IRDiRC
INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

Advancing Rare Disease Research through International Collaboration: IRDiRC

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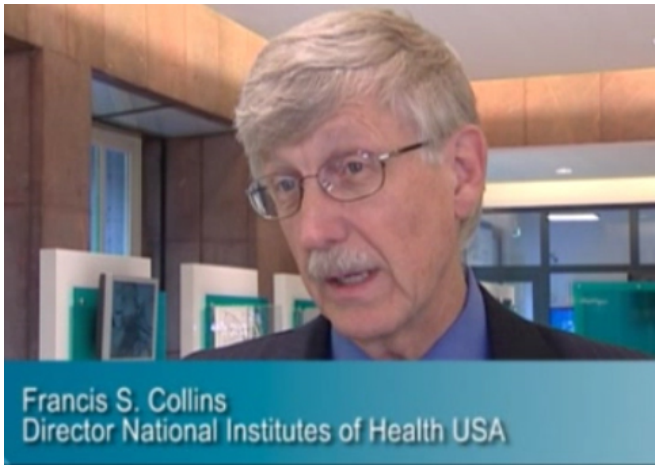
Children's Hospital of Eastern Ontario
University of Ottawa, Canada

Co-Chair, Diagnostics Committee, IRDiRC

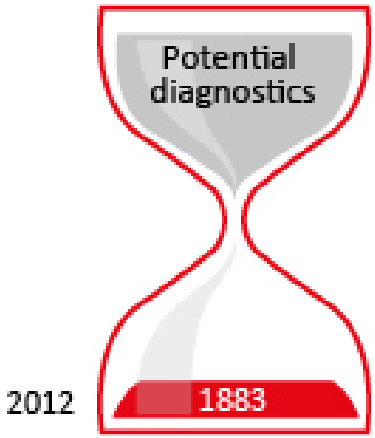
The idea - 2009….

Improved international collaboration and coordination could better facilitate research and could reduce inequities for patients.



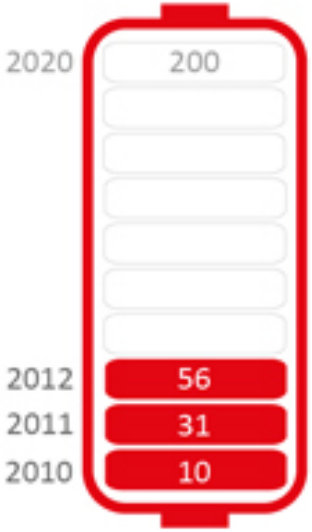
IRDiRC—Ambitious Goals

NEW DIAGNOSTICS



Objective 2020: diagnostics for all rare diseases

NEW THERAPIES



Objective 2020: 200 new therapies

Published online 4 April 2011 | *Nature* **472**, 17 (2011) | doi:10.1038/472017a

News

Rare-disease project has global ambitions

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Australia
- Western Australian Department of Health


Canada
- Canadian Institutes for Health Research
- Genome Canada


China
- Beijing Genomics Institute
- Chinese Rare Disease Research Consortium


EU
- European Commission


Finland
- Academy of Finland


France
- French Association against Myopathies
- Agence National de la Recherche
- Lysogene


Georgia
- Children's New Hospital Management Group


Germany
- Federal Ministry of Education and Research


Italy
- Italian Higher Institute of Health
- Telethon Foundation


International Consortium
- E-RARE 2 Consortium


Netherlands
- The Netherlands Organization for Health Research and Development
- Prosensa


Republic of Korea
- Korean National Institute of Health

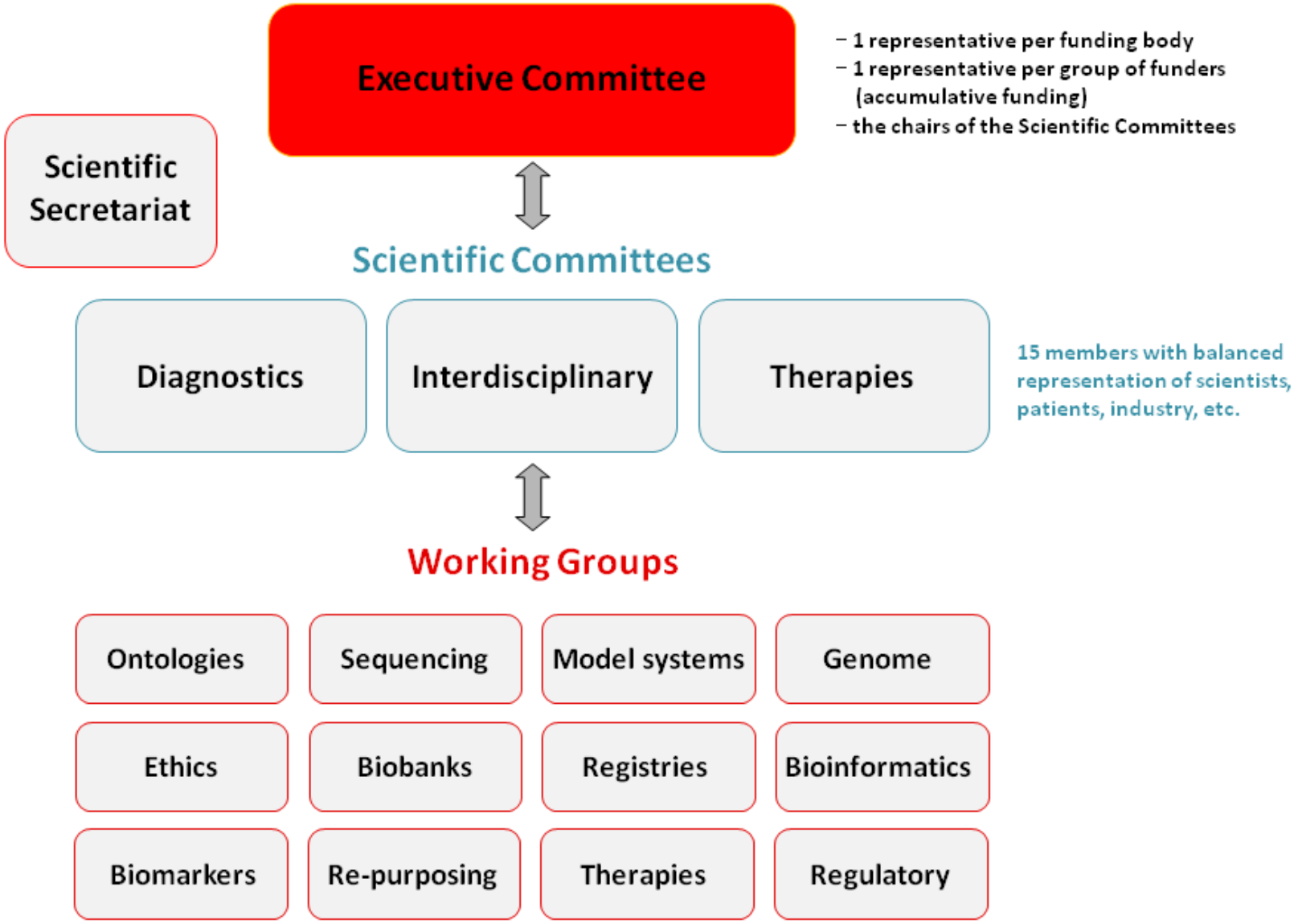

Spain
- National Institute of Health Carlos III


UK
- National Institute for Health Research


USA
- Food and Drug Administration Orphan Products Grants Program
- National Human Genome Research Institute (NIH)
- National Center for Advancing Translational Sciences(NIH)
- National Cancer Institute (NIH)
- National Eye Institute (NIH)
- National Institute of Neurological Disorders and Stroke (NIH)
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIH)
- National Institute of Child Health and Human Development (NIH)
- National Eye Institute (NIH)
- NKT Therapeutics
- Office of Rare Diseases (NIH)
- PTC Therapeutics
- Sanford Research Institute
- Shire

Present commitment exceeds $1B worldwide

IRDiRC Organizational Structure



Diagnostics Scientific Committee

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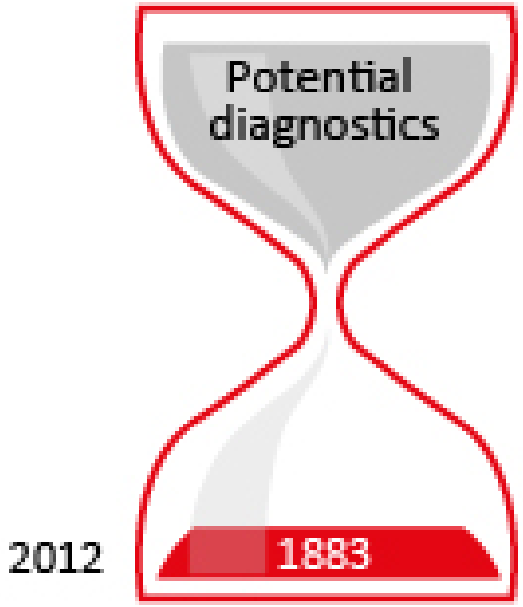
NEW DIAGNOSTICS

No. of new causative genes discovered



1. Understand the mechanism of most RD by 2020
2. Enable the clinical translation of genomic sequencing for patients with RDs

Objective 2020: diagnostics for all rare diseases

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The Challenge

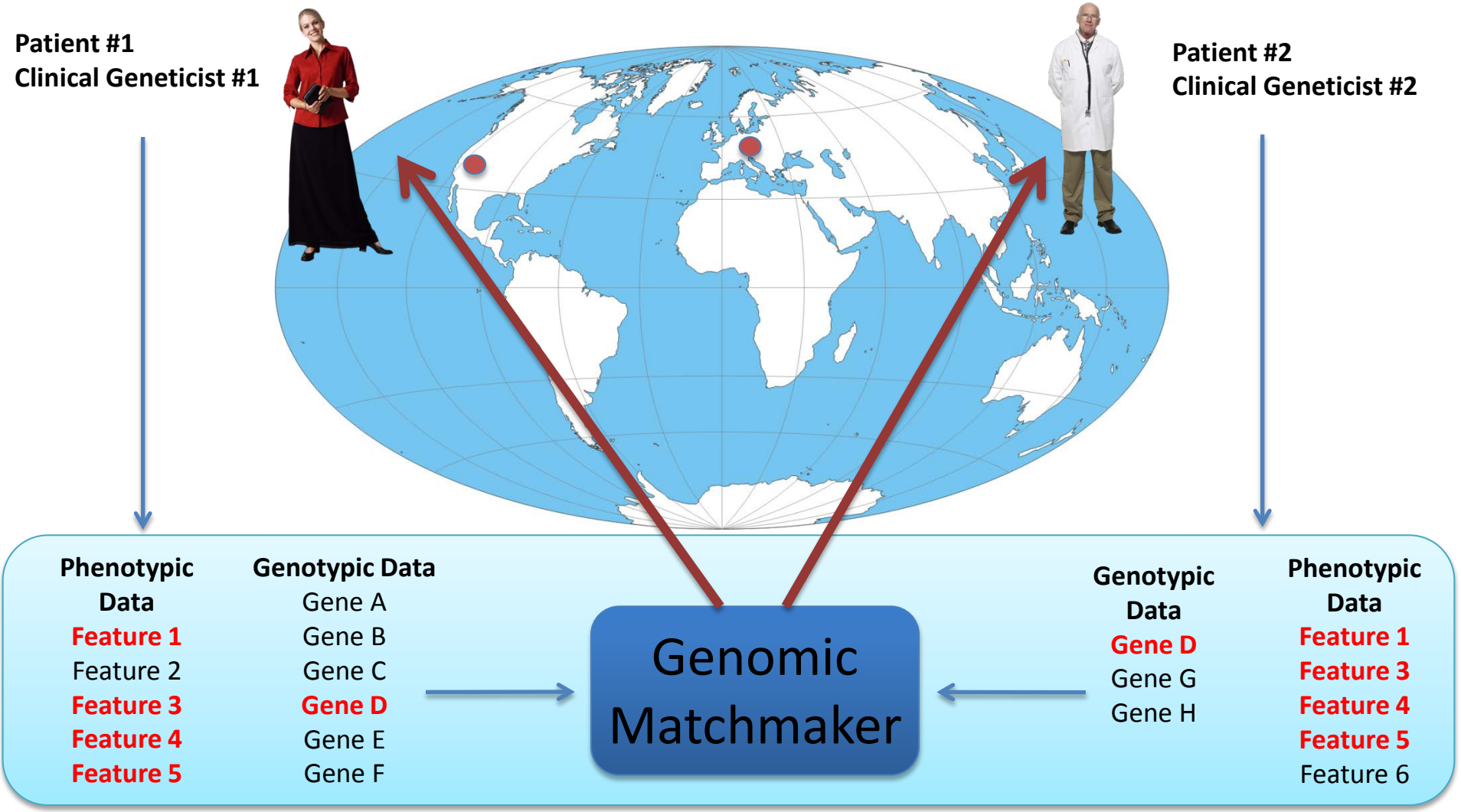
- ~75% of exome sequencing cases unsolved
- No unified database exists for patients with unsolved rare genetic disease
- Phenotypic data is under-represented in most genomic datasets

Challenge: N-of-1

Patient #1
Clinical Geneticist #1

Phenotypic Data	Genotypic Data
	Gene A
Feature 1	Gene B
Feature 2	Gene C
Feature 3	**Gene D**
Feature 4	Gene E
Feature 5	Gene F

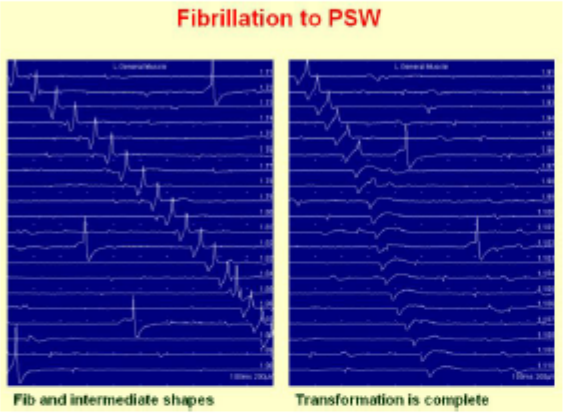
Challenge: N-of-1



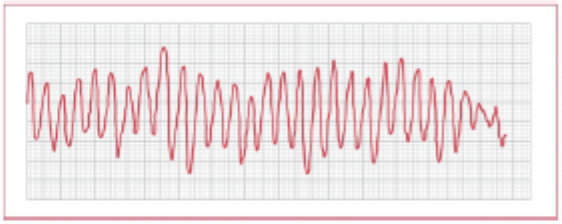
Courtesy of Joel Krier

Describing the Phenotype

Why Ontologies?



fibrillation . . .



fibrillation . . .

muscle fibrillation $=$ fibrillation $\neq$ fibrillation $=$ ventricular fibrillation

- Need to make sure each term is well defined

Peter Robinson et al.

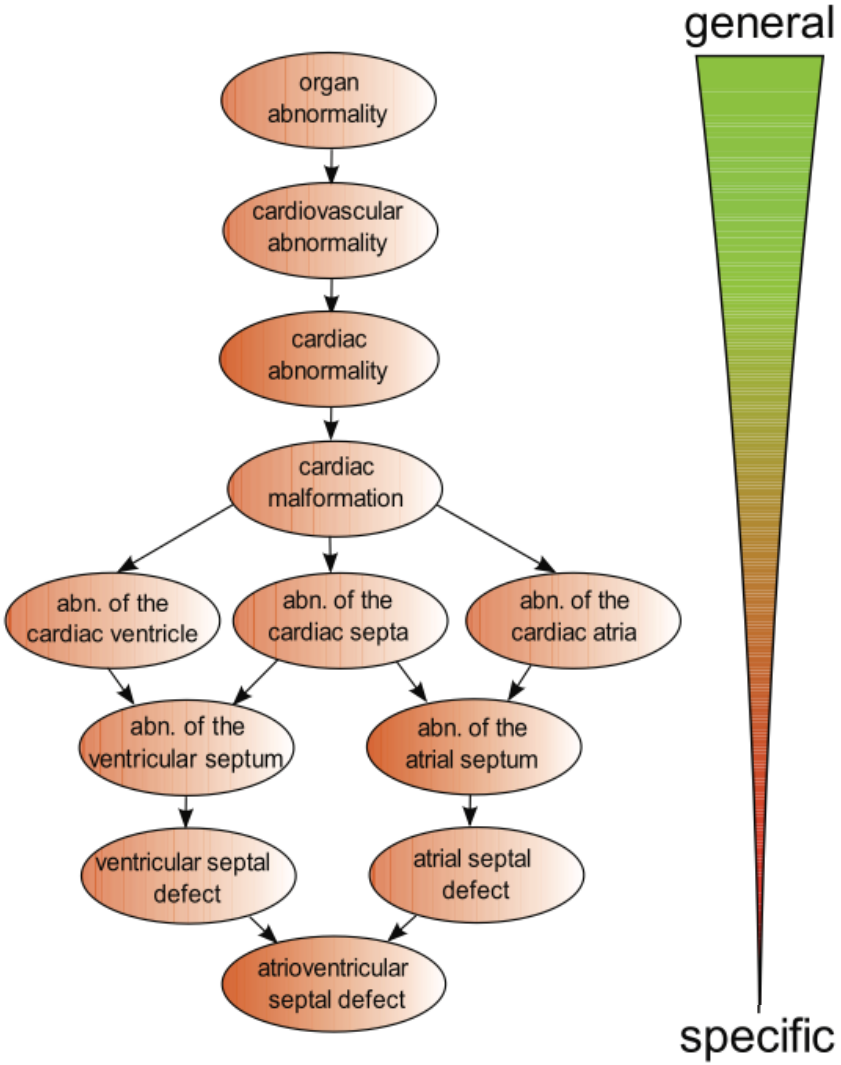
Ontologies

Standardized vocabulary to describe clinical phenotypes

Computer readable terms

Hierarchichal structure representing subclass relationships

Human Phenotype Ontology



Robinson, PN and Mundlos, S. 2010

2300 Standard Terms for RD

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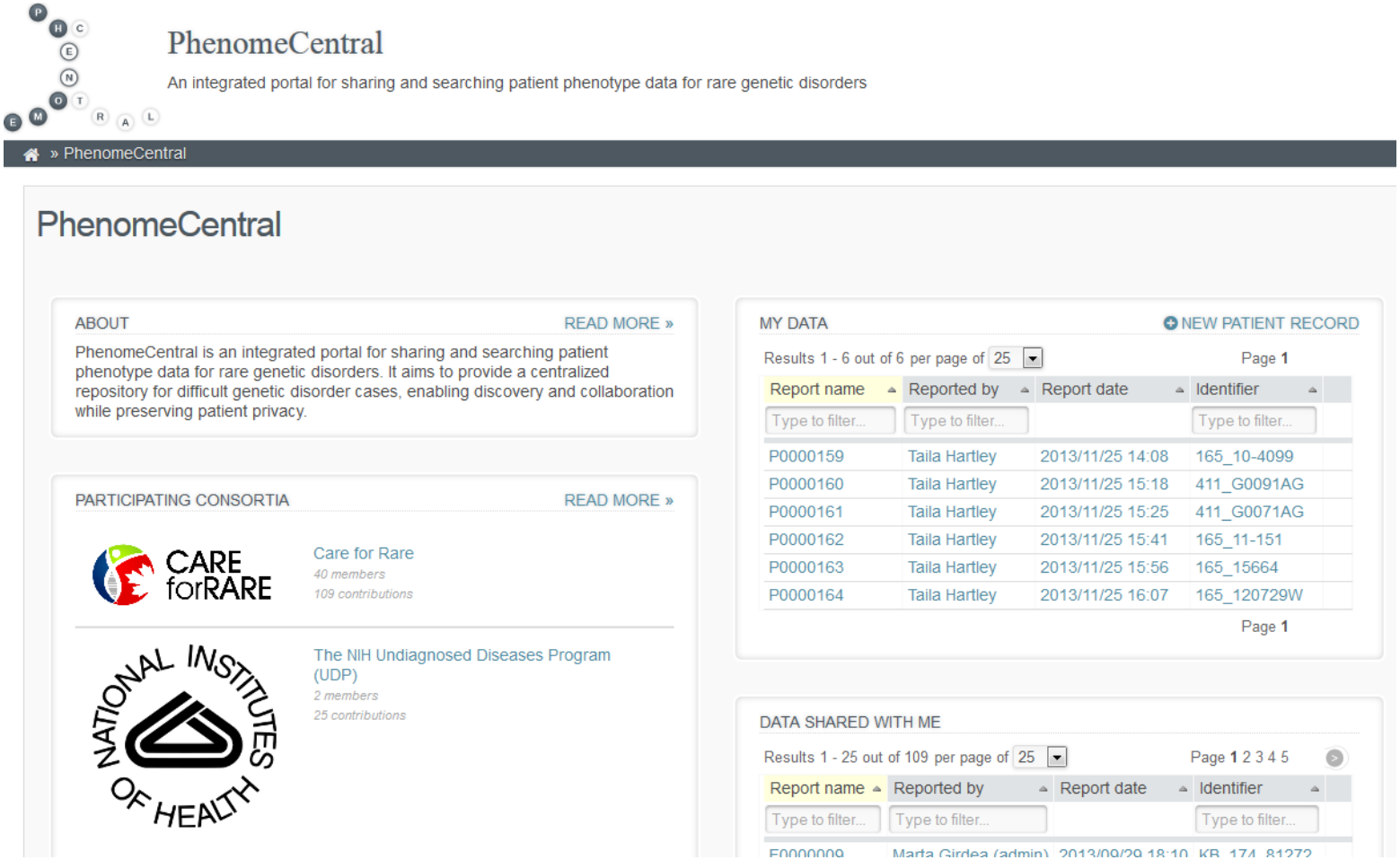
POSSUM web
Pictures Of Standard Syndromes and Undiagnosed Malformations

SimulConsult®
A Simultaneous Consult On Your Patient's Diagnosis

- Human Phenotype Ontology
- Orphanet
- LDDB
- Elements of Morphology
- PhenoDB
- UMLS
- SNOWMEDCT
- MeSH
- MedDRA

International Consortium of Phenotype Terminologies

Matchmaker Needed

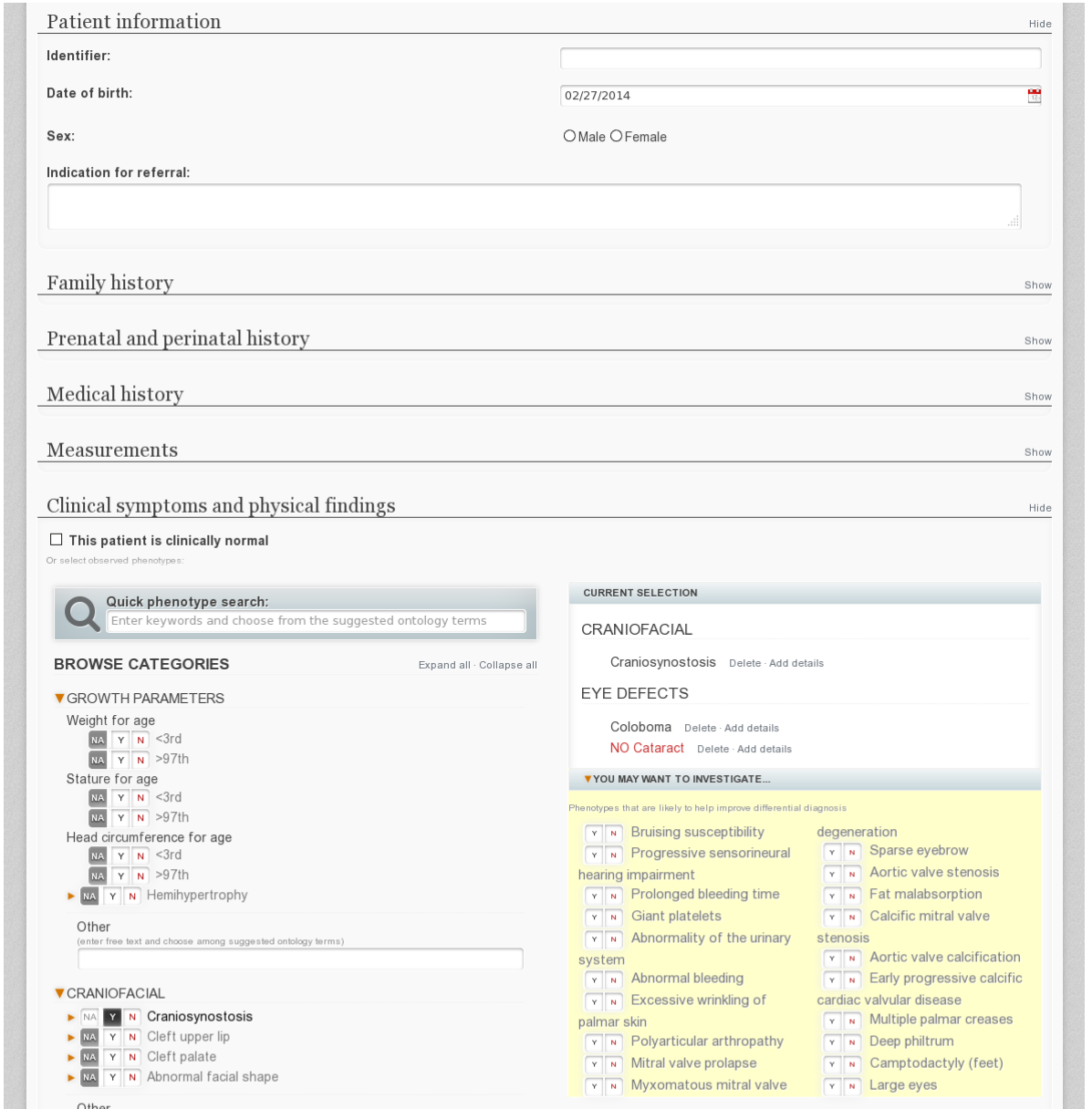


www.phenomecentral.org

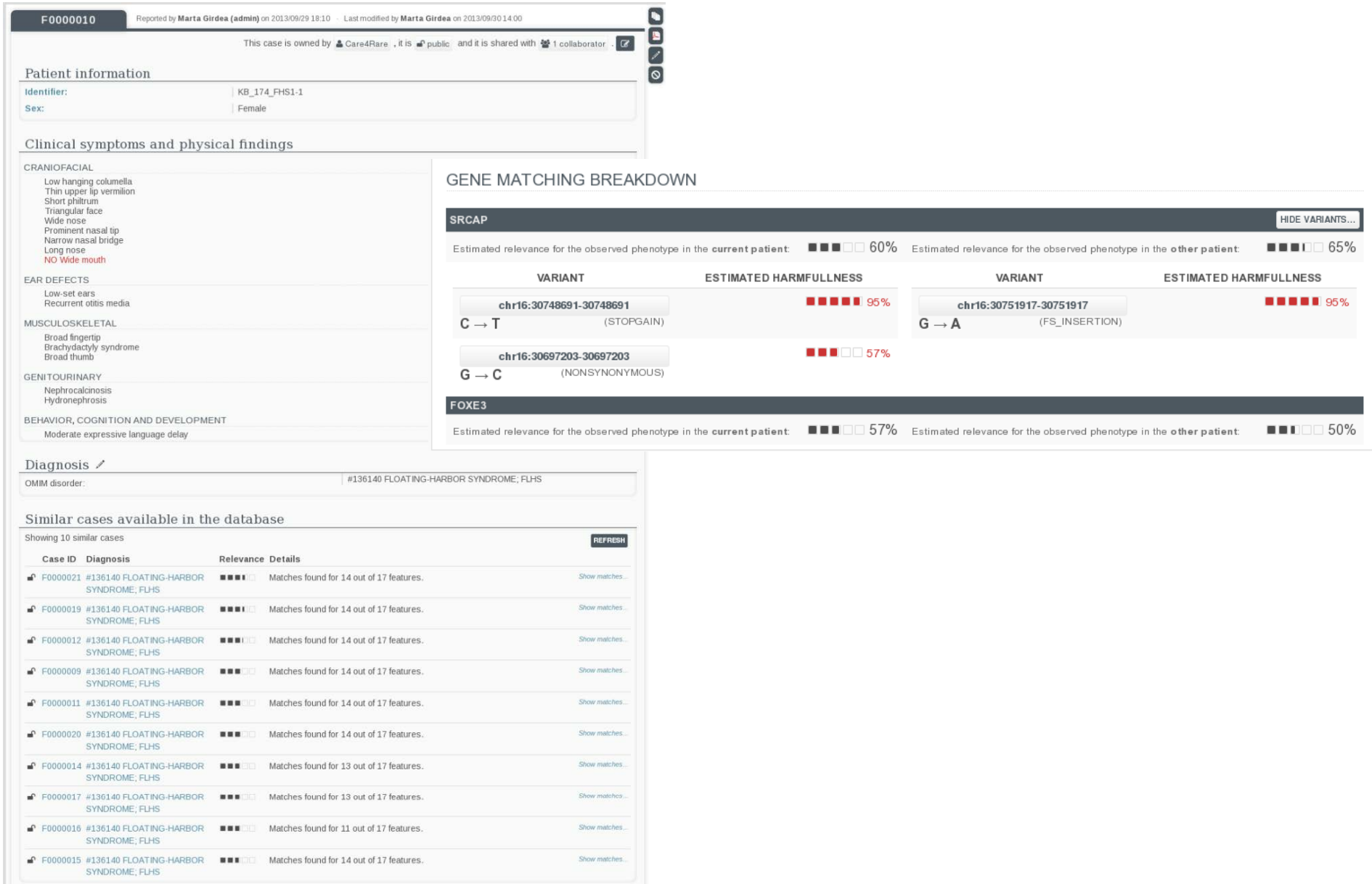
Dr. Mike Brudno
U of T

Step 1: Add Patient

- Predictive Search: allowing rapid entry with Human Phenotype Ontology (HPO) terms
- Selection of positive and negative terms
- Add a vcf file (or list of genes)
- Set each record as Private, Public or **Matchable**



Step 2: See Patients Similar To Yours



F0000010

Reported by **Marta Girdea (admin)** on 2013/09/29 18:10 · Last modified by **Marta Girdea** on 2013/09/30 14:00

This case is owned by Care4Rare , it is public and it is shared with 1 collaborator .

Patient information

Identifier:	KB_174_FHS1-1
Sex:	Female

Clinical symptoms and physical findings

CRANIOFACIAL
- Low hanging columella
- Thin upper lip vermilion
- Short philtrum
- Triangular face
- Wide nose
- Prominent nasal tip
- Narrow nasal bridge
- Long nose
- NO Wide mouth

EAR DEFECTS
- Low-set ears
- Recurrent otitis media

MUSCULOSKELETAL
- Broad fingertip
- Brachydactyly syndrome
- Broad thumb

GENITOURINARY
- Nephrocalcinosis
- Hydronephrosis

BEHAVIOR, COGNITION AND DEVELOPMENT
- Moderate expressive language delay

Diagnosis

OMIM disorder:	#136140 FLOATING-HARBOR SYNDROME; FLHS

Similar cases available in the database

Showing 10 similar cases — REFRESH

Case ID	Diagnosis	Relevance	Details	
F0000021	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■■□	Matches found for 14 out of 17 features.	Show matches...
F0000019	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■■□	Matches found for 14 out of 17 features.	Show matches...
F0000012	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■■□	Matches found for 14 out of 17 features.	Show matches...
F0000009	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■□□	Matches found for 14 out of 17 features.	Show matches...
F0000011	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■□□	Matches found for 14 out of 17 features.	Show matches...
F0000020	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■□□	Matches found for 14 out of 17 features.	Show matches...
F0000014	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■□□	Matches found for 13 out of 17 features.	Show matches...
F0000017	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■□□	Matches found for 13 out of 17 features.	Show matches...
F0000016	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■□□	Matches found for 11 out of 17 features.	Show matches...
F0000015	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■□□	Matches found for 14 out of 17 features.	Show matches...

GENE MATCHING BREAKDOWN

SRCAP — HIDE VARIANTS...

Estimated relevance for the observed phenotype in the **current patient**: ■■■□□ 60%

Estimated relevance for the observed phenotype in the **other patient**: ■■■▮□ 65%

VARIANT	ESTIMATED HARMFULLNESS
chr16:30748691-30748691 C → T (STOPGAIN)	■■■■■ 95%
chr16:30697203-30697203 G → C (NONSYNONYMOUS)	■■■□□ 57%

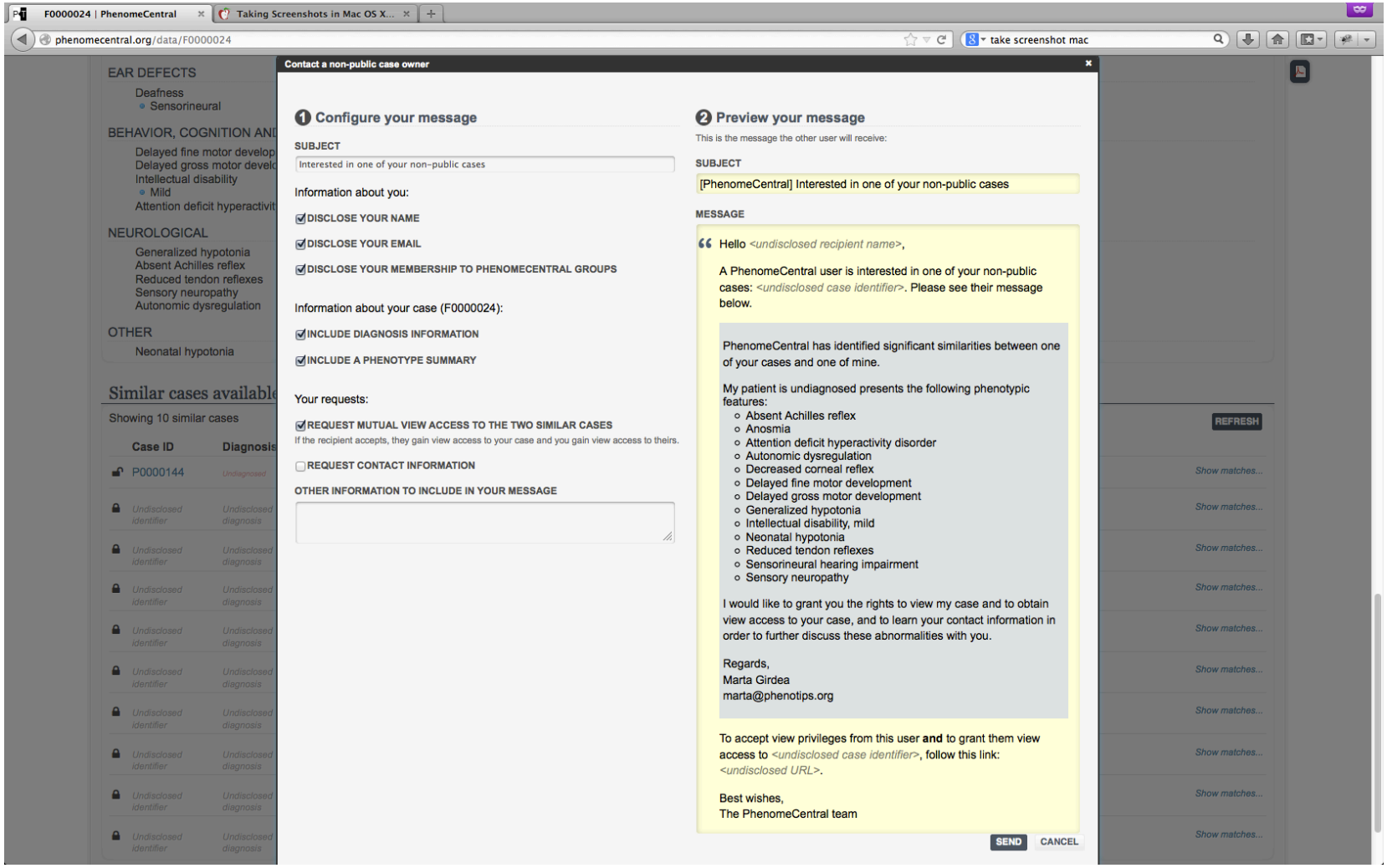
VARIANT	ESTIMATED HARMFULLNESS
chr16:30751917-30751917 G → A (FS_INSERTION)	■■■■■ 95%

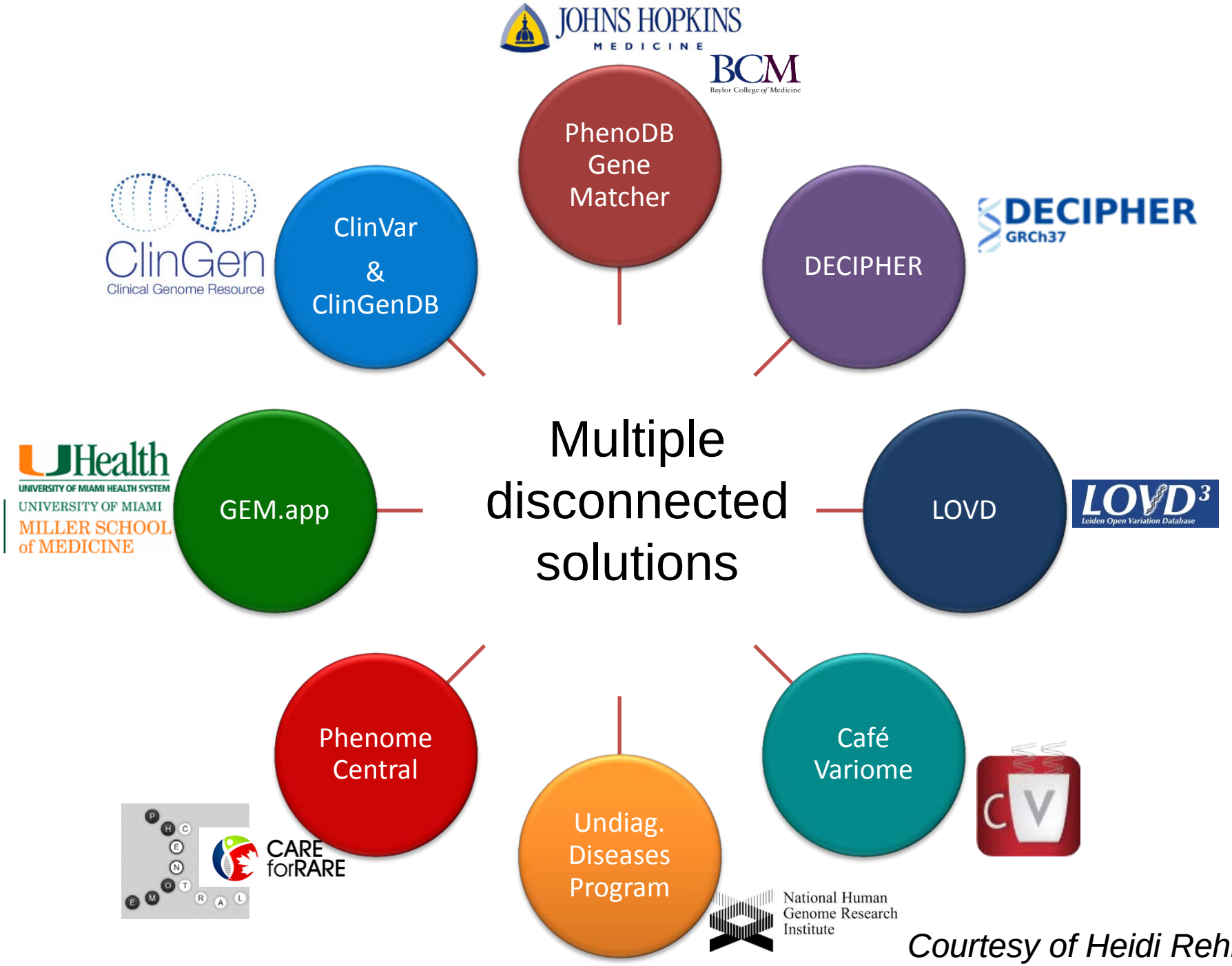
FOXE3

Estimated relevance for the observed phenotype in the **current patient**: ■■■□□ 57%

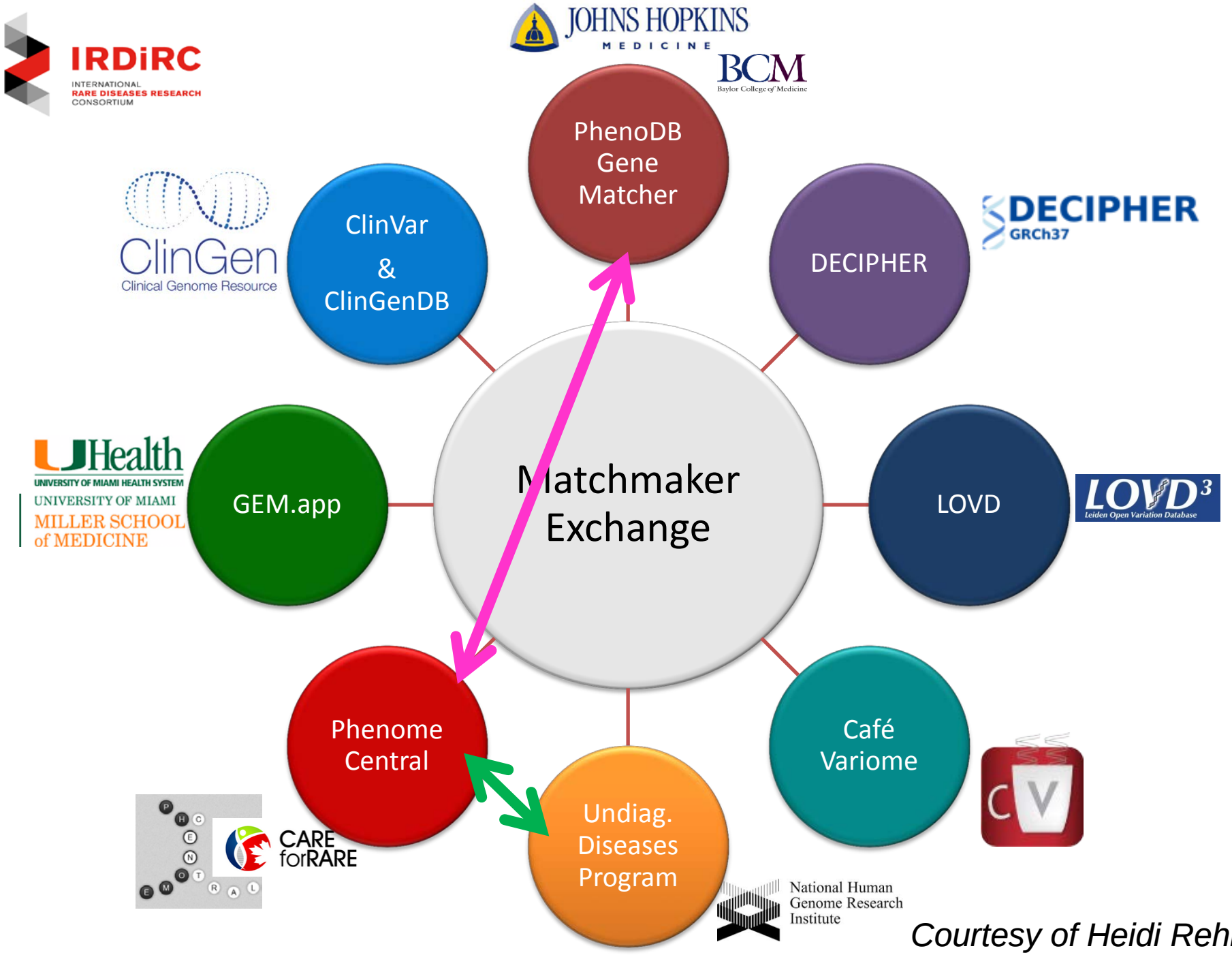
Estimated relevance for the observed phenotype in the **other patient**: ■■▮□□ 50%

Step 3: Contact the Submitter of the Other Dataset





Courtesy of Heidi Rehm



Courtesy of Heidi Rehm

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