Newborn and carrier screening in southwestern Ontario FORGE Canada – a history of collaboration

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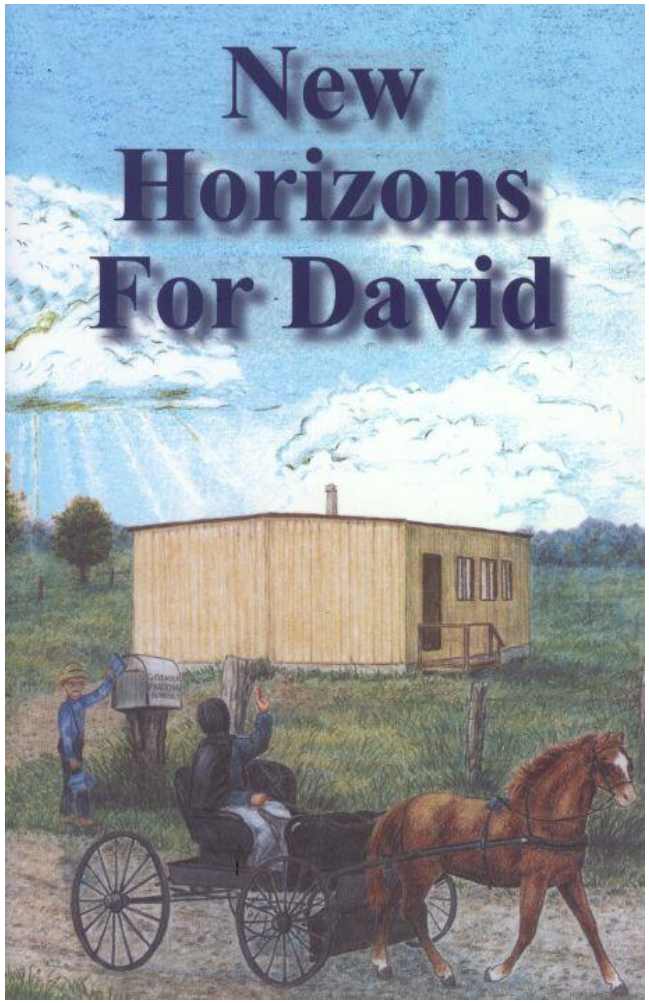
FORGE CANADA CONSORTIUM

Anabaptist groups in SW Ontario

- Old Order Mennonite
- Old Order Amish
- Old Colony Mennonite

In the beginning…



- High fever precipitates visual hallucinations and psychosis, eventual hearing loss and pigmentary retinopathy
- Sudden death
- Now ID’d as HARS

Collaboration with The Clinic for Special Children in Pennsylvania

-Dr. Holmes Morton

Migration of Old Order Amish (in Aylmer, Ontario) and Old Order Mennonites

First settled in Pennsylvania, then migrated to Ontario after 1776

Many ties to American families

Many disorders shared between Ontario and Pennsylvania

Maple syrup urine disease

Spinal muscular atrophy

Amish microcephaly

Pretzel syndrome

Specific mutation identified for 9 disorders in Old Order Amish in population of about 1200

Specific mutation identified for 10 disorders in Old Order Mennonite population of about 2500

Migration of Amish to Perth County, Ontario

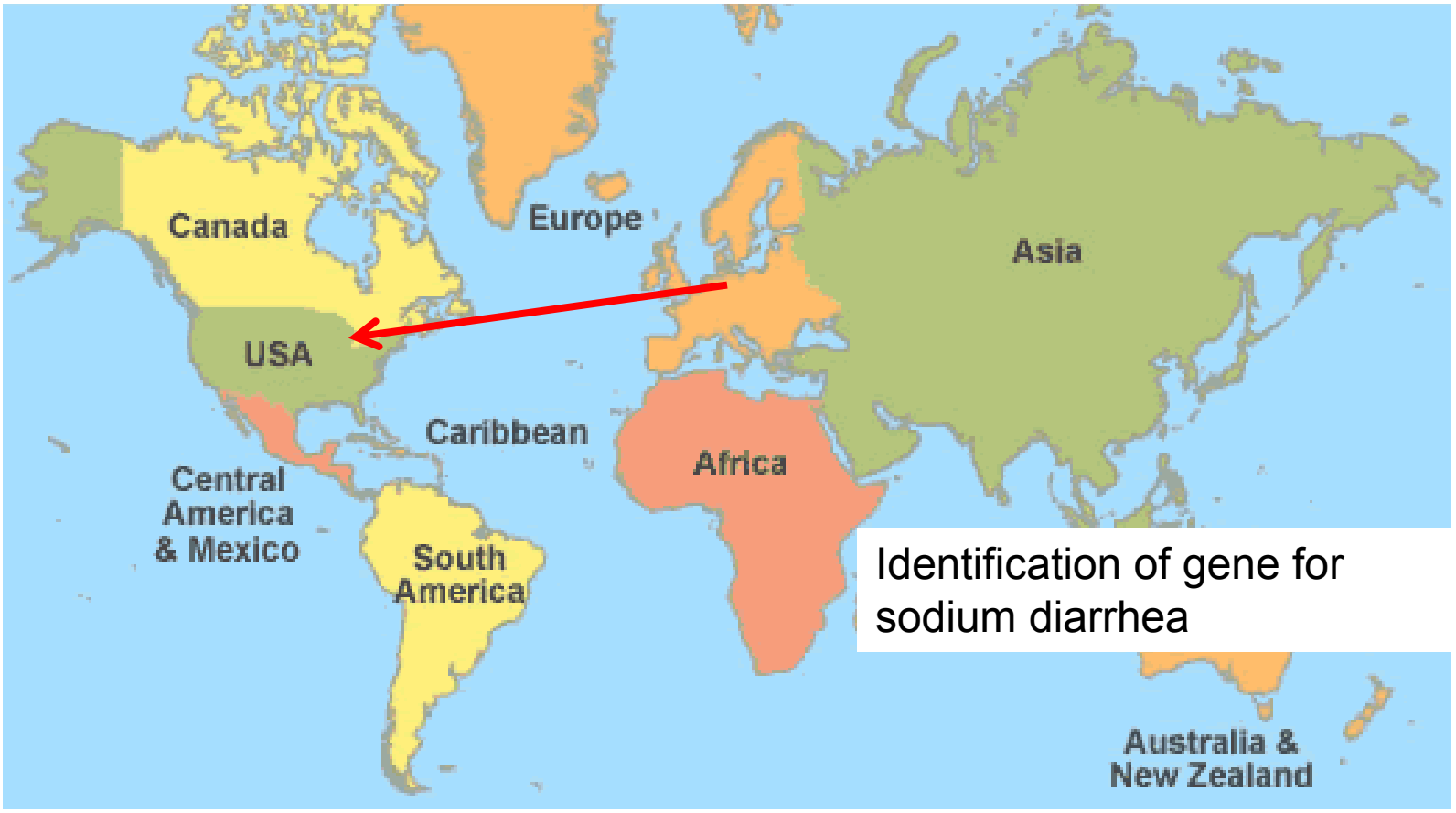
Immigrated directly to Canada from Alsace-Lorraine (France) and Bavaria beginning in 1825

Genetically isolated from American Amish

Many disorders unique to Old Order Amish in Ontario, not seen in Lancaster Amish

- Cerebral atrophy syndrome
- Fraser syndrome
- ECO syndrome
- Sodium diarrhea

Collaboration with European colleagues (A. Janecke)



Migrations of the Old Colony Mennonites to Ontario

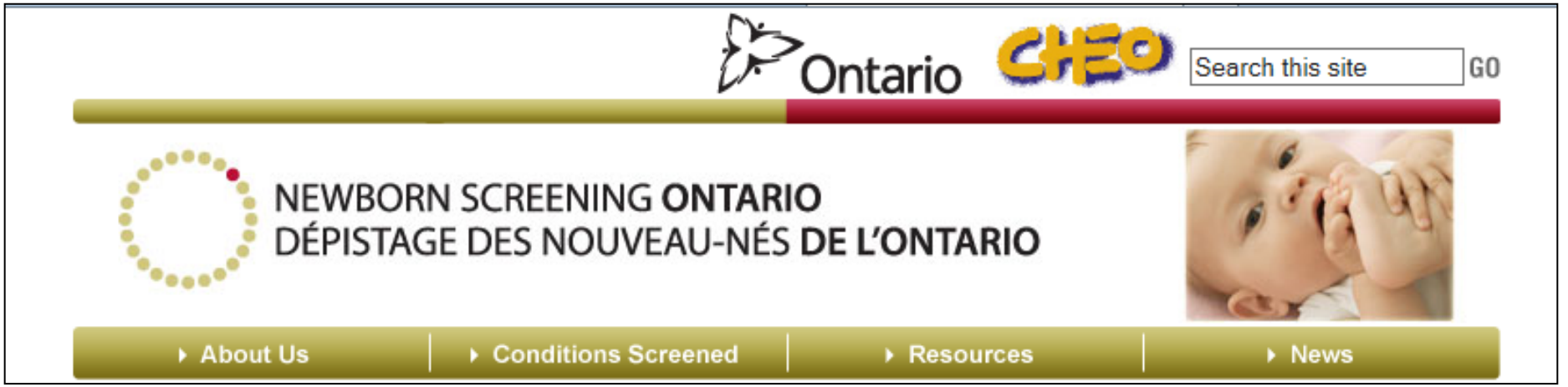
Old Colony Mennonites

- Largest group in Ontario, with many assimilated into general population
- Often not aware of their genealogy
- Many migrate between Mexico (winter) and Canada (summer)
- Difficult to provide consistent medical care and investigate for genetic disorders

Old Colony (Low German speaking) Mennonites

- 3 different types of SCID
  - ZAP70 kinase
  - CD3 delta
  - ADA deficiency

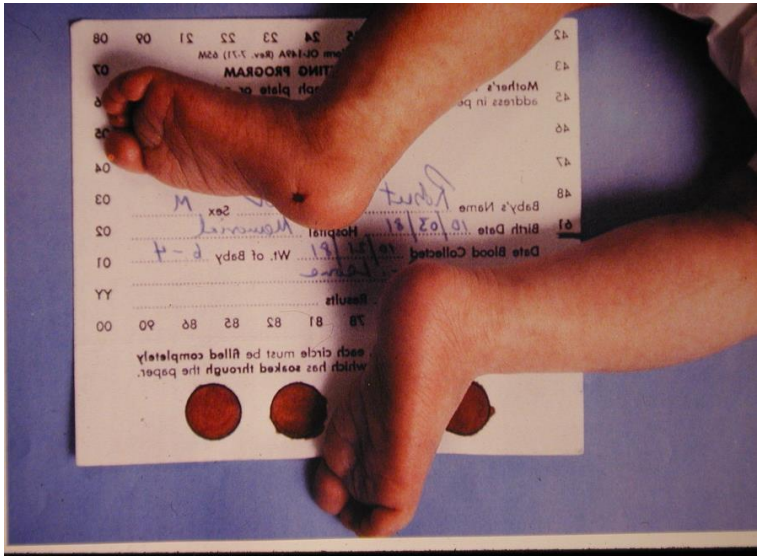
SCID screening in Ontario to begin in August 2013 for entire population (part of Ontario Newborn Screen)



- Will be screening with TRECs
- Benefits Mennonite and non-Mennonite babies

- See list of Amish and Mennonite disorders in Ontario

The Amish newborn screening project:



- Population about 1200
- About 200 families
- 30-40 newborns each year

2004: Newborn DNA testing for treatable disorders in the Amish community of Perth County

initiated following discussions with community leaders, public health providers, and midwives

research funding was obtained for a pilot project

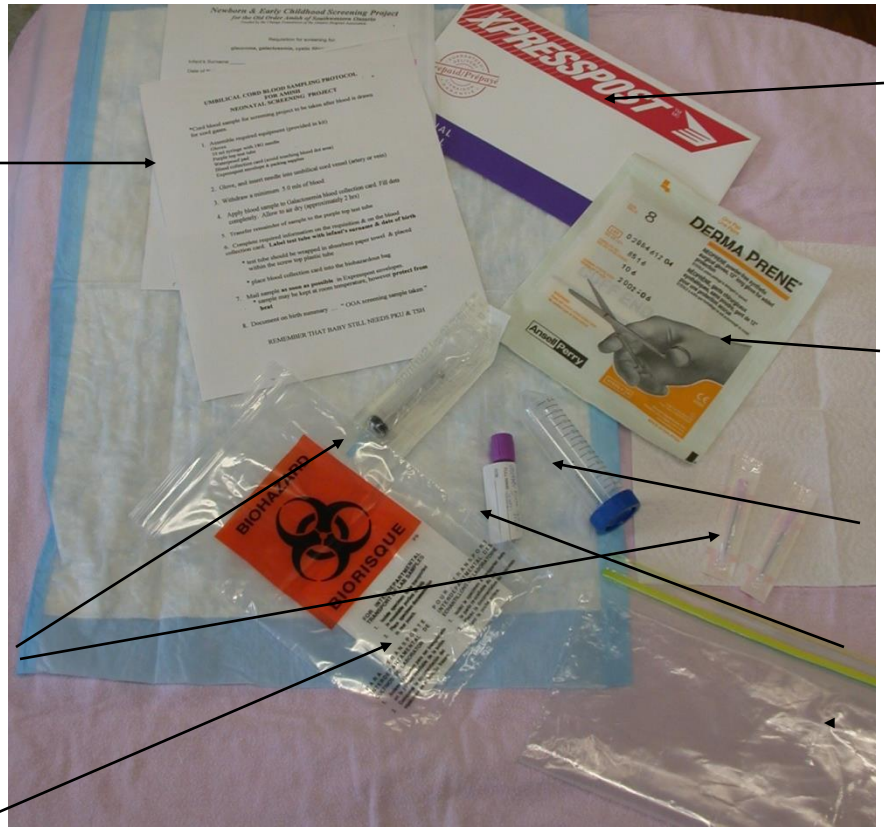
disorders chosen were all amenable to treatment

Disorders screened:

- Juvenile glaucoma (2 mutations)
- Cystinosis.
- Cystic fibrosis (2 mutations)
- Galactosemia

The cord blood sampling kit

instructions and requisition



courier package

gloves

mailing container

5 cc tube

needles, syringe

blood dot card

Targeted newborn screening in the Old Order Amish

- 370 babies (90%) have been screened using a combination of biochemical and DNA based analysis for targeted mutations

Outcomes of targeted newborn screening

Detected one child affected with each of the disorders out of 370 screened

High carrier rate in newborns tested

cystinosis	1:5
cystic fibrosis	1:7
galactosemia	1:7
glaucoma	1:11

Has been incorporated into routine care

Screening led to reporting of other disorders:

Out of 92 consecutive pregnancies:

- 5 lethal anomalies:
  3 ECO, 2 Fraser syndrome with renal agenesis
- 1 cystic fibrosis
- 1 oligodactyly
- 1 stillbirth at term
- 3 cleft palates
- 2 with cerebral atrophy and neurodevelopmental regression
-

13/92 = **14%** with major anomalies

Limitations of targeted newborn screening

- Turnaround time for DNA results
- Amish Newborn screen is only applicable for Amish infants
- Other treatable genetic disorders in the population are not routinely screened
- Inefficient to test one gene at a time
- Increasing number of disorders identified

Carrier screening of newborns

- Occurs automatically with DNA testing
- Bishops have decided that carrier status is not to be revealed

What about adult carrier testing?

- If we test married couples and find that they are not carriers for the same disorder, none of their offspring are at risk, and therefore their babies do not need to be tested for the disorder
- If a couple is at risk, we can do targeted testing ASAP after birth to identify affected babies while still asymptomatic

Family members began requesting adult carrier testing

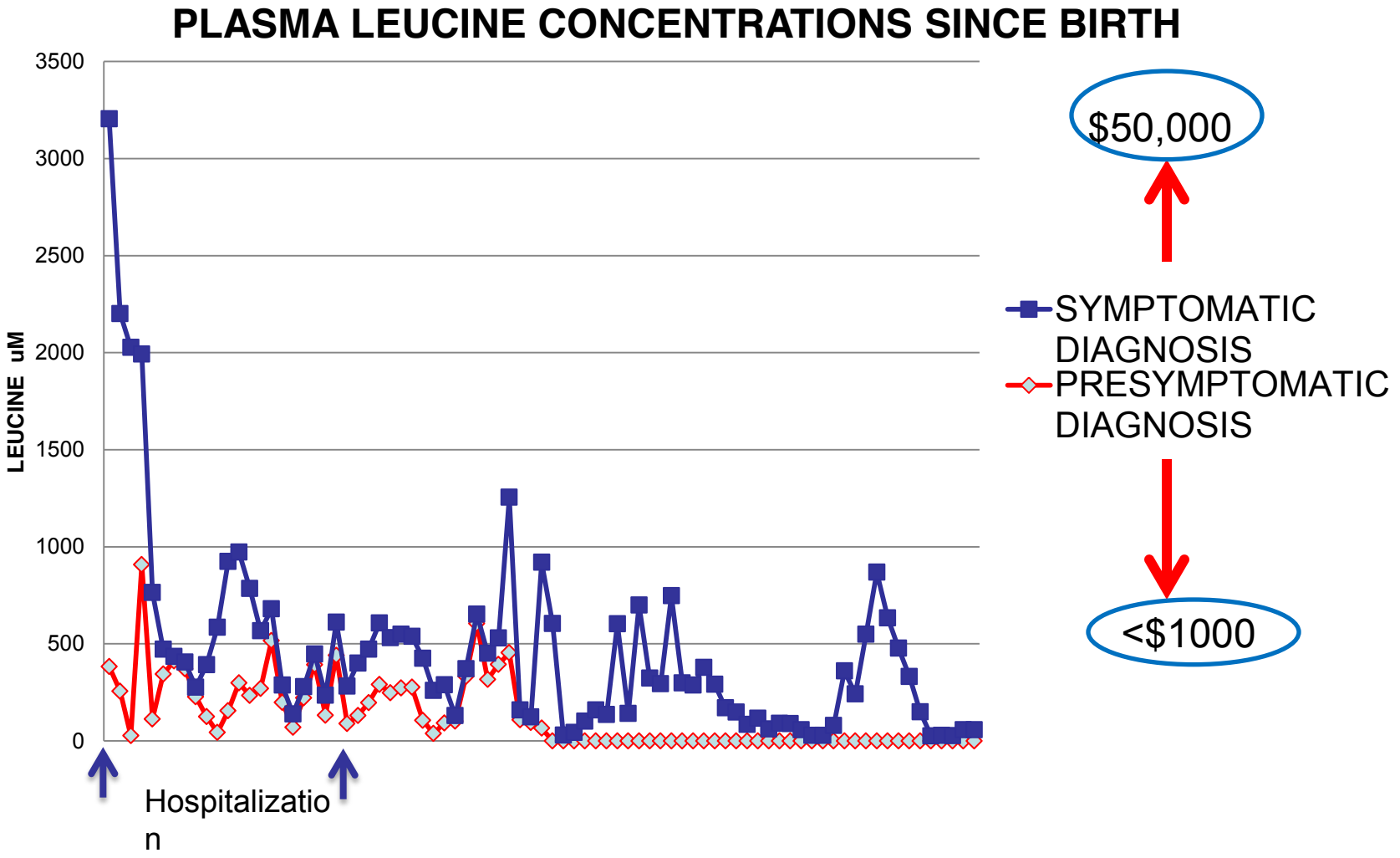
- Clinics were held for testing of large groups for single disorders
  - Galactosemia (OOA)
  - Glaucoma (OOA)
  - HLH (OOM)
  - MSUD (OOM)

- Inefficient to test individual genes as often carriers for more than one disorder

Current strategy

- Research grant to develop TaqMan assay to screen for 14 Amish and Mennonite disorders at the same time
- Offer testing to married couples
- If not at risk to have any of the disorders, no targeted testing of newborn will be done
- At-risk babies will be rapidly tested for specific disorder

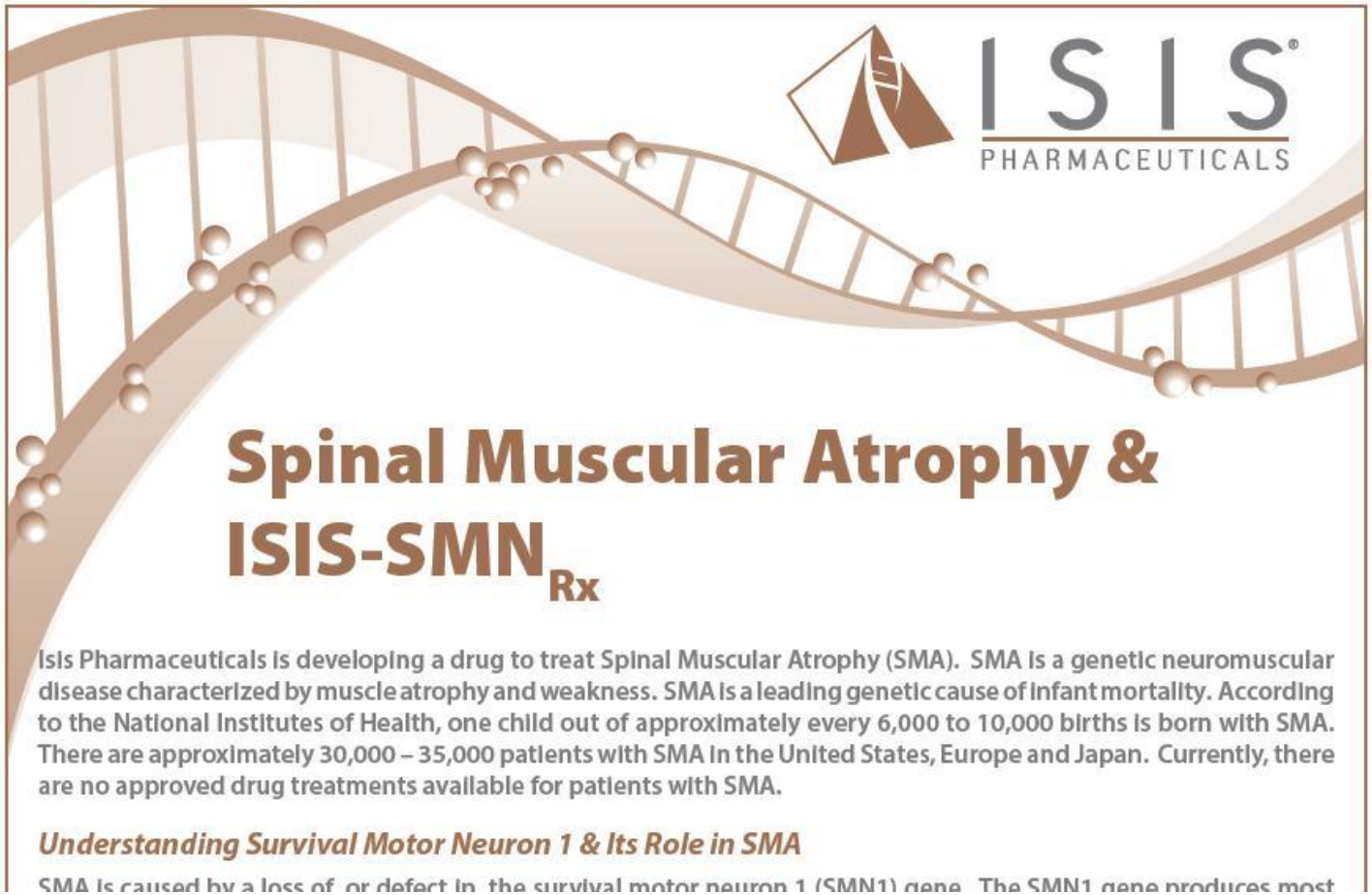
Maple syrup urine disease: Tale of two babies



Ethical concerns

- Do married couples want to know their carrier status?
- Do couples want to have a child diagnosed before symptoms occur if there is no treatment? (eg SMA)

A potential clinical trial for treatment of SMA

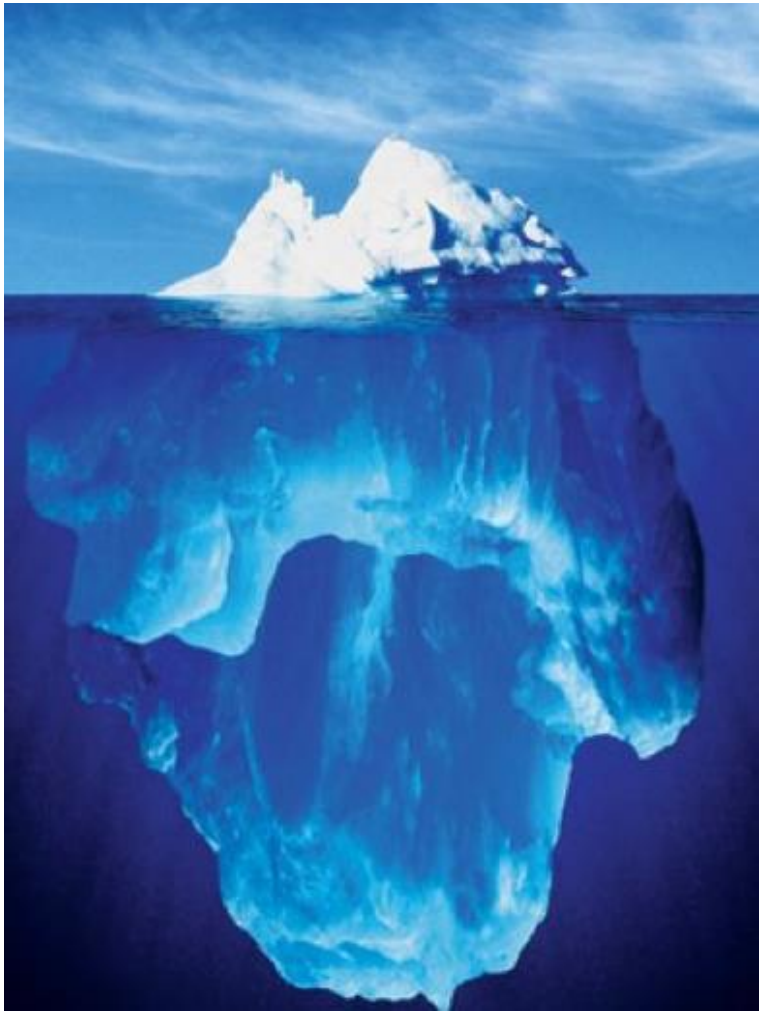


Clinical exome sequencing: Transforming the care of patients with rare genetic diseases

Kym Boycott, PhD, MD, FRCPC, FCCMG

Children's Hospital of Eastern Ontario Research Institute
University of Ottawa, Canada

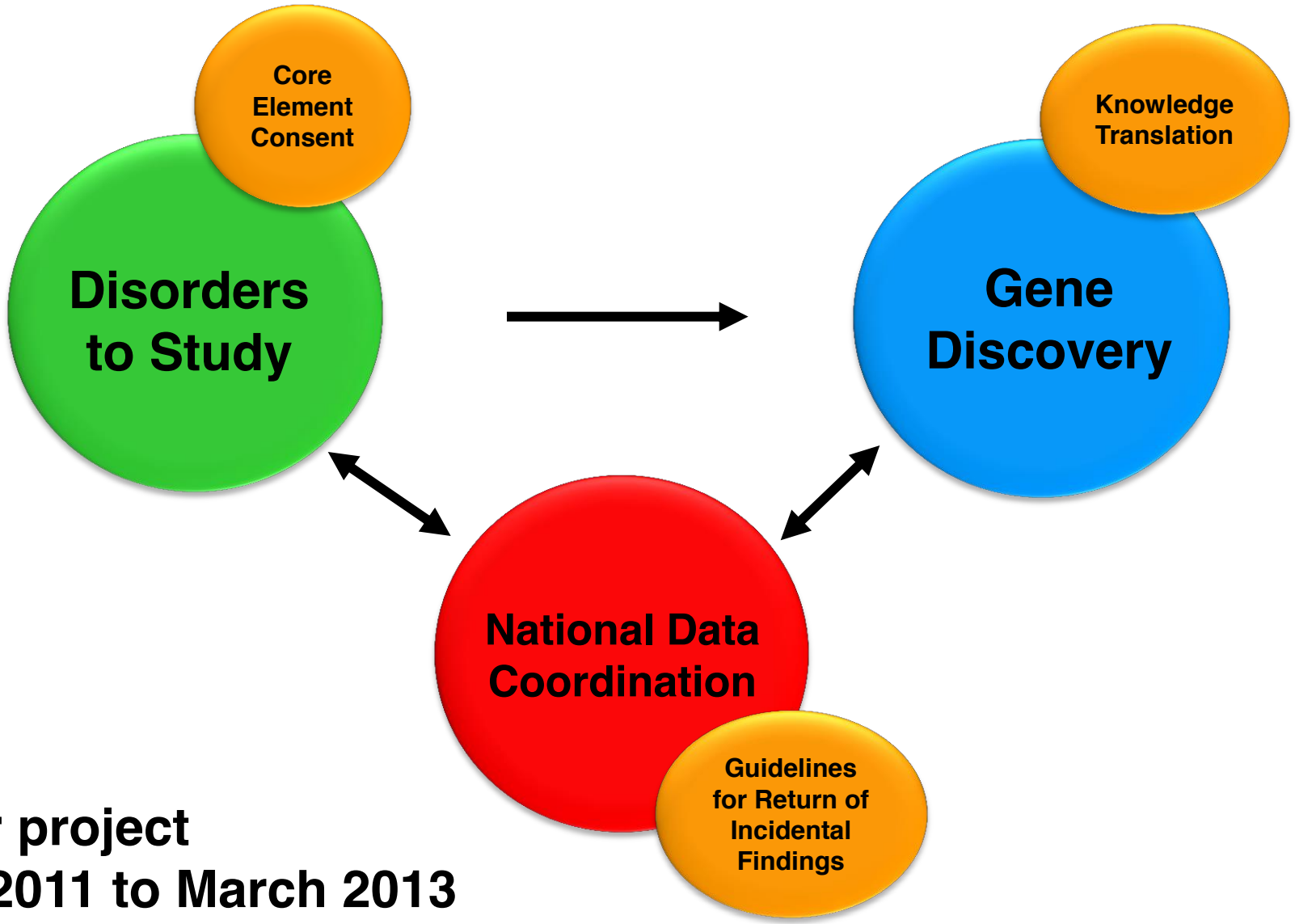
More disorders to be discovered!



gene known

gene unknown

FORGE Canada Consortium

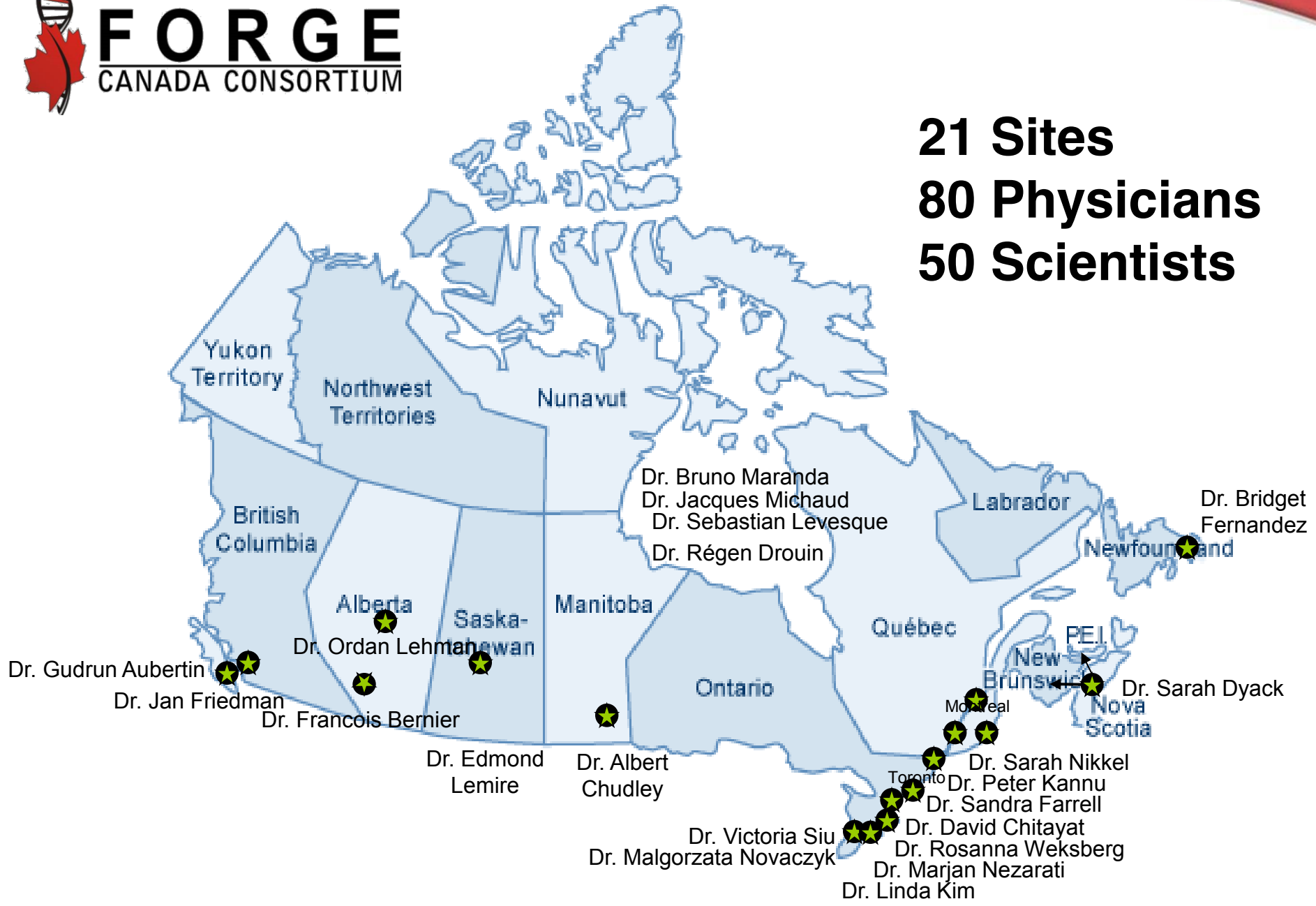


2 year project
April 2011 to March 2013

Finding Of Rare Disease GEnes

FORGE
CANADA CONSORTIUM

21 Sites
80 Physicians
50 Scientists



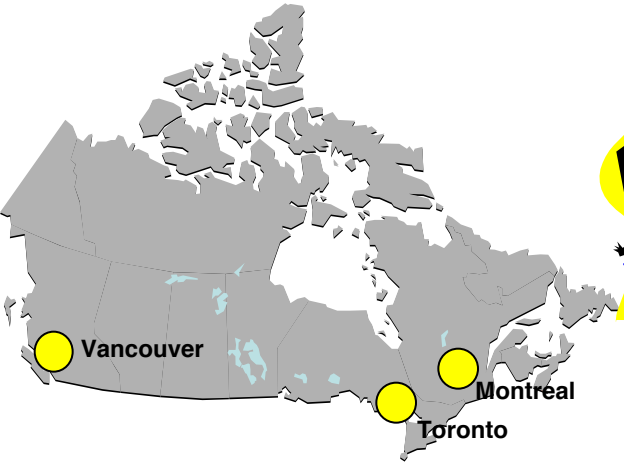
What disorders do we study?

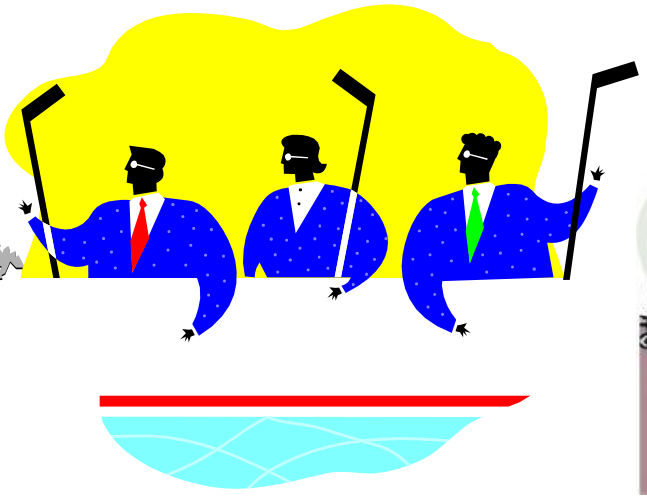
>400 Diseases Proposed

>200 Diseases Selected for Study

- Congenital or develops in childhood or adolescence
- 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

Data generation and analysis



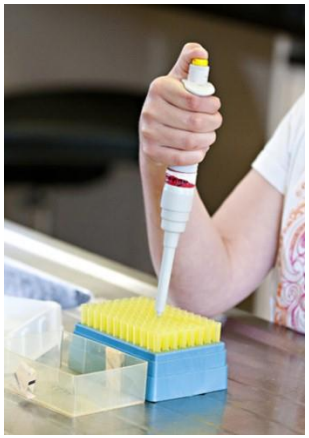


3 centres for exome sequencing

Project Teams -validation studies-

National Data Coordination Centre

101 Disorders into pipeline …



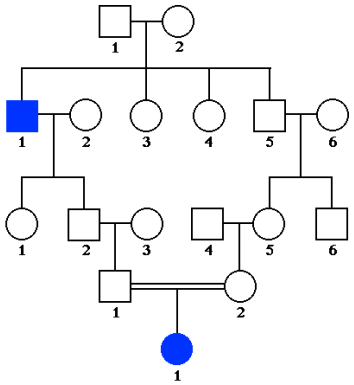
Multiple alleles

Mapping data

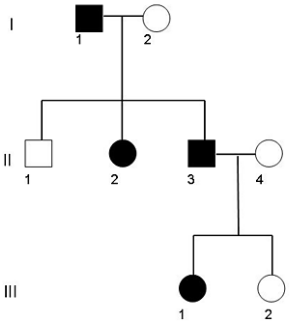
Compound heterozygous

3 Approaches

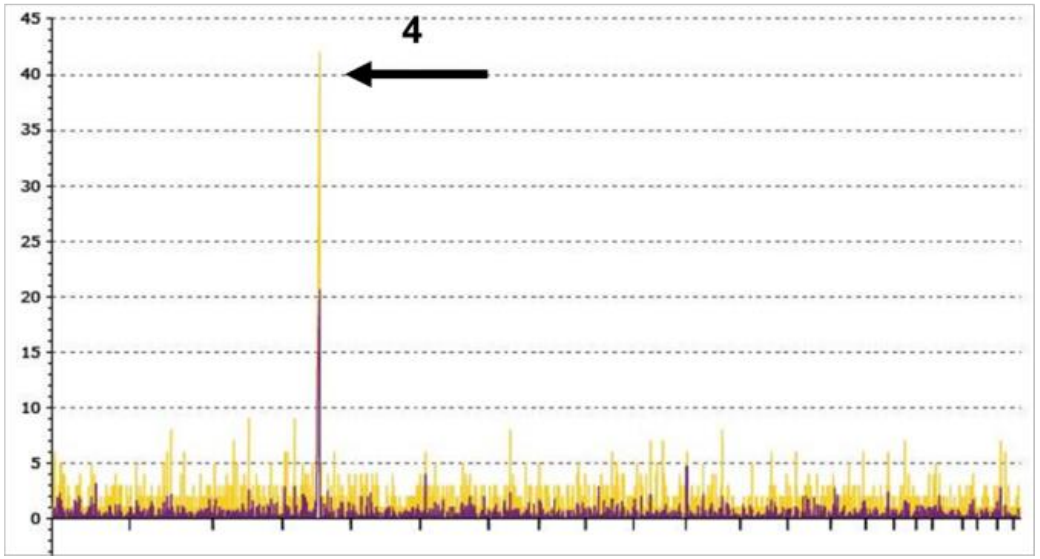
Approach 1- Mapping



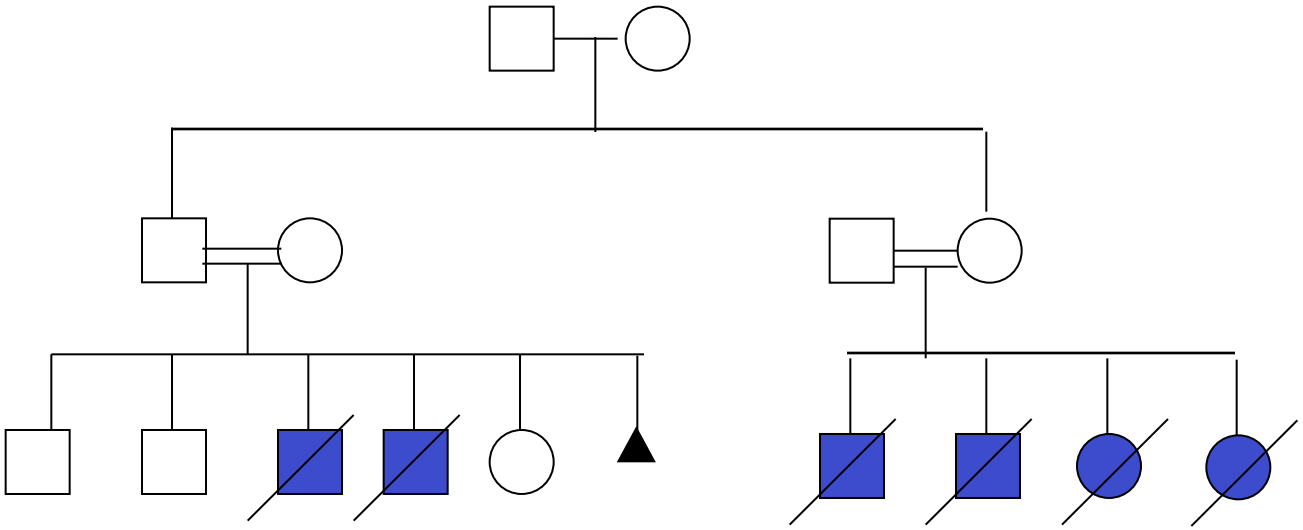
Consanguineous families



AD families with multiple affected members

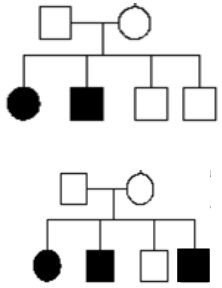


ECO syndrome (endocrine-cerebro-osteodysplasia)

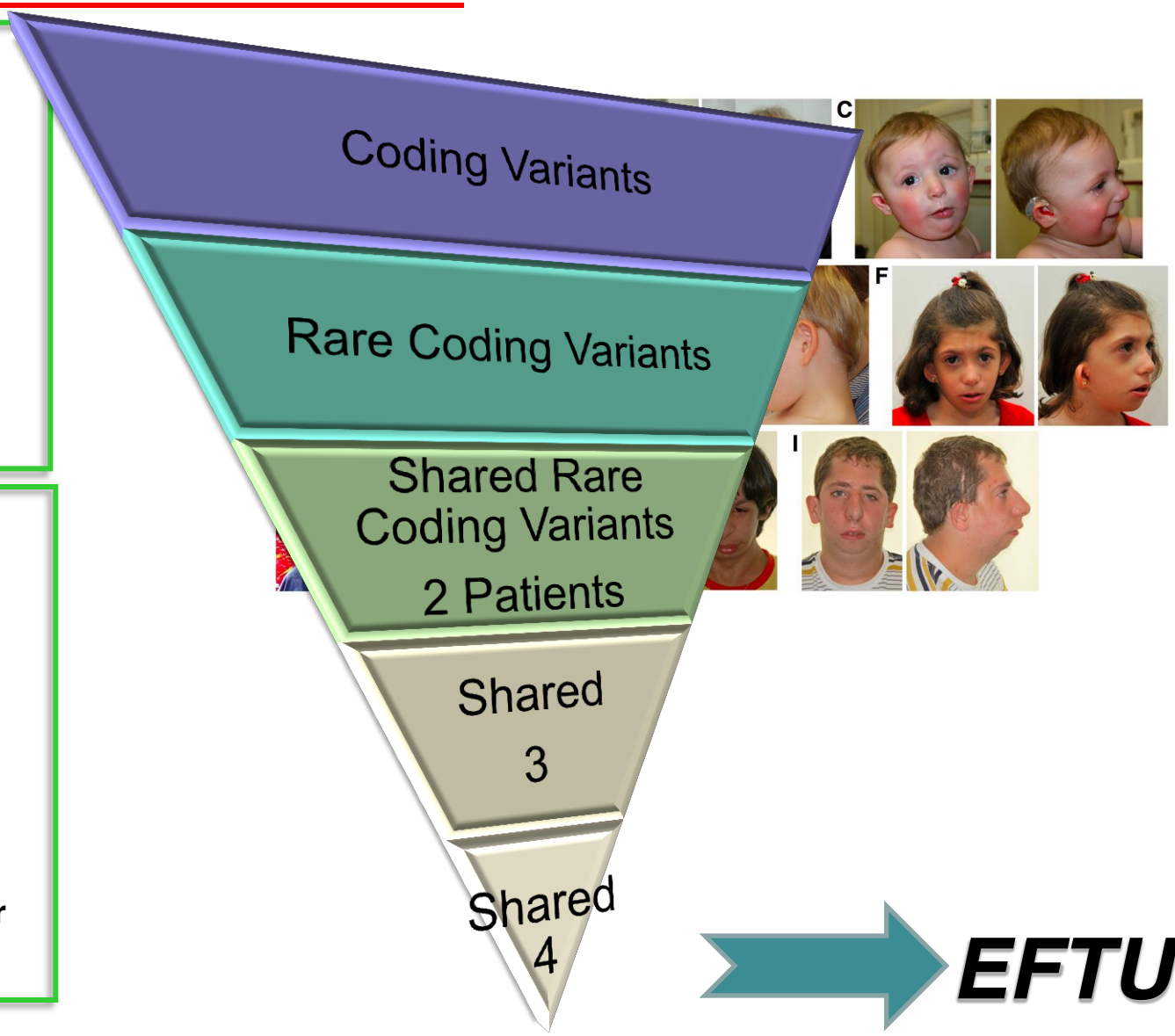


Approach 2 – Multiple Alleles

Unrelated patients with same disorder

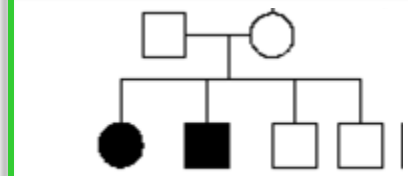


Unrelated families with same disorder AR, AD, X-L



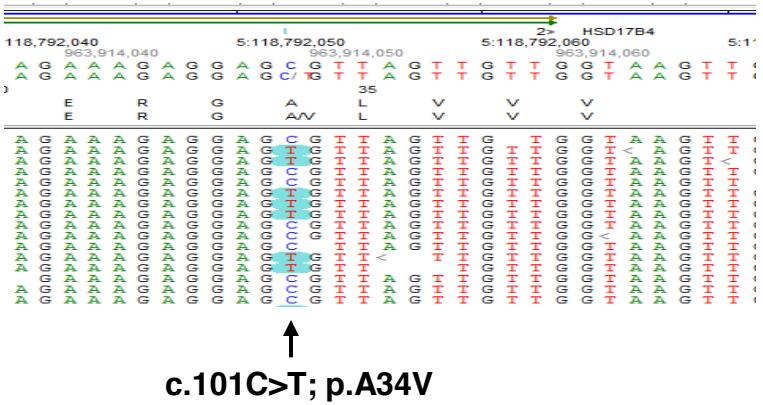
EFTUD2

Approach 3 - Sibpairs

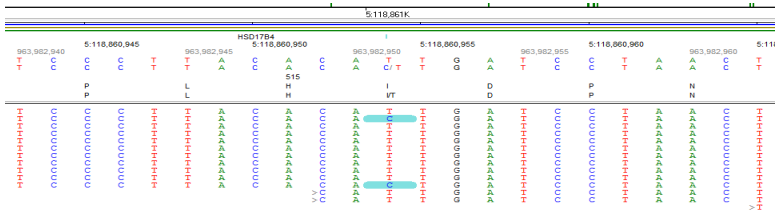


Nonconsanguineous families – AR disorder

Genes with missense, nonsense, indel or splice variants	**6453**
Genes with rare mutations *	**372**
Genes with mutations shared by sibs	**109**
Genes with homozygous/ multiple heterozygous variants	**2**



c.101C>T; p.A34V



c.1547T>C; p.I516T

http://www.ottawacitizen.com/technology

December 4, 2011

Success rate with FORGE

- Out of 101 samples:
  - About 1/3 had unique disorder in new gene
  - About 1/3 had mutation in known gene
  - About 1/3 unsolved

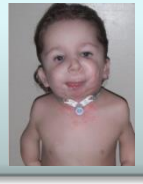
FORGEing On!
Enhanced *CARE for RARE* Genetic Diseases in Canada

Kym Boycott, PhD, MD
Alex MacKenzie, PhD, MD

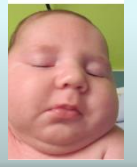
Children's Hospital of Eastern Ontario Research Institute
University of Ottawa, Canada

CARE for RARE Overview





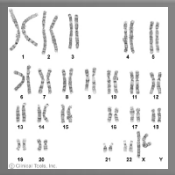
Canadian Patients with Rare Diseases

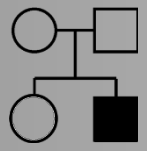
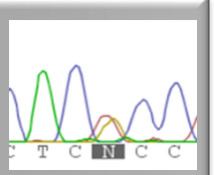

Expand Human Mutation Atlas

Clinical Exome Workflow

ID Therapeutic Opportunities

Molecular Diagnosis

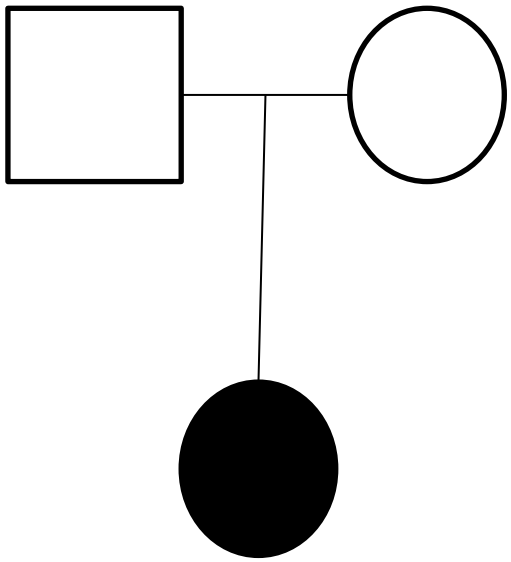



Optimized Platform

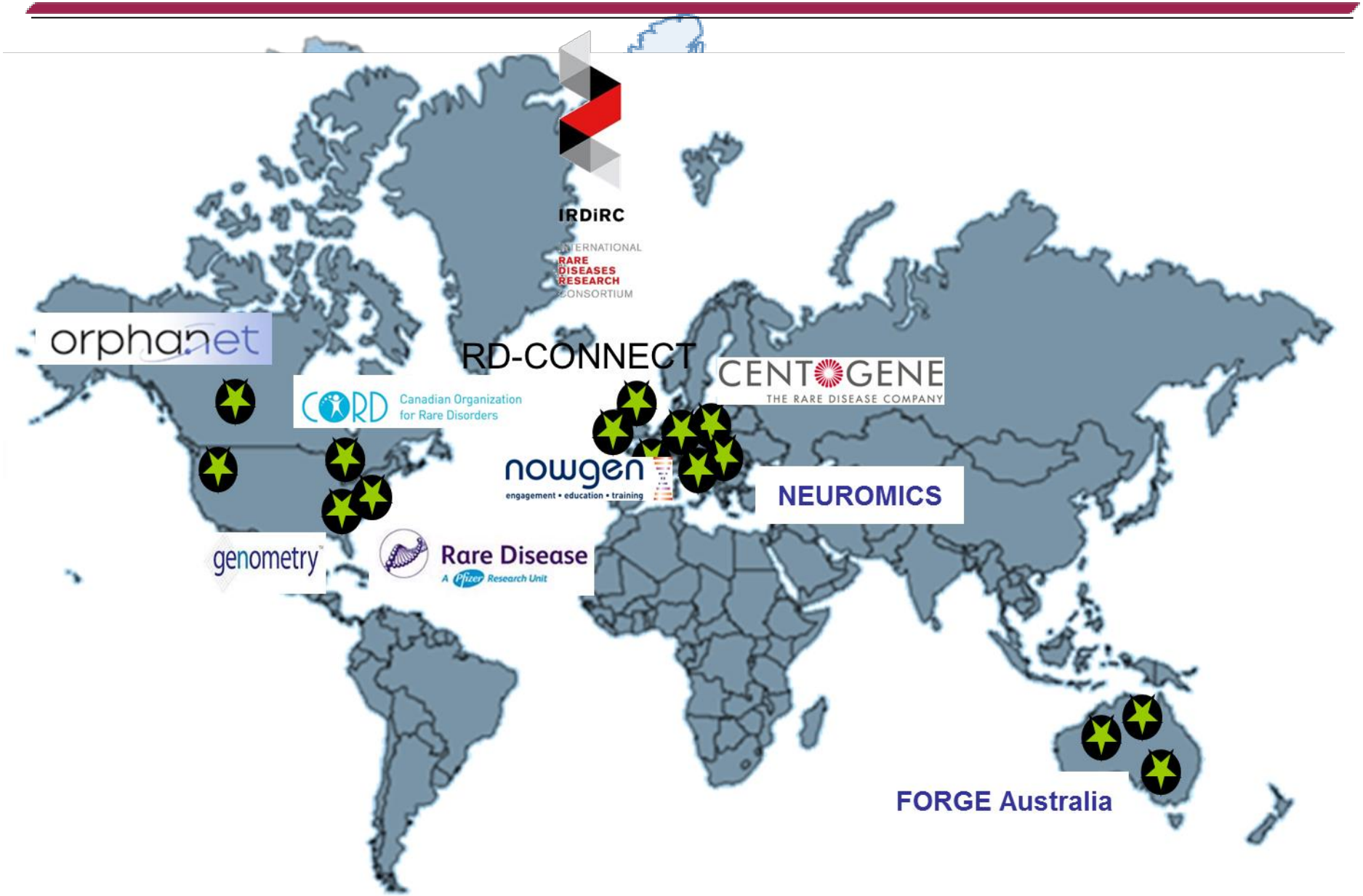

Enhanced Care


Approach 4 – exome sequencing of trios

- Single case
- Presumed de novo



CARE for RARE Team



Can we design a similar pipeline together to share phenotypes, identify genes, and look at treatments?

http://www.biochemgenetics.ca/plainpeople/

Benefits of the database

- Ability to search on symptoms to aid in the diagnosis of a rare disorder

Please let us know about your publications and gene discoveries to enter into the database
Also, let us know about your unknowns

Canadians know how to play together in the sandbox (K. Boycott)

Thank you

- CSC
- Jane Leach
  PHN extraordinaire
- Piya Lahiry
- Sali Farhan
- The families, midwives, physicians, laboratory staff