IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Meeting report series

Report of the 13th Diagnostics Scientific Committee Meeting

Teleconference
October 12, 2017

Participants

Prof Kym Boycott, Ottawa, Canada – Chair
Assoc Prof Gareth Baynam, Perth, Australia – Vice Chair
Prof Fowzan Sami Alkuraya, Riyadh, Kingdom of Saudi Arabia
Prof Kenjiro Kosaki, Tokyo, Japan
Prof Milan Macek, Prague, Czech Republic
Prof Ann Nordgren, Stockholm, Sweden
Prof Jürgen Reichardt, Urcuquí, Ecuador
Prof Francois Van Der Westhuizen, Potchefstroom, South Africa
Dr Feng Zhang, Shanghai, China

Ms Christine Cutillo, NCATS, Washington DC, USA
Dr Anneliene Jonker, Scientific Secretariat, Paris, France
Dr Marlene Jagut, Scientific Secretariat, Paris, France
Dr Lilian Lau, Scientific Secretariat, Paris, France

Apologies

Prof Michael Bamshad, Seattle, USA
Prof Anthony Brookes, Leicester, UK
Prof Han Brunner, Nijmegen, the Netherlands
Prof Xavier Estivill, Barcelona, Spain
Prof Gert Matthijs, Leuven, Belgium
Dr Yiming Wang, Shenzhen, China

Agenda

1. Welcome
2. Introduction new DSC members
3. Update on Solving the Unsolved Task Force
4. Update on Clinical Data Sharing for Gene Discovery Task Force
5. Preparation ahead of Tokyo Consortium Assembly meeting

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REPORT

1. Welcome

The Chair welcomed members to the teleconference and thanked them for their participation.

2. Introduction to new DSC members

Members who recently joined the DSC are:

- Ann Nordgren
  - Professor in Clinical Genetics at Karolinska Institutet, Sweden
  - Project Manager at the Karolinska Center for Rare Diseases
  - Directs a rare disease research group on novel human disease genes
  - Part of an expert team for syndrome diagnostics, which is part of the Undiagnosed Diseases Network International
  - Board member of Agrenska, a national competence centre for rare disease

- Francois Van der Westhuizen
  - Professor of Biochemistry at the North-West University in South Africa
  - Researcher on mitochondrial function and disease
  - Recently formed new international neuromuscular disease research group, involving several other developing countries – South Africa, India, Brazil, Turkey, Zambia
  - Brings representation from the perspective of Africa and developing countries

- Jürgen Reichardt
  - Professor at the Yachay University in Ecuador, Vice Chancellor Research & Innovation
  - Experience in gene discovery and the functional assessment of DNA variants
  - Brings representation from the Human Variome Project, as well as the interest of Latin America and developing countries

3. Update on Solving the Unsolved (STU) Task Force

A briefing document was sent prior to the call and contains the objectives, scope, timeline and a list of the current TF members.

- A call was held in late September to identify the scope of the TF and develop the framework of where unsolved mechanism of diseases may be lying
  - Additional expertise required for the TF was considered from the following areas:
    - Multi-omics data integration (i.e. integrative omics)
    - Oligogenic/digenic mutations
    - Quantitative genetics
    - 3D structure

- Mathematics-system biology
- Representative from the SOLVE-RD project (European Commission-funded €15 million-project that will look beyond the exome)

- DSC members suggested the following potential members:
  - A representative of the SOLVE-RD project
  - An expert in multi-omics data integration
  - Mathematics-system biology
  - Non-coding variation

➔ DSC members **to send in ASAP any additional nominations** of expertise needed as listed above

- DSC thoughts on the areas that might benefit from additional expertise:
  - Many require large datasets and most likely more time to be actualized (more than 5 years) than the other probable mechanistic causes we have discussed in the past (e.g., mosaicism, regulatory mutations, rearrangements, repeats and imprinting).
  - Better tools should be developed to phenotype animal models, e.g., using artificial intelligence to look at zebrafish with pattern recognition techniques
  - A majority of the recessive unsolved cases can be solved at the RNA level, such as cryptic/deep slicing mutations that can be identified by transcriptome analysis
    - Only a fraction due to oligogenic/digenic mutations therefore perhaps not a priority at present but down the road
  - The other need identified was the need for automation in deposition of variants into databases such as ClinVar

4. Update on Clinical Data Sharing for Gene Discovery Task Force

- This TF has not been launched yet
  - It will get started later this fall, after the STU TF is fully up and underway
  - Timing also depends on availability of the Scientific Secretariat (Sci Sec)
- The Sci Sec is compiling names and contacts of potential participants

5. Preparation ahead of the Tokyo Consortium Assembly meeting

The Vice Chair of the DSC will attend the Tokyo meeting and represent the DSC. He will also present the outcome of the discussion re: actions of the DSC to contribute towards new IRDiRC goals.

Action template:

- Compiles various actions and sorted accordingly to the new IRDiRC's goals
  - Some actions have been previously discussed by the DSC
  - Instruction sheet provided on how to complete this action template
- For each action, members are to propose the **timeline, methods, implementation tools, and metrics** to evaluate the success of this action
  - Possibility to **add additional action(s)** if missing from the spreadsheet

  - Members can also **remove action(s)** if inappropriate for the DSC to consider
  - Members should **answer based on their expertise**; it is not mandatory to fill every single cell of the spreadsheet
- If a Task Force is needed to complete an action:
  - Members who would like to participate are invited to self-nominate
  - Members can also suggest names of persons with relevant expertise
- Members can also suggest if an action should be carried out in cooperation with another IRDIRC committee
- The collated outcome will be used by the Chair and Vice Chair to construct the DSC roadmap for 2017-2027, although it remains possible to re-assess in due course

➔ Each member to **fill in the action template and return to the Sci Sec by October 23**

Discussion points during the call:

- Most of the actions collapse into the following higher level concepts
  - Patient matching (matchmaker) type of activities
  - Approaches to solve the unsolved cases
  - Clinical translation and clinical diagnostic workflows
  - Access to diagnostics services
- The DSC has ongoing work around the three of the four broader topics
  - We can expand these activities and focus on gaps
  - To get started on access to diagnostic services – this is a health services type of challenge in both developed and developing countries as well as for underrepresented populations (e.g. aboriginals) in developed countries
- Access to testing in developing countries
  - Need inventory of diagnostic services worldwide
    - To encourage submission of services information to Orphanet
  - Development of cost-effective testing and interpretation platforms might enable access
    - Will require cost-effective and robust tests
    - One approach to provide a cost-effective solution would be to include only known pathogenic variants e.g. a chip of known pathogenic variants/ analytic approaches (i.e. filtering) to only known pathogenic variants
    - Advantage of this is it could be relatively cheap and ease of interpretation reduces downstream uncertainty and costs of e.g. variants of unknown significance. Also, simplifies consenting processes, supports timely diagnosis for a significant proportion, and allows for graduated building of laboratory expertise and genetic counselling resources.
    - Only a 10% improvement in developing countries would deliver a very significant magnitude of increased diagnoses globally.
- Ultimately need to structure actions where outputs also include recommendations to funders of much needed methodology and/or tools to enable timely diagnoses and access to testing for rare disease patients

Action points

- Contact potential STU TF members
- Send suggestions of additional experts for the STU TF
- Fill in the action template and return to Sci Sec by **October 23**
- Collate action template points and forward to DSC Chair/Vice Chair
- Draft DSC roadmap based on members' input
- Present DSC's action plans and roadmap in Tokyo