhanced CARE for RARE Genetic Diseases in Canada

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Canada
Shared Pipeline and Resources

>1300 Diseases Proposed

- Caused by 1 gene?
- All clinical testing complete?
- Patient lives in Canada?

>1000 Diseases Selected for Study
Shared Pipeline and Resources

Clinical Database

PhenomeCentral

Analysis Teams
Matchmaker exchange
Exome sequencing
845 disorders out of the pipeline

47% Solved

32% diagnosis in known gene

Disorders Solved
- Known 267
- Novel 131

Disorders Unsolved
- Single surviving candidates 447

C4R 2.0
Why were known genes not identified in the clinic?
Diagnostic utility

Review

Utility of whole-exome sequencing for those near the end of the diagnostic odyssey: time to address gaps in care

Clin Genet 2015. © 2015 The Authors. Clinical Genetics published by John Wiley & Sons A/S. Published by John Wiley & Sons Ltd., 2015
Cost of Rare Disease

Genetic disease patients cost:
- 20x more than healthy individuals
- 5x more than chronic diseases
  (asthma, diabetes)

Chart review of 300 patients with a molecularly-diagnosed genetic disease
Value of a Diagnosis

Discrete Choice Experiment survey with 300 Canadian rare disease families

Families are willing to spend $5,000 out-of-pocket for a diagnosis

Most important attributes:
1) time to obtain an answer;
2) chance of diagnosis;
3) cost;

Least Important attributes:
1) type of test;
2) impact of results.
Education Program

**Audience:** medical genetics trainees, and interested individuals in current medical genetics practice

**Module 1:** Technical Aspects  
**Module 2:** Ethical Issues  
**Module 3:** Clinical Reporting  
**Module 4:** Clinical Cases

Plan to develop into Podcasts
Clinical sequencing pilot study: 400 children from 3 provinces
C4R activity 2a

400 probands

First presentation (125)

Second-Tier (125)

Diagnostic odyssey (150)

Randomized

Clinome

WES

WES
C4R activity 2a: Clinome

- Solved: 14
- Unsolved: 30
### C4R activity 2a: Clinome

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<thead>
<tr>
<th>CATEGORY 1: Initial presentation</th>
<th>2/5 (40%)</th>
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<td>&gt; 3 genes on differential</td>
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<th>CATEGORY 2: Second-tier testing</th>
<th>6/15 (40%)</th>
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<td>Follow-up appointment, first investigations normal</td>
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<th>CATEGORY 3: Diagnostic odyssey</th>
<th>6/24 (20%)</th>
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<td>No diagnosis following standard-of-care</td>
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Diagnostic translation

ORIGINAL ARTICLE

The clinical application of genome-wide sequencing for monogenic diseases in Canada: Position Statement of the Canadian College of Medical Geneticists

Kym Boycott, Taila Hartley, Shelin Adam, Francois Bernier, Karen Chong, Bridget A Fernandez, Jan M Friedman, Michael T Geraghty, Stacey Hume, Bartha M Knoppers, Anne-Marie Laberge, Jacek Majewski, Roberto Mendoza-Londono, M Stephen Meyn, Jacques L Michaud, Tanya N Nelson, Julie Richer, Bekim Sadikovic, David L Skidmore, Tracy Stockley, Sherry Taylor, Clara van Karnebeek, Ma’n H Zawati, Julie Lauzon, Christine M Armour, on behalf of the Canadian College of Medical Geneticists

Journal of Medical Genetics 2015
Canadian Guidelines: Primary indication is the focus

Approach to Incidental Findings

**Children**
Report medically actionable.
Adult onset only if prevents harm in them or other family members

**Incapable adults**
Report medically actionable

**Adults**
Report medically actionable or incidental
Do not report medically actionable or incidental

Boycott et al., JMG 2015
Care for Rare Next Steps

1. National Centre of Excellence
2. Canadian RD 30K project
3. Care for Rare 2.0
   - Solve RD
   - Treat RD

(CARE for RARE logo)