Meeting report series

Report of the 10th Diagnostics Scientific Committee Meeting

Lyon, France
March 14, 2016

Participants

Prof Kym Boycott, Ottawa, Canada, Chair
Assoc Prof Gareth Baynam, Perth, Australia
Prof Anthony Brookes, Leicester, UK
Prof Han Brunner, Nijmegen, the Netherlands
Prof Johan den Dunnen, Leiden, the Netherlands
Prof Xavier Estivill, Barcelona, Spain
Prof Gert Matthijs, Leuven, Belgium

Dr Christopher Austin, Executive Committee Chair, Bethesda, USA
Prof Hugh Dawkins, Executive Committee Vice Chair, Perth, Australia
Ms Sandra Peixoto, Scientific Secretariat, Paris, France

Apologies

Prof Fowzan Sami Alkuraya, Riyadh, Kingdom of Saudi Arabia
Prof Michael Bamshad, Seattle, USA
Prof Milan Macek, Prague, Czech Republic
Prof Woong-Yang Park, Seoul, Republic of Korea
Prof Pak Chung Sham, Hong Kong
Prof Hendrik Stunnenberg, Nijmegen, the Netherlands
Dr Feng Zhang, Shanghai, China

Agenda

1. Welcome and introduction
2. Consortium update
3. “IRDiRC Recommended”
4. IRDiRC Task Forces under the DSC: updates and proposals
5. Draft DSC commentary
6. DSC membership and Chair
1. Welcome and introduction

The Chair of the Diagnostics Scientific Committee (DSC) welcomed its members to the meeting, and each participant briefly introduced themselves. The new Chair of the Executive Committee (Exec Comm) partially attended this meeting and took the opportunity to present himself, to meet the DSC members, and to become acquainted with the work of the DSC.

2. Consortium update

Membership of the Consortium is increasing and currently represents over 2 billion dollars of investment.

IRDiRC has 2 main goals: deliver 200 new therapies for rare diseases and means to diagnose most of them by 2020. The first goal is expected to be achieved this year, although it is not clear how IRDiRC has directly contributed to this achievement. The second goal, which is under the purview of the DSC, most likely will not be achieved by 2020, although it may come close. Successful outcome will depend on a number of factors including the mechanistic complexity of those rare diseases that are currently not understood and the actual number of genes/mechanisms that remain to be discovered. While next generation sequencing, primarily whole-exome sequencing (WES), has provided molecular insight into many rare diseases over the past five years, it has not dramatically increased the pace of discovery, instead it has largely replaced the technological approach to discovery. If our goal is to maximize discovery from WES/WGS of Mendelian diseases caused by coding, or other readily interpretable, variants, we will likely be able to achieve this by 2020, by enabling greater access to WES as part of clinical care and ensuring sharing of data from unsolved cases to facilitate discovery.

Pace of Gene Discovery by NGS
3. “IRDiRC Recommended”

Currently, 10 resources have been awarded the “IRDiRC Recommended” label. OMIM databases’ award should soon be official. A number of applications have been refused, not due to lack of quality but because they were focused on a single rare disease and/or had only national impact. Overall, members are satisfied with the initiative and found the review process itself not time consuming.

There are still some gaps in the “IRDiRC Recommended” catalogue. Matchmaking databases (e.g. ClinGen and LOVD), variant databases, mutation nomenclature guidelines, and tools with more than one purpose that can be applied to rare diseases are some of the resources of value that should be pursued by the Committee. Members should encourage the investigators to apply for “IRDiRC Recommended”.

4. IRDiRC Task Forces under the DSC: updates and proposals

The implementation of Task Forces by the Scientific Secretariat (Sci Sec) has been a positive step forward from the previous organization based on Working Groups. The Sci Sec can support 4-5 Task Forces per year, including the elaboration of background documents, identification of key experts, and organization of workshops.

4.1 Implemented Task Forces

Two Task Forces have been operating under the purview of the DSC: International Consortium of Human Phenotype Terminologies (ICHPT) and Matchmaker Exchange (MME).

- ICHPT aims to establish a core set of terms to be incorporated in any human phenotype terminology intended to describe rare diseases. The list of terms and their mapping has been available at http://www.irdirc.org/ichpt/ since last September.

- MME aims to discovery new disease genes for patients with rare disease by facilitating the matching of cases with similar phenotypic and genotypic profiles through standardized API and procedural conventions. A full day workshop and a community engagement event were held in October 2015, and Human Mutation dedicated its October issue to MME; these successes represent the outcomes of this Task Force.

4.2 Future Task Forces

As previous Task Forces have reached their outcomes, the DSC will now focus on the establishment of 2 new Task Forces for 2016-2017. Two main areas of action were identified:

- Solving the unsolved; and,
- Clinical data sharing for gene discovery.

A teleconference will be organized to define the roadmap of these new Task Forces in detail.
4.2.1 Solving the unsolved

To address “solving the unsolved”, topics for consideration:

- Ontologies to enable data-sharing
  Ontologies are already being addressed by other international consortia (e.g. GA4GH) and so were not prioritized.

- MME- next phase
  MME will continue to operate as it has done, its objectives aligned with IRDiRC and GA4GH, but given its relative independence it was felt to not be necessary to run it under the umbrella of an IRDiRC Task Force in 2016.

- New approaches to understand challenging disease mechanisms
  - Genome and other technologies (RNA seq)
  - Population and genomics datasets
  - Beyond monogenic inheritance (e.g. di-genic, tri-genic inheritance)
  - Mosaicism and other mechanisms of disease
  - Multidisciplinary diagnostic approaches

This Task Force will focus on development of new approaches, best practices, and tools to study the ‘intractable to WES/WGS’ diseases (noncoding/other mechanisms) and was prioritized to move forward for consideration by the Exec Comm. The Task Force could meet for its workshop coupled with the ASHG.

4.2.2 Clinical data sharing for gene discovery

The thinking behind this focus was to facilitate access to clinical genome-wide sequencing for appropriate patients and ensure secondary use of data for discovery of disease mechanism.

Topics for consideration included:

- Strategies for diagnostic approach for patients with RD, including patient indication
- Public health systems integration (economics and clinical outcomes)
- Enabling secondary use of data from clinical genome-wide sequencing to facilitate rare disease discovery:
  - Core data elements for secondary use of data and justification
  - Strategies for sharing
  - Interface, consent, workflow
  - Patient-driven sharing
  - Multi-stakeholder engagement (Diagnostics Labs, Patients, Clinicians, Payers)

This Task Force will focus on maximizing secondary use of data generated in clinics. Among the priorities are strategies for data sharing, interface for sharing within a clinical workflow, data use consent, and patient-driven sharing. This will be a multi-stakeholder initiative. Potential deliverable of this Task
5. **Draft DSC commentary**

The Editors of both the European and the American Journals of Human Genetics have agreed to consider a joint publication of the commentary currently being drafted by the DSC.

The Chair of the DSC took the opportunity to discuss this draft article, which includes factors contributing to bottlenecks in the gene discovery pipeline and strategies to enable progress in this regard.

The authorship of this publication will include all members of the DSC, and any other member from committees who have contributed with text and/or comments. This publication can only be endorsed by the scientists of the Sci Comms, not by the Exec Comm.

6. **DSC membership and Chair**

There are 14 members in the DSC. The membership policy has evolved and it is no longer mandatory to be nominated by funder members of the IRDiRC. New members can be strategically suggested from external organizations. Members who have not been active may be excused.

The current Chair’s mandate of 3 years has been reached; the Chair is happy to continue for another year, with a view that there is a Vice Chair to share the work load. Moreover, this facilitates a transition for the Vice Chair to take over in due course. Any member who is interested should inform the Chair.

The DSC members have been invited to circulate by email any additional suggestions. They will also approach some of the suggested new members to gauge interest.

**Action points**

- Organize teleconference to discuss and refine new Task Force proposals
- Put together final edits for the commentary and submit the paper
- Approach potential new members of the DSC
- Expression of interest to be Vice Chair