IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Meeting report series

Report of the 4th IRDiRC Diagnostics Scientific Committee meeting

Prague, Czech Republic
2 December 2013

Organization

Organized by: Scientific Secretariat and Milan Macek, University Hospital Motol Campus
Hosted by: Milan Macek, University Hospital Motol Campus, Department of Biology and Medical Genetics

Participants

Dr Kym Boycott, Ottawa, Canada, co-chair
Prof Xavier Estivill, Barcelona, Spain
Prof Milan Macek Jr., Prague, Czech Republic
Prof Gert Matthijs, Leuven, Belgium
Prof Woong-Yang Park, Seoul, Korea
Prof Pak-Chung Sham, Hong Kong, China

Dr Sophie Höhn, Scientific Secretariat

Apologies

Prof Michael Bamshad, Seattle, USA, co-chair
Prof Han G. Brunner, Njimegen, Netherlands, co-chair
Prof Andrea Ballabio, Naples, Italy
Prof Johan den Dunnen, Leiden, Netherlands
Prof Peter Propping, Bonn, Germany
Prof Jun Wang, Shenzhen, China

Agenda

1. Update from the IRDiRC Executive Committee
2. Update from SUPPORT-IRDiRC
3. Diagnostics Scientific Committee Road Map
    a. Review and next steps for the WG on Ontologies and Rare Disease Prioritization
    b. Review and next steps for the WG on Sequencing
    c. Review and next steps for the WG on Genome/Phenome
    d. Review and next steps for the WG on Model Systems
4. Other topics
5. Next steps

EXECUTIVE SUMMARY

The fourth meeting of the IRDiRC Diagnostics Scientific Committee (DSC) took place in Prague (Czech Republic) on December 2, 2013. This meeting was organized in the Department of Biology and Medical Genetics, at the University Hospital Motol Campus, Prague.

During this meeting, two new members, Dr Woong-Yang Park from Seoul, Korea and Dr Pak-Chung Sham from Hong Kong, China were welcomed. An update from the IRDiRC Executive Committee meeting and from SUPPORT IRDiRC was done. The DSC worked on the road map reviewing the progress of the four Working Groups and next steps. A new Working Group on Population Controls will be created. A 3-year roadmap was developed to outline the standards and tools that will be generated and disseminated by the DSC as well as editorials that will be written.

REPORT

1. Update from the IRDiRC Executive Committee

The fifth IRDiRC Executive Committee meeting took place on September 23-24, 2013 in Miami, USA, and the sixth IRDiRC Executive Committee meeting (teleconference) was held on November 25, 2013.
The updates are the following:

- The Interdisciplinary Scientific Committee made recommendations for the IRDiRC road map.
- The next Executive Committee meeting will be held on May 7-8, 2014, right before the European Conference on Rare Diseases meeting to be held in Berlin on May 9-10.
- The following Executive Committee meeting will be held in China in October-November 2014, if the IRDiRC conference is confirmed.

2. Update from SUPPORT-IRDiRC

The IRDiRC private website allows IRDiRC members to have access to confidential and not finalized documents, as well as to shared documents of other groups (if members are allowed to access these groups). The DSC members do not wish to have other functionalities added to the private website at the moment.
The DSC would like IRDiRC to highlight the following efforts/projects:

- MATCHMAKER
- PhenomeCentral
- Workshop on Rare Disease Standard Terminology held in Boston in October

3. Diagnostics Scientific Committee Road Map

The Committee discussed the goals of IRDiRC, specifically, the objective of **identifying all rare diseases genes by 2020 to enable diagnosis of most patients with RDs**. This may be a challenge as the DSC expects the increasing discovery of new genes secondary to exome sequencing to slow down as the more straightforward Mendelian diseases are solved. However, large scale data sharing of phenotypic and genotypic data from unsolved patients, and tools to enable discovery based on this data, will enable the pace to be maintained. The DSC discussed that a database of population specific variants would be very useful for interpretation of variants as potentially disease-causing and a new WG should be formed to facilitate development of such a resource. The DSC also discussed that many rare diseases will require investigation that will need to go “beyond the exome to solve the unsolvable” and that we must plan for this eventuality in future funding opportunities (see fig p 10). The progress of each WG was reviewed and the DSC felt that in the future, three of the existing WGs of the DSC (Ontologies and RD Prioritization, Sequencing, and Genome/Phenome) are expected to collapse into one: the WG on Genome/Phenome.

New Working Group on Population Controls

In order to coordinate a population-specific control data set that will represent international variation as much as possible, a new short-term WG will be mandated. This WG will facilitate the aggregation of variant frequency data from specific populations. Data would be accumulated from 50 or so exomes, be collected in a standard format and be unidentifiable. The WG will be formed in early 2014 and is expected to complete its task in 6-12 months.

Working Group on Ontologies and Rare Disease Prioritization

- A Rare Disease Terminology Workshop took place on October 21-22, 2013 in Boston, USA, to select 2 500 common terms (appearing in at least two classifications) to describe phenotypic features of rare diseases. A consortium was created, the International Consortium of Human Phenome Terminology (ICHPT), with its corresponding website that will be hosted on the IRDiRC website. The ~2 500 terms will be mapped across the other ontologies so there is a standard interoperable language to describe phenotypic features of rare diseases.
- A guideline should be developed for IRDiRC reviewing the existing ontologies, identifying the standard (likely HPO) and endorsing the utility of the ~2 500 standard terms.
- There needs to be a plan developed for on-going infrastructure support for maintenance and further development of the accepted IRDiRC standard ontology.
- The group discussed the prioritization of rare diseases for therapies. A consensus was reached: a list of rare diseases prioritization should not be generated, however, a list of diseases potentially therapeutically tractable diseases could be developed as a resource (but this would be the responsibility of the Therapies Scientific Committee).
- The work of this WG is well advanced and should have completed its tasks in approximately one year.
- A possible evolution of this WG could be to create a WG on Ontology for model organisms.

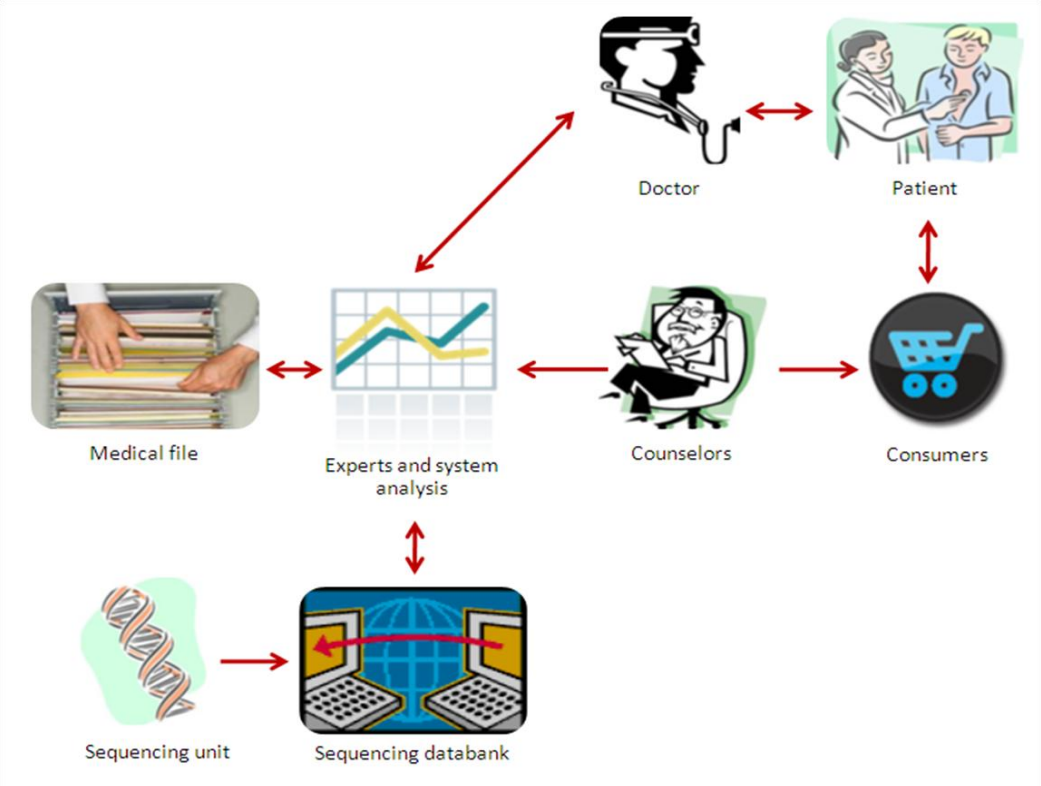
Working Group on Sequencing

- The adoption of next-generation sequencing (NGS) standards/guidelines for IRDiRC is required. Thanks to the EuroGentest initiative, the work is well-advanced. A draft is expected in early 2014 and at that time it will be proposed to be accepted as the IRDiRC standard.
- IRDiRC should survey, summarize and disseminate strategies used by countries where healthcare systems have successfully translated exome sequencing into rare disease clinics.
- Variant interpretation is an area with investment to date by ClinVar and the Human Variome Project and as we go forward IRDiRC will also contribute. Other possibly interested groups include Illumina, CLC Workbench and Cartagenia.
- Genome Leaders in Genomic Medicine workshop has been organized at NHGRI and the member of the DSC participating to this workshop will report back to the DSC. This workshop will focus on clinical translation of genomic sequencing.
- The DSC would like to see laboratories accredited for the use of exome sequencing in 2014/2015.

- The DSC would like to write an editorial in late 2014 on "Solving the Unsolvable: What Comes After Exomes to Identify Mechanisms for Rare Diseases" – to include the challenges of rare disease mechanism discovery that we will face over the coming years as the more readily identifiable coding mutations are discovered.
- Research funding directed by IRDiRC to level 2-5 of the pyramid will be needed to reach the 2020 goal of diagnostics for most rare diseases (see fig p10).

Working Group on Genome/Phenome

The DSC spent some time discussing the complexities of determining the pathogenicity of variants with clinical confidence. The DSC sees the area of direct-to-consumer testing (DTC) to be poorly understood by the general public in this regard; there are only a few diseases where you can competently judge carrier status (e.g. CFTR.org project) and thus carrier screening is being 'oversold'. We are only just beginning to understand the complexities of penetrance and what factors modify disease expression as the data we have collected to date is completely biased since it is based on affected individuals with RDs. The DSC would like this WG to write an editorial on determining causality of genomic variants and all caveats of current analysis, including DTC testing. Engagement of the RD-SympathI workshop participants – many of whom are members of this WG – would be a useful product of this workshop. Including comment in the editorial about possible ways to integrate DTC into the healthcare system would be useful (see example below).



- A cross-talk platform needs to be created to allow different data sets (hypothesis free and Decipher-like) to communicate.
  The collaborative platform Matchmaker will achieve this goal in the short-term and could evolve over the longer-term.

- Representatives from PhenomeCentral (Canada), LOVD, U Miami (Gem.app), DECIPHER, GeneMatcher (Centers for Mendelian Genomics), Café Variome met on October 23, 2013, in conjunction with the ASHG meeting in Boston, co-organized by ICCG and IRDiRC. There was wide-spread enthusiasm to develop two WGs to look at 1) levels of data sharing and 2) API to connect discoverable data. The time line for the latter to be operational would be fall 2014.

- The sixth Joint Transnational Call for Research Projects on Rare Diseases of E-Rare could contribute to this new version of Matchmaker.
- A list of databases to use for data deposition needs to be developed and made available on the IRDiRC website.
- Funding going forward to maintain and build such 'IRDiRC' supported websites will be needed.
- It was decided not to write a paper about how IRDiRC could have a central role in rare diseases in the Global Alliance initiative for the moment. The chair of the DSC is a member of the clinical expert working group of the Global Alliance and will present IRDiRC's achievements to this group. IRDiRC will need to wait for the Global Alliance to make more progress to have a better idea of what it can offer and where we can align.
- The WG on Genome/Phenome could join forces in terms of technicality with the research teams working in the cancer area of the Global Alliance.

Working Group on Model systems

- The Canadian Institutes for Health Research in partnership with Genome Canada has launched a call named "Research Catalyst Network: expediting collaboration between basic and clinician scientists in functional studies of novel rare disease genes". The goal of this call is to establish a national consortium that will enable clinical geneticists who are identifying rare disease gene mutations to collaborate with model organism researchers with expertise in the cognate gene's function.
- Propose this WG come under the scope of both the Therapies Scientific Committee and the DSC.
- More feedback to this WG is needed around direction.
    - The WG should discuss the utility of functional assays to interpret rare variants that may be associated with disease and platforms that might achieve this.
    - The WG should expand on the idea of a "market place" that would support catalogues of expert groups on model systems.
    - The WG should further explore coordination of cellular assays to model disease for therapeutic screening.
    - We would also like to hear from the WG about the activities at the level of different model organisms for coordination with investigation of rare diseases – for example the way that the mouse community collaborates through several large consortia to model human disease genes. Do other such platforms exist for other model systems?
    - We would be interested to know if the WG feels that a list of rare diseases that are potentially therapeutically tractable based on clinical criteria would be of interest to their community.

Metrics of Progress

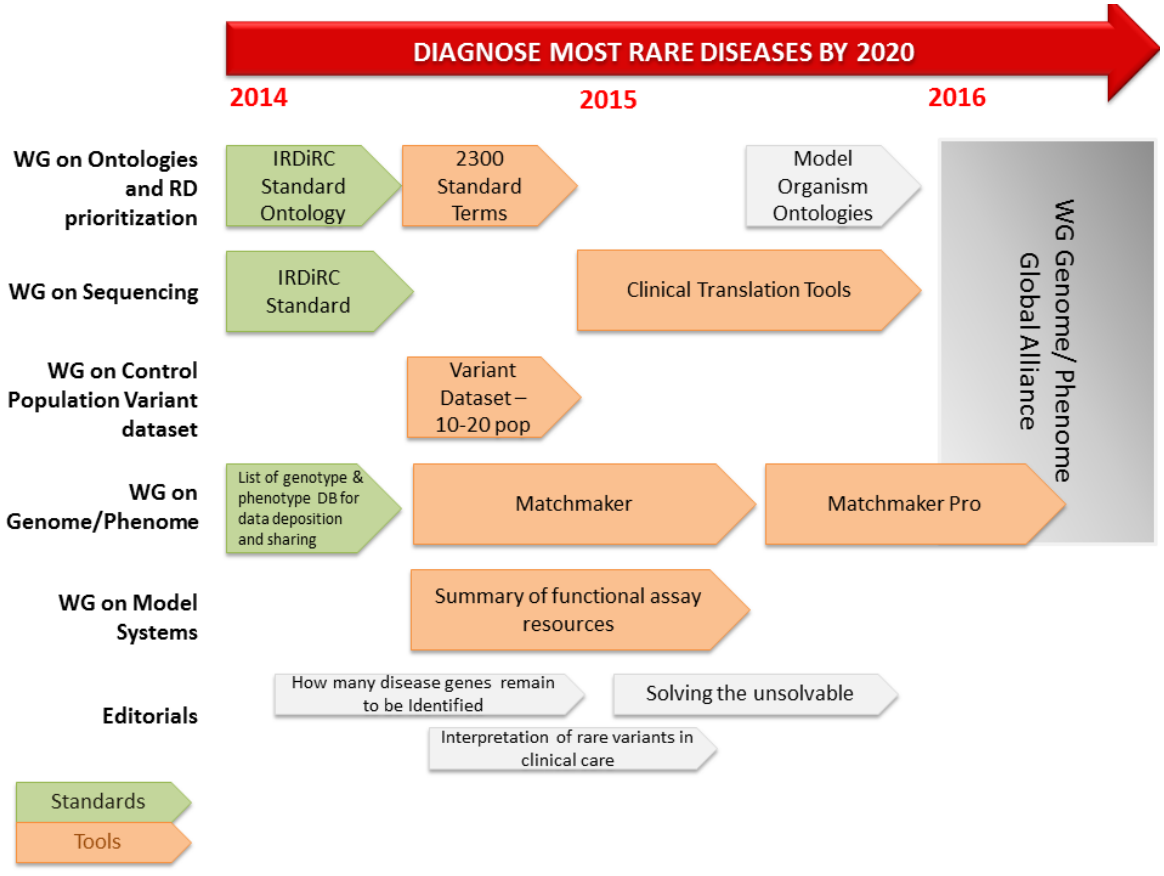
The overarching goals of the IRDiRC are to make possible the diagnosis of as many rare diseases as possible and to develop 200 new rare diseases treatments by 2020. IRDiRC intends to monitor progress towards these goals through a set of direct and indirect indicators.

The DSC would like to contribute to the calculation of these indicators. In order to do so, the DSC would like:

- The data of the number of new genes identified as being causal for rare diseases to be extracted from Orphanet and OMIM databases.
- The definition of a new gene should be "a gene that has never been linked as causative to any rare disease".
- A graphic to summarize the "new" genes and another graphic to summarize the "repurposing" of genes (distinct mechanism of disease for a different phenotype for a previously reported disease gene).
- The number of rare diseases (distinct phenotypes) should be counted.
- To write an editorial for the *American Journal of Human Genetics* predicting how many genes are there to be found for rare diseases, involving Orphanet and OMIM.

Summary of the road map

In summary, the road map for IRDiRC will include the following:

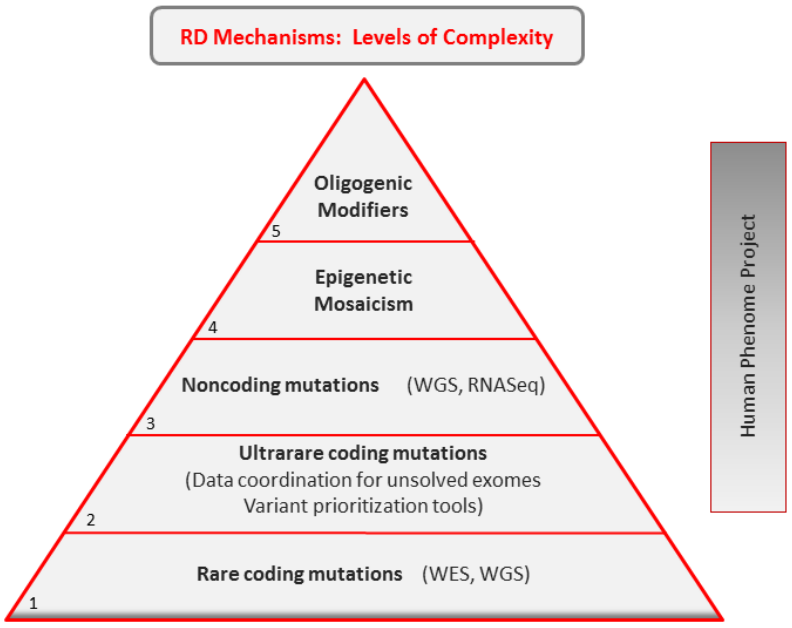


6. Other topics

- IRDiRC needs a budget to support its members travelling in the name of IRDiRC.
- The next teleconference of the DSC will take place after the DSC WGs have met.
- The DSC will aim to meet a minimum of four times a year (combination of in-person and teleconference). The next DSC in-person meeting will take place in conjunction with ECRD 2014 in Berlin, and/or in conjunction with the IRDiRC conference in Shenzhen.

7. Next Steps

- Create the WG on Population Controls.
- Propose the WG on Model systems come under the scope of both the Therapies Scientific Committee and the DSC.
- **Working groups** – provide a summary of the discussion relevant to each WG will be communicated to the Chairs
    - Roadmap
    - Tools and Standards to be developed
- **Metrics** - contribute to the calculation of the indicators of the overarching goals of the IRDiRC.
- **Editorials** to increase the visibility of IRDiRC:
    - Write an editorial for the *American Journal of Human Genetics* predicting how many genes could be found by 2020.
    - Write an editorial on the interpretation of rare variants in clinical care.
    - Write an editorial in late 2014 on 'Solving the Unsolvable: What Comes After Exomes to Identify Mechanisms for Rare Diseases' – to include the challenges summarized in the pyramid.



IRDiRC Goal: Diagnostics for most RD by 2020

DSC Objectives:

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

- Propose to the Executive Committee that a budget to support IRDiRC members travelling in the name of IRDiRC would be valuable.
- Organize the next teleconference of the DSC and the next meeting.