

Meeting report series

Report of the 12th Diagnostics Scientific Committee Meeting

Paris, France
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Participants

Prof Kym Boycott, Ottawa, Canada – Chair
Assoc Prof Gareth Baynam, Perth, Australia – Vice Chair
Prof Anthony Brookes, Leicester, UK
Prof Johan den Dunnen, Leiden, Netherlands
Prof Xavier Estivill, Doha, Qatar
Prof Kenjiro Kosaki, Tokyo, Japan
Dr Feng Zhang, Boston, USA

Dr Lilian Lau, Scientific Secretariat, Paris, France

Apologies

Prof Fowzan Sami Alkuraya, Riyadh, Kingdom of Saudi Arabia
Prof Michael Bamshad, Seattle, USA
Prof Han Brunner, Nijmegen, Netherlands
Prof Milan Macek, Prague, Czech Republic
Prof Gert Matthijs, Leuven, Belgium
Prof Hendrik Stunnenberg, Nijmegen, Netherlands
Prof Yiming Wang, Shenzhen, China

Agenda

1. Welcome and roundtable of members
2. IRDiRC new goals and areas of focus
3. Task Forces and work plans
4. DSC membership
5. E-Rare funding call

REPORT

1. Welcome and roundtable of members

The Chair of the Diagnostics Scientific Committee (DSC) welcomed its members to the meeting, and a roundtable took place for members to introduce themselves to the committee and give a brief update on rare disease research progress in their organisation/country.

2. IRDiRC new goals and areas of focus

2.1 IRDiRC's diagnostics goal by 2020: a means to diagnose most rare diseases

The success of IRDiRC's diagnostics goal by 2020 is hard to quantify, and DSC members opined it has not yet been achieved despite good progress made over the years. Data from OMIM and Orphanet show a peak in new gene discovery around 2013, but in 2016 a big drop in discovery was observed – indicative that perhaps the low-hanging fruit/easy discoveries have been made and/or there are limits to the technologies and approaches currently available? The number of genes left to find is currently unknown and is estimated differently by different researchers. Meanwhile, repurposing of a gene (i.e. known gene but new disease-gene relation) has been increasing in recent years.

MME is not yet at its sweet spot with a number of challenges currently being addressed. A DSC member published a set of 35-40 of single surviving candidate genes and followed the outcome to see how long it takes to validate these in a second patient; in general, 2-3 years is needed. There remains a risk of publishing bias with this type of approach of course; this is where additional clinical and functional evidence is helpful to confirm a new disease gene association.

2.2 New goal 1: Diagnosis of all RD patients will occur within 1 year

- ▶ Is the objective for patients to get diagnoses or have the technological potential to diagnose them within a year?
 - ▶ A relatively complete list of disease genes is needed, without yet considering the enormous number of disease-associated variants
 - ▶ Infrastructure may be available in developed countries but what about other countries?
 - ▶ There are healthcare system problems that will not be resolved easily
 - ▶ May need to qualify RD, perhaps to monogenic and coding diseases?
 - ▶ Clinical work is critical, and sharing captured data is key
 - ▶ A change in practice may be needed, e.g. patients to be research participants from day 1
- Proposal: Diagnosis of all RD patients will typically occur within 1 year of diagnostic assessment enabled by clinical data sharing

2.3 New goal 2: Rate of RD therapy approvals will have increased 10-fold against the 2016 data

- ▶ “Rate” would infer an outrageously high number of therapy approvals (i.e. 300-400 in 2027)
 - ▶ May need to extend to approvals captured in other global regions (e.g. include Japan and Canada), and include therapies without orphan designation and off-label repurposed molecules
 - ▶ To be clear, the DSC recognized that the estimated 7,000 – 10,000 rare genetic diseases are not all treatable in terms of disease-modifying or curative therapies, in all likelihood only about 30% have clinical tractability – most neurodevelopmental conditions won’t be treatable
- Prefer a total number of therapies rather than rate (e.g. 1,000 by 2027)

2.4 New goal 3: All RD patients will receive available treatment within 1 year of diagnosis

- ▶ Beyond the scope of research, as access and approvals are out of researchers’ control
 - These are most often political decisions
- ▶ Also, what is the definition of ‘available’ treatment within a jurisdiction?

2.5 Proposed DSC actions to advance towards new IRDiRC goals

- ▶ Activities
 - Promote RD biomarker and modifier discovery and validation → ISC
 - Incorporate undiagnosed disease program evaluation into RD diagnostic paradigm → yes, and to note cross-disciplinary aspect
 - Foster RD research, diagnosis, and treatment in developing countries → yes, although should be collaborative thus “with developing countries”; looking for synergies with existing projects in the more common disease space, e.g. H3Africa
 - Promote RD HTA and health economics research → yes, to be prioritised
 - Identify solutions or better interface to enable structured clinical data capture
 - Negotiate with healthcare system vendors to enable common format export
 - Create a work flow system so clinicians can capture data in real time without putting on additional, undue burden to get buy in
 - Incorporate elements that aid work flow (e.g. PhenoTips, Patient Archive, electronic consent)
- ▶ Metrics
 - Create globally inclusive methodology to count RD diagnostics and therapies
 - Re new genes: OMIM and Orphanet are main sources but each has its own SOP
 - Re diagnostic tests: Orphanet is already tracking based on its SOP
 - Re therapies: IRDiRC Secretariat tracks from EMA and FDA approvals
 - Quantify the number of RD patients who receive diagnosis and treatment to ensure that research reaches and benefits patients
 - Alternatively, have a curated list of genes definitively associated or not associated to diseases (including the types of variants known/excluded – frame shift, missense – and whether they are dosage sensitive – deletion, duplication),

specify if they present clinical tractability and there is a window for intervention
→ collaborate with ClinGen?

▶ Other ideas

- Develop **number** of diseases that can be diagnosed
 - If hypothesizing the ceiling number of RDs, it's too theoretical
 - If establishing how many can be diagnosed, Orphanet is already tracking
- Develop recommendations/approaches for interpretation of exome/genome/other omics data for **discovery**
 - Current thinking: types of diseases seen in clinical genetics are often caused by coding mutations so robust exomic sequencing and analysis should solve many undiagnosed cases
 - Genomic rearrangements and splice mutations are likely under-diagnosed
 - Discover undescribed links between genetics and RD “Solving the Unsolved” TF
- Facilitate **diagnostic translation** by improving the way diagnostics are developed, evaluated and valued
 - For diagnostics lab – is this an accreditation issue?
 - Offer benchmarked analysis pipeline
 - Who could do it? HVP? GA4GH? WHO?
 - Could download data of “Genome in a Bottle” and use pipeline to check result how close to the truth
 - Similarly, create a “RD patient in a bottle” and provide dataset to test pipeline?
 - A 2000 EU-wide study showed up to 17% error rate in clinical practice!
 - Currently, there is no good guidelines to validate NGS for clinical service
- Enable translation of WGS approaches into clinical care with secondary use of data for discovery considered standard-of-care → “Clinical Data Sharing” TF
- Develop NBS tests for RD and publish recommendations for implementation
 - Must first generate knowledge base to support future translation to screening
 - Establish a range of penetrance
 - Establish a picture of expressivity
 - Establish data on function (e.g. if a SNP modifies a gene and makes the disease milder with low penetrance)
 - Set up policies and guidelines
 - Collaboration with NBS community, when and what is the best method to do so, or leave it with them to tackle?
- Pre-conception carrier screening also an important area

3. Task Forces and work plans

3.1 Solving the Unsolved

- ▶ Where do the genetic mechanisms of disease for the unsolved RD patients lie?
 - Mosaicism (?10% of unsolved cases)

- Splicing mutations (?15-20% of unsolved cases)
- Other regulatory mutations
- Rearrangements – long-range
- Imprinting
- Digenic inheritance/modifiers for expression of disease
- ▶ Approaches: WGS and RNAseq to identify mosaicism and non-coding mutations will be the first responders
- ▶ Goal: organise a workshop at the ASHG Orlando to present cutting edge research in this area
 - Product: identify gap and missing tools, recommendations to advance these techniques

3.2 Clinical Data Sharing for Gene Discovery

- ▶ To identify barriers and bottlenecks to clinical data sharing:
 - To do a horizon scan and select what to focus on, e.g.
 - Is it a front-end issue, where loop starts and ends?
 - Is it blocked by ethics or health policy?
 - Map existing platforms that support managing, sharing and discussing RD cases
 - Interaction with laboratory analysis and reporting
 - Change title to “Making Clinical Data Shareable”?
 - Can encompass making data discoverable – often not considered by consent
 - Define data, meta data, and how to make data shareable
 - Coordinate with other TFs, e.g. ADA TF, PPRL TF
- ▶ Activity: teleconferences to get started before planning next steps and identify product(s)
 - Product should have clinical integration/workflow/best practices focus
 - Also, focus on phenotypic data rather than variant?

4. E-Rare funding call

The DSC has previously provided E-Rare with suggested areas for funding for its RFA, but the call has been postponed to 2018 (call will be launched in late 2017). The 2018 call should be complementary to different actions and projects financed by the EC, NIH etc, and fully exploit the added value of E-Rare call.

The DSC suggested focusing on challenges that require significant research expertise and development to advance but currently would benefit from the level of funding that E-Rare could provide to develop proof of concept to proceed further:

- ▶ Moderate through-put platforms to establish the causality of variants
- ▶ Multi-omic integrated approaches to understand rare genetic diseases