

## Meeting report series

# Report of the 1<sup>st</sup> DSC Working Group on Sequencing teleconference

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### Organization

Organized by: IRDiRC Scientific Secretariat  
Teleconference

### Participants

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## REPORT

### Presentation of IRDiRC

IRDiRC is an initiative of the NIH and the European Commission with the purpose of reaching the following two main goals:

- ▶ Produce diagnostic tools for most of rare diseases by 2020
- ▶ Develop 200 new therapies for rare diseases by 2020

IRDiRC is a consortium of funders investing at least 10 million USD over 5 years in research projects contributing towards IRDiRC objectives and invited patient advocacy group. IRDiRC has three Scientific Committees:

- ▶ Diagnostics Scientific Committee (DSC)
- ▶ Interdisciplinary Scientific Committee (ISC)
- ▶ Therapies Scientific Committee (TSC)

The purpose of the DSC is to try to translate research in rare diseases into diagnostics for patients. The DSC oversees four Working Groups:

- ▶ WG on Model systems
- ▶ WG on Genome/Phenome
- ▶ WG on Ontologies and disease prioritization
- ▶ WG on Sequencing

### Items of IRDiRC Action plan related to the WG on Sequencing

#### Items directly related to the WG on Sequencing:

- ▶ #14: Establish guidelines for the clinical reporting of genomic sequencing in a clinical setting, including the approach to incidental findings.
- ▶ #8: Contribute to the development and evolution of standards for RD diagnostics testing and reporting.

#### Items where the WG can contribute for the sequencing part:

- ▶ #2: Promote the discovery of all genes that underlies RD and facilitate the development of diagnostic testing for all RD.
- ▶ #7: Promote a single set of standards for collecting, storing, annotating and communication data.
- ▶ #13: Promote the interoperability between genotype-phenotype databases that collect and curate information on all variants causing specific human disease phenotypes.

The working group proposes to mainly focus on #14 and #8 indeed.

## **Actions for the WG**

### **Identify opportunities and gaps**

- ▶ Where is something missing at the international level? It is mostly about uniformity in next generation sequencing (NGS) like e.g. exome offer and interpretation. There is a need for guidelines for the sake of the patients. Also, NGS is not solely applied to RD, thus one can learn from experience in other fields, like cancer genetics. Hence, liaison with different groups is important.

### **Identify redundancies**

- ▶ Where do we all get in trouble or make the same mistakes? Where do we all reinvent the wheel again and again? Every lab seems to go through the same learning phase, and the total cost of development (and trial and error) is huge. Again, guidelines and exchange programs would be welcome.

### **Develop quality standards and write guidelines**

The best approach to write general guidelines under the umbrella of IRDiRC would be to adapt at the international level what already exists. The proposed strategy is to:

- ▶ Identify all the groups and organizations that are issuing guidelines,
- ▶ Compare them for contradiction and come to a resolution,
- ▶ Find what is missing and what should be addressed.

When comparing the guidelines of the different groups, it would be important to consider the goal of each group and how their focus may differ (accreditation of diagnostic laboratories, clinical operations, etc.).

### **Generation of data in clinical/ research context**

The WG would recommend for sequencing to be only done in clinical setting and covered by the health system so that research money could be allocated to other research topics. It is by no means interesting nor efficient to enroll each and every patient that walks into a rare disease/genetic service in a research project for sequencing. It is indeed impossible to sequence all the patients in a research context.

Another point of interest – and concern – is the direct transfer of research results back to the clinic: patient's safety should be warranted by confirming the result of the genome sequencing conducted in research laboratories in a clinical setting. This is again something to be addressed in the discussions with the health care system.

- ▶ An analysis of the situation in different countries to determine if there is progress in terms of transferring the sequencing from a research to a clinical context would be useful.
- ▶ Guidelines on how to translate research results and report them on a clinical level to patients and their family are necessary.

## Classification/nomenclature of variants

- ▶ It is necessary to develop minimal standards for the collection and annotation of data to facilitate data sharing as each clinical diagnostic laboratory have a different approach to sequencing. This is a task that is too broad for the sequencing work group alone, but initiatives at the international level are needed, and have to be supported. This is mostly about the creation of open databases that list variants with their clinical interpretations.

An international database with matching genotypes and phenotypes would be particularly useful for diagnosticians and researchers. There are already at least 3 initiatives in matchmaking (LOVD, Decipher and PhenoDB); Canada is also developing such an initiative and it is one of the goals of RD-Connect. Crucial is also a digested, easy to understand report format for the clinician that makes prediction on the key diagnostic observations (causative variants, but also modulating variants).

## Detection and clinical sensitivity for variants

This is about support and collaboration on the technical (analytical) validation of NGS platforms. What would be a golden standard? Can we share reference materials to promote standardization?

- ▶ Guidelines should propose recommendations on set of variants from a specific DNA to test the sensitivity of the detection system (quantitative or qualitative approach).
- ▶ Definition, generation and distribution of reference materials should also be considered for developing test and proficiency testing. Once again, comparison of existing initiatives would be a good strategy.

It may well be that the Joint Research Centre (JRC) of the European Commission could take up a role and thus promote standardization in this area.

## Other topics

- ▶ Defining the minimal set of genes and total set of genes to include for any test for a particular phenotype would be really useful but is beyond the scope of this WG.
- ▶ Importance of also sharing the whole content of genome sequencing, including neutral and what is considered as non-important for this particular patient, for better sharing of information.

## Practical issues

The WG also discussed the problem of finding funding for travel expenses to allow the participation of 1-2 WG members to specific meetings as observers to encourage collaborations and the promotion of IRDiRC

- ▶ WG members are invited to join the meeting organized by EuroGenTest on November 21-22 in the Netherlands aiming to finalize guidelines. Invitations will follow.