IRDiRC: a review of its achievements in its first six years

3rd IRDiRC Conference
Université Pierre et Marie Curie
Paris, 8 February 2017

IRDiRC

INTERNATIONAL
RARE
DISEASES
RESEARCH
CONSORTIUM

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

News

Rare-disease project has global ambitions

Consortium aims for hundreds of new therapies by 2020.

Alison Abbott

Prader–Willi syndrome. Fabry renal disease. Spinocerebellar ataxia. Few people have heard of these and the other 'rare diseases', some of which affect only hundreds of patients worldwide. Drug companies searching for the next blockbuster pay them little attention. But the diseases are usually incurable — and there are thousands of them.

This week, the US National Institutes of Health (NIH) and the European Commission launch a joint assault on these conditions, whose small numbers of patients make it difficult to test new treatments and develop diagnostic methods. The International Rare Disease Research Consortium being formed under the auspices of the two bodies has the ambitious goal of developing a diagnostic tool for every known rare disease by 2020, along with new therapies to treat 200 of them. "The number of individuals with a particular rare disease is so small that we need to be able to pool information from patients in as many countries as possible," says Ruxandra Draghia-Akli, the commission's director of health research.

IRDiRC – basic principles

- Co-operation at international level to stimulate, better coordinate & maximise output of rare disease research efforts around the world

- Teams up public and private organisations investing in rare diseases research
- Research funders can join & work together
- Each organisation funds research its own way
- Funded projects adhere to a common framework

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Growth of IRDiRC

- Third coordination meeting was held in Montreal (9-10 Oct 2011), sponsored by IG and Genome Canada.
- Initially involved EU, NIH, Canada, Italy, Spain.
- Funder members commit a minimum of USD 10M to rare disease research over a 5-yr period.
- Present commitment exceeds $1B worldwide.
- Formally launched in 2012, first public symposium held in Dublin in April 2013, 25 members by early 2013.
- Second public symposium held in Shenzhen, China, November 7-9, 2014 with over 600 participants.
- Third IRDiRC symposium in progress now!

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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
- WuXi Apptec

EU
- European Commission

Finland
- Academy of Finland

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

Georgia
- Children's New Hospital Management Group

Germany
- Federal Ministry of Education and Research

Italy
- Italian Higher Institute of Health
- Telethon Foundation
- Chiesi Farmaceutica

International Consortium
- E-RARE 3 Consortium

Japan
- Japan Agency for Medical Research and Development
- National Institutes of Biomedical Innovation, Health, and Nutrition

Today over 40 members from 17 countries

Republic of Korea
- Korean National Institute of Health

Netherlands
- The Netherlands Organization for Health Research and Development

Kingdom of Saudi Arabia
- Saudi Human Genome Project

Spain
- National Institute of Health Carlos III

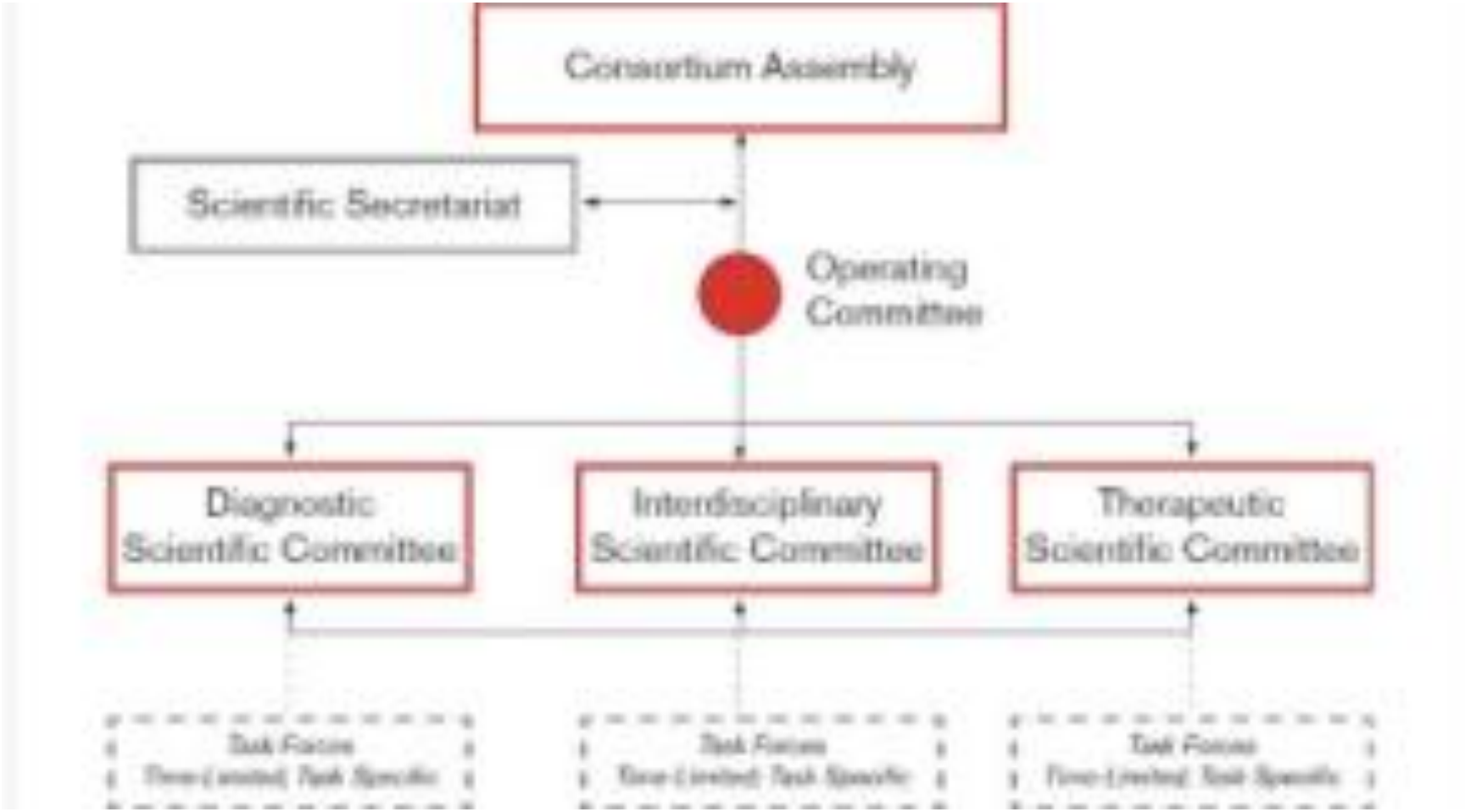
UK
- National Institute for Health Research

USA
- Food and Drug Administration Orphan Products Grants Program
- Isis Pharmaceuticals
- 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)
- NKT Therapeutics
- Office of Rare Diseases (NIH)
- PTC Therapeutics
- Sanford Research Institute

- International Pharma Companies
  - Genzyme (Sanofi)
  - Novartis
  - Pfizer
  - Shire

IRDiRC establishes task forces to investigate specific issues

IRDiRC organizational structure



International Consortium of Human Phenotype Terminologies

The development and adoption of standards to be used to achieve interoperability between databases, in particular to allow the linking of phenotype and genotype databases for rare diseases.

Patient-Centered Outcome Measures

The development and adoption of patient-centered outcome measures are instrumental in accelerating research and development in rare diseases.

Small Population Clinical Trials

Collaborative effort on adaptive design, statistical methods and acceptability of new methods in small population clinical trials.

Matchmaker Exchange

The joint IRDiRC-Global Alliance Matchmaker Exchange project aims at providing data sharing tools to match unsolved genome/exome sequence cases.

Automatable Discovery and Access

In order to make the most of clinical data sources worldwide, accessing the level of patient consent towards data sharing and research participation becomes crucial.

Data Mining/Repurposing

This effort gathers expertise and identifies opportunities for collaborations to efficiently exploit data mining tools to identify new therapeutic targets and to repurpose drugs.

Privacy-Preserving Data Linkage

The joint IRDiRC-GA4GH Task Force aims to develop a guiding policy for the generation of participant-specific identifiers that enable data from the same individual to be connected across multiple projects without directly revealing the participant's identity.

International Consortium of Human Phenotype Terminologies (ICHPT): Core set of 2,086 terms to be incorporated in any Human Phenotype Terminology intended to describe rare diseases (2012-2015)

Free access data from IRDiRC.org.

Contributors

The IRDiRC Task Force members in charge of the development of ICHPT are (in alphabetic order): Ségolène Aymé (IRDiRC), Ada Hamosh (OMIM), Ana Rath (Orphanet) and Peter Robinson (HPO).

Other contributors

The process to elaborate of this core set of terms was supported by the expertise of many colleagues who attended two workshops: Joanna Amberger, Ségolène Aymé, Larry J Babb, Sergi Beltran, Judith Blake, Kym Boycott, John Carey, Andrew Devereau, Koenraad Devriendt, Dian Donnai, Heather Dozier, Helen Firth, Ester Garne, Ada Hamosh, Raoul Hennekam, Robert Jakob, Odile Kremp, Martine Le Merrer, David Miller, Ana Rath, Peter Robinson, Catherine Rose, Albert Schinzel, Michael Segal, Jan-Eric Slot, Nara Sobreira.

OVERVIEW

Human Mutation

OFFICIAL JOURNAL
HGVS
HUMAN GENOME VARIATION SOCIETY
www.hgvs.org

The Matchmaker Exchange: A Platform for Rare Disease Gene Discovery

Anthony A. Philippakis,[1,2,3] Danielle R. Azzariti,[4] Sergi Beltran,[5] Anthony J. Brookes,[6] Catherine A. Brownstein,[3,7] Michael Brudno,[8,9,10] Han G. Brunner,[11,12] Orion J. Buske,[8,9,10] Knox Carey,[13] Cassie Doll,[14] Sergiu Dumitriu,[10] Stephanie O.M. Dyke,[15] Johan T. den Dunnen,[16] Helen V. Firth,[17] Richard A. Gibbs,[18] Marta Girdea,[8,10] Michael Gonzalez,[19] Melissa A. Haendel,[20] Ada Hamosh,[21] Ingrid A. Holm,[3,7] Lijia Huang,[22] Matthew E. Hurles,[23] Ben Hutton,[23] Joel B. Krier,[3,24] Andriy Misyura,[10] Christopher J. Mungall,[25] Justin Paschall,[26] Benedict Paten,[27] Peter N. Robinson,[28,29,30,31] François Schiettecatte,[32] Nara L. Sobreira,[21] Ganesh J. Swaminathan,[23] Peter E. Taschner,[16,33] Sharon F. Terry,[34] Nicole L. Washington,[2] Stephan Züchner,[35] Kym M. Boycott,[36] and Heidi L. Rehm[1,3,4,37]*

ABSTRACT: There are few better examples of the need for data sharing than in the rare disease community, where patients, physicians, and researchers must search for "the needle in a haystack" to uncover rare, novel causes of disease within the genome. Impeding the pace of discovery has been the existence of many small siloed datasets within individual research or clinical laboratory databases and/or disease-specific organizations, hoping for serendipitous occasions when two distant investigators happen to learn they have a rare phenotype in common and can "match" these cases to build evidence for causality.

IRDiRC formally recognizes certain research resources with a quality indicator

POLICY

'IRDiRC Recognized Resources': a new mechanism to support scientists to conduct efficient, high-quality research for rare diseases

Hanns Lochmüller[1], Yann Le Cam[2], Anneliene H Jonker[3], Lilian PL Lau[3], Gareth Baynam[4,5], Petra Kaufmann[6], Paul Lasko[7], Hugh JS Dawkins[8], Christopher P Austin[6] and Kym M Boycott*[,9]
on behalf of the IRDiRC Scientific Committees

The International Rare Diseases Research Consortium (IRDiRC) has created a quality label, 'IRDiRC Recognized Resources', formerly known as 'IRDiRC Recommended'. It is a peer-reviewed quality indicator process established based on the IRDiRC Policies and Guidelines to designate resources (ie, standards, guidelines, tools, and platforms) designed to accelerate the pace of discoveries and translation into clinical applications for the rare disease (RD) research community. In its first year of implementation, 13 resources successfully applied for this designation, each focused on key areas essential to IRDiRC objectives and to the field of RD research more broadly. These included data sharing for discovery, knowledge organisation and ontologies, networking patient registries, and therapeutic development. 'IRDiRC Recognized Resources' is a mechanism aimed to provide community-approved contributions to RD research higher visibility, and encourage researchers to adopt recognised standards, guidelines, tools, and platforms that facilitate research advances guided by the principles of interoperability and sharing.
European Journal of Human Genetics (2017) **25,** 162–165; doi:10.1038/ejhg.2016.137; published online 26 October 2016

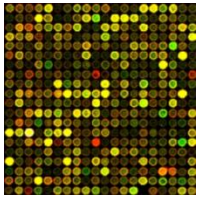
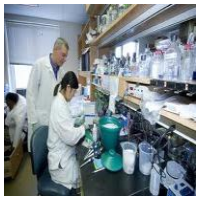
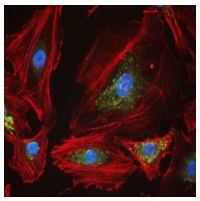
How does a public funder join IRDiRC?

- An organization must agree to support IRDiRC's policies, guidelines, and recommendations.
- An organization must commit to a minimum investment of USD 10M over five years in its own rare disease research programmes.
- IRDiRC as an organization does not collect funds to support research, rather it engages, for example, in activities that enable better international collaboration and data sharing.

The Canadian example

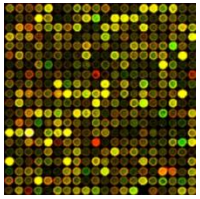
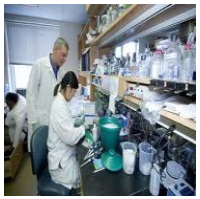
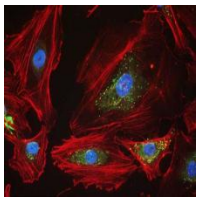
- Two entities, the Canadian Institutes of Health Research (CIHR), and Genome Canada, collectively committed to $25M in rare disease research.
- This was exceeded, and rare disease research was funded through several initiatives.

Rare Diseases Emerging Teams--Funders

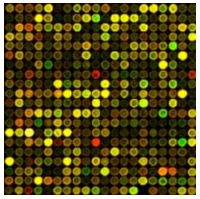
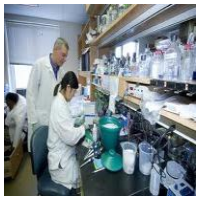
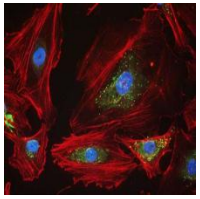
- $17.0 M total funding over five years (2012-17) from the following sources:
- CIHR
  - IG, INMD, IMHA, ICR, INMHA, IHSPR, Ethics Office
- Ataxia of Charlevoix-Saguenay Foundation
- Kidney Foundation of Canada
- Canadian Organization of Rare Diseases
- Choroideremia Research Foundation Canada
- Foundation Fighting Blindness--Canada

Rare Diseases Emerging Teams—Successful Applicants

- Group 1
  - Bernard BRAIS (McGill) ARSACS
  - David CABRAL (UBC) Chronic childhood vasculitis
  - Ian MACDONALD (Alberta) Choroideremia
  - Jeffrey MEDIN (Toronto) Fabry's disease
  - Guy ROULEAU (Montréal) Hereditary spastic paraplegia
- Group 2
  - Larry LYND (UBC) Evaluation of drugs for rare disease
  - Devidas MERON (Alberta) Policies for managing technologies for rare disease
  - Elizabeth POTTER (Ottawa) Care for inborn errors of metabolism
  - Brett THOMBS (McGill) Scleroderma patient-centred intervention network

Advancing Technology Through Innovation

- Massively parallel next-generation sequencing has enhanced our ability to identify genetic mutations
- Need was identified to accelerate use of genomics technology to help identify genetic causes of disease
- **CIHR/Genome Canada/Genome BC/Génome Québec partnership** to support pan-Canadian teams for which genes can be identified in a short time frame and with a small number of subjects
- Funding: ~$5.5M for first year for two teams, one on rare cancers, one for FORGE (Finding of Rare Disease Genes in Canada).

In Canada, rare disease research has been funded through a larger Personalized Health Initiative

2012

Personalized Medicine Initiative

- Enhance health outcomes through patient stratification approaches by integrating evidence-based medicine and precision diagnostics into clinical practice
- $240M ($85M from CIHR)
- 110 competition and application partners, including Genome Canada, funded Care4Rare ($11.7M with partner contributions).

eHealth Innovation Initiative

- Enhance health outcomes and health care delivery, through the implementation, evaluation and scale-up of eHealth innovations
- $34.4M ($16.2M from CIHR)
- 77 application partners

2016

Personalized Health Initiative

- Drive evidence-based implementation of PH that will identify solutions that can contribute to more cost-effective and sustainable healthcare
- CIHR/Genome Canada partnership of $70M launched January 2017. $5M CIHR funds earmarked for rare disease, should end up leveraged to $10-20M
- Alignment with IC PerMed

FORGE Canada (2011-13) focused on deeply phenotyped patients and partnered closely with clinicians

COMMENTARY

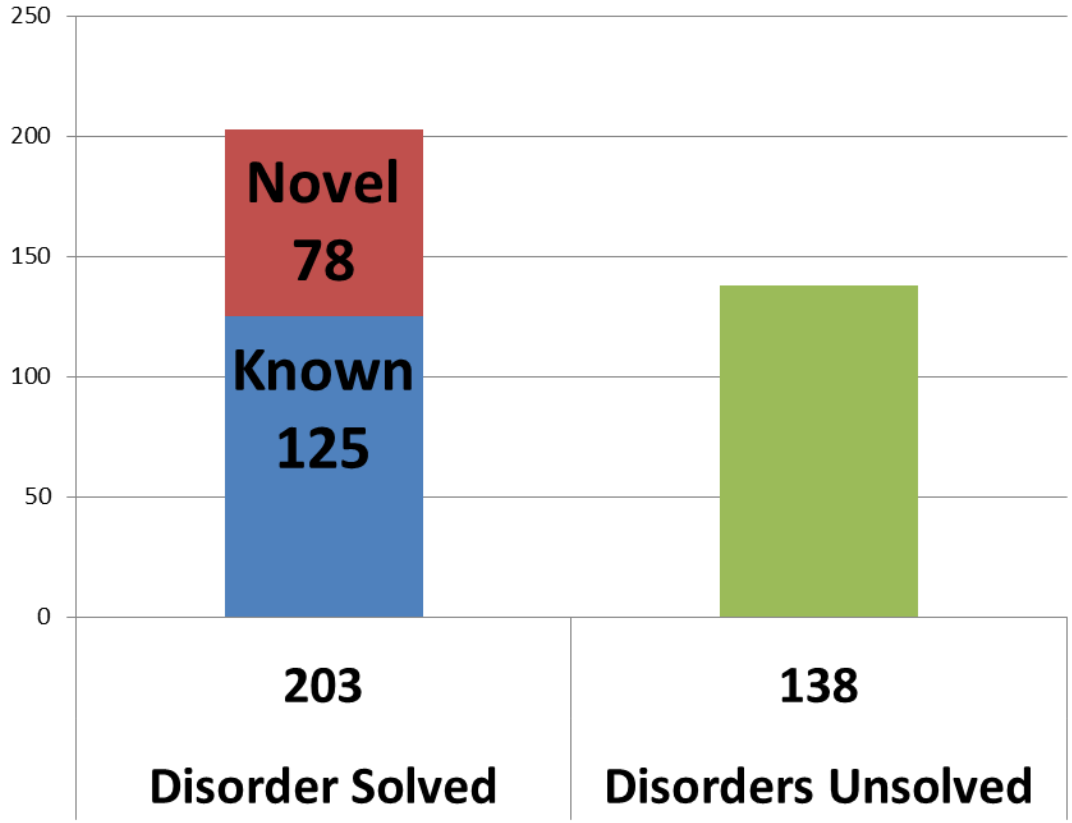
FORGE Canada Consortium: Outcomes of a 2-Year National Rare-Disease Gene-Discovery Project

Chandree L. Beaulieu,[1] Jacek Majewski,[2] Jeremy Schwartzentruber,[3] Mark E. Samuels,[4] Bridget A. Fernandez,[5] Francois P. Bernier,[6] Michael Brudno,[7,12] Bartha Knoppers,[8] Janet Marcadier,[1] David Dyment,[1] Shelin Adam,[9] Dennis E. Bulman,[1] Steve J.M. Jones,[10] Denise Avard,[8] Minh Thu Nguyen,[8] Francois Rousseau,[11] Christian Marshall,[12] Richard F. Wintle,[12] Yaoqing Shen,[10] Stephen W. Scherer,[12,13] FORGE Canada Consortium,[1] Jan M. Friedman,[9] Jacques L. Michaud,[4] and Kym M. Boycott[1,*]

FORGE CANADA CONSORTIUM

CARE forRARE

FORGE Canada: 365 disorders were investigated…



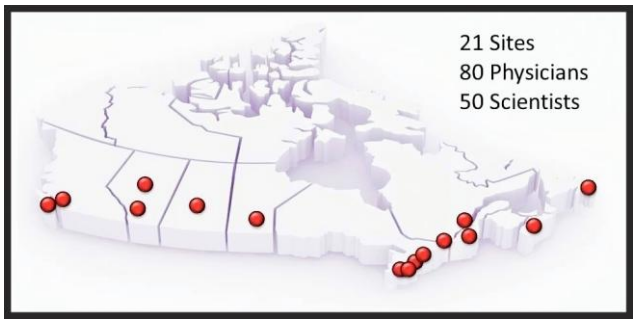
203 disease genes found

55% success

Am J Hum Genet 2014; 94:809-817

CARE forRARE

- Recruited over 3000 patients and family members to study;
- Studied 637 different rare diseases;
- Have provided a diagnosis to over 1000 patients;
- Have identified 85 novel rare disease genes;
- Are developing three experimental therapies;
- Contribute to international data sharing standards.



Progress toward IRDiRC's goals for rare disease research

(source: www.irdirc.org)

- Diagnostics (goal: most rare diseases by 2020)
  - Nearly 3,600 rare diseases for which there is a genetic test available, as compared with 2,200 in 2010.
- Therapies (goal: 200 new therapies by 2020)
  - Achieved! 222 as of end 2016.

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IRDiRC's own role in achieving the 200 therapies goal is difficult to measure

- Some therapies were developed by IRDiRC's industry members.
- Some likely resulted from publicly-funded drug discovery studies.
- However, the therapeutic development pipeline is lengthy and many new therapies result from initiatives that predate IRDiRC.
- Many developers of therapies are not members of IRDiRC yet all new FDA and/or EMA approvals are counted.
- No therapies other than FDA/EMA-approved drugs or devices were counted.

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Diagnostic projects funded by IRDiRC members

- Have been the major factor in the discovery of ~1,400 new rare disease genes.
- Have led to the optimization of next-generation sequence pipelines in a clinical setting.
- Have increased the diagnosis rate for patients with unknown disorders from ~10% to 30-50%.
- Have established diagnostic pipelines that can be, and have been in some jurisdictions, translated out of research programs and into normal clinical practice.

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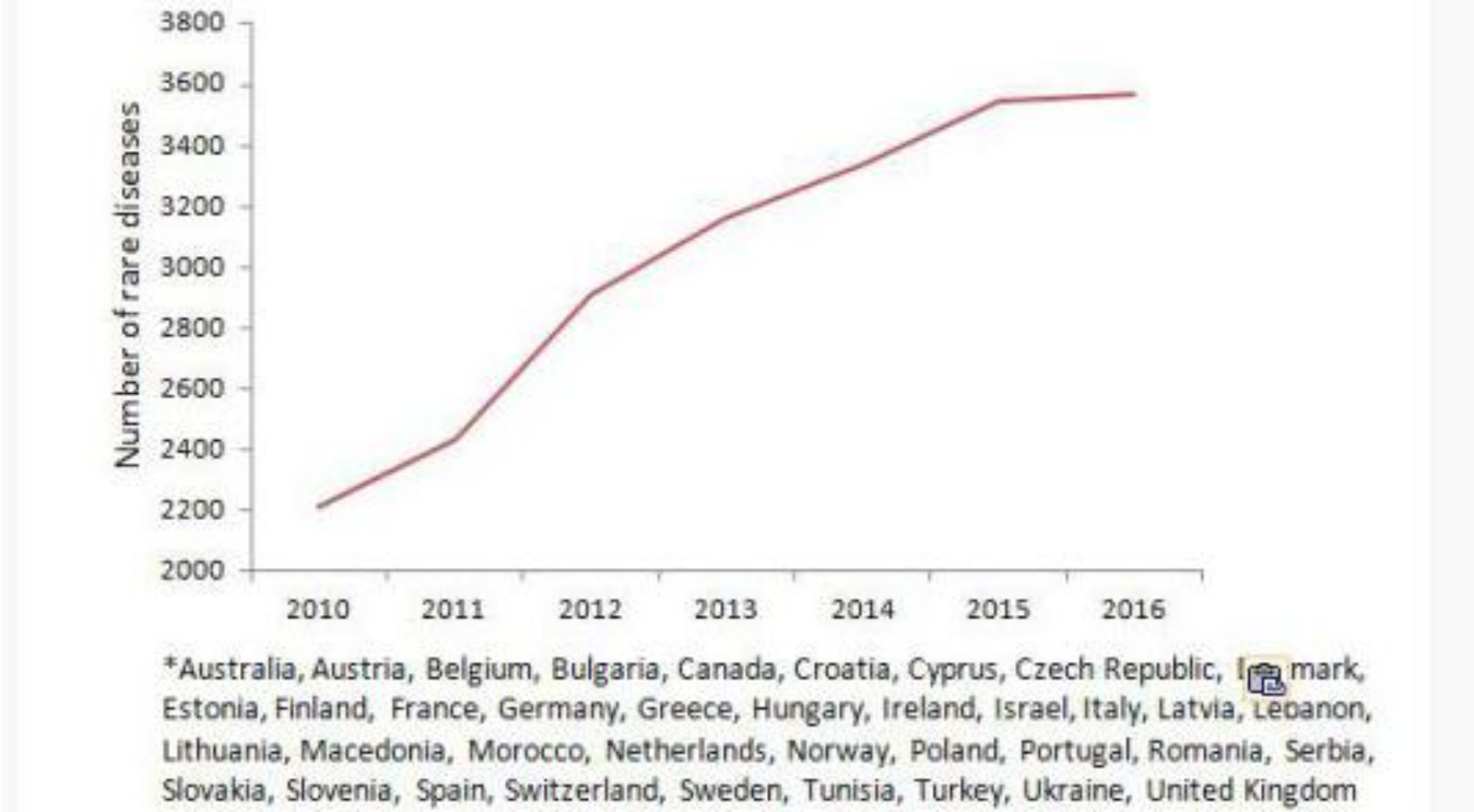
Rate of development of new diagnostics may be slowing



Data from Orphanet, figure retrieved from irdirc.org

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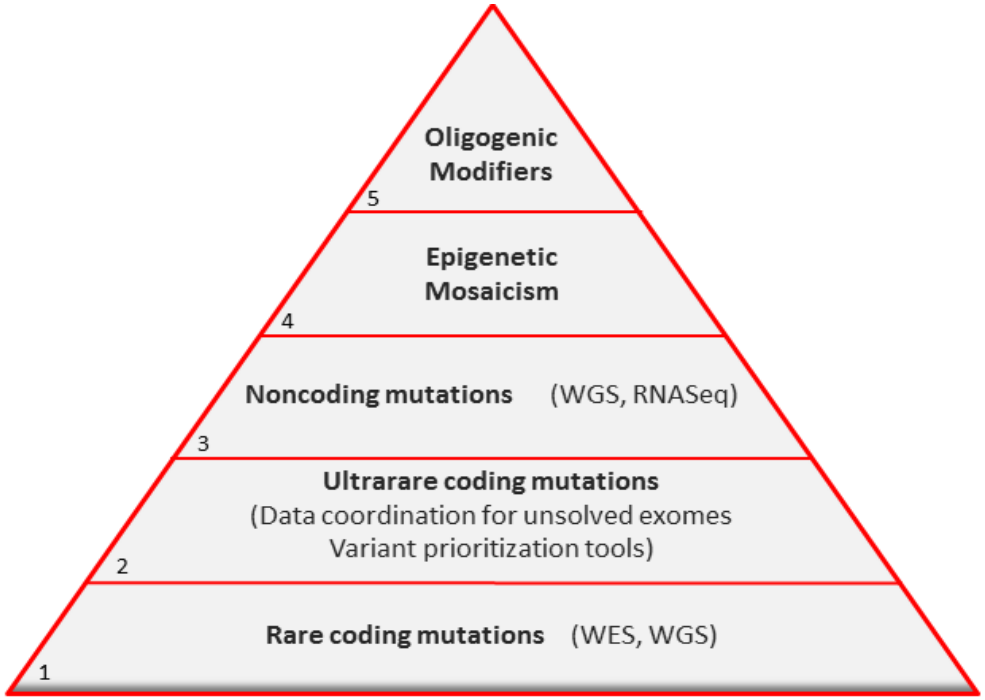
Complexity of disease mechanism



Identification and interpretation of non-coding mutations and other more complex disease mechanisms

from K. Boycott

Future of diagnostics research

- Genomics technology exists to diagnose many rare diseases that affect most rare disease patients.
- This technology is being transferred from research programs to healthcare but implementation in healthcare is spotty—serious inequities among and within jurisdictions remain to be addressed.
- Many genetic diseases still elude diagnosis by genomics—substantial discovery research is still needed to improve diagnostic yield.

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Thank you for your attention.