IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Meeting report series

Report of the 3rd DSC WG Genome/Phenome teleconference

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Organization

Organized by: IRDiRC Scientific Secretariat
Teleconference

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Agenda

1. Welcome
2. Review of the topics previously discussed
3. Patient Matchmaker effort

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REPORT

Update on Global alliance

Members of the WG agreed on the following actions during the previous (2nd) teleconference:

- Write a proposal explaining why IRDiRC should take a leading role in rare disease related aspects of the Global Alliance, emphasising what IRDiRC could do and what would be the issues
- Present that proposal during the next IRDiRC Executive Committee meeting in Miami on September 23-24th
- Given approval from the Executive Committee, make an approach to the Global Alliance in order for IRDiRC to take a leading role in the rare disease aspect

The Executive Committee agreed with the general logic of the idea. However, it noted that it will take some time for the Global Alliance to launch as resources, infrastructures and support from the hundred of bodies interested in joining Global Alliance. It is expected that the Global Alliance will emphasise standards and strategies, with a few big nodes (mostly US and Wellcome Trust). To date, three working groups have been nominated: Informatics/security, Clinical expert, and Regulatory issues.

⇨ **In conclusion, this WG should stay in touch with Global Alliance, particularly with the Clinical expert WG, but for now move forward regarding its own priorities independently of Global Alliance.**

The Patient Matchmaker project

Update and discussion

The Patient Matchmaker project aims to allow researchers to search for similar patients across federated RD patient datasets pertaining to genes, phenotypes and mutations. Once hits are found, then contacts between the data sources will be facilitated. The data themselves will remain private at all time; the system will do the matching.

Several independent initiatives (with good representation from IRDiRC and this WG) managing large datasets and with an interest in the Patient Matchmaker concept met during at ASHG to discuss collaboration on a global scale. Participants included representatives from the Center for Mendelian Genomics, Care4Rare, LOVD, Café Variome, RD-Connect, and the GEM.app from the University of Miami.

Two working groups were created to 1) 'Matchmaker Tiers Workgroup', to agree a set of levels of data matching/sharing to target over short and medium timeframes, and 2) 'Matchmaker API Workgroup', to define solutions to interface the systems.

Data sharing would need to start in the next 6 months, perhaps with GeneMatcher, PhenomeCentral and GEM.app because of their state of development and similar system construction.

The Genome/Phenome WG concluded that other projects/organisation should be reached out to, and at least kept regularly informed about this area of development, such as:

- ClinVar
- BGI
- Independent diagnostics/research laboratories and disease consortia

Discussion on the priorities for matchmaking

The WG then discussed the priorities, challenges and bottlenecks for gene matching. It appears that the main areas of need to target include:

- Understanding monogenic disease by exome or genome sequencing plus phenotype data
- Elucidating frequency data of DNA variants, especially for isolated population
- Clinical genetics diagnostics support based increasingly on NGS, by capture and sharing of primary evidence considered in making each inference of mutation pathogenicity

For which the WG also agreed that the Patient Matchmaker project requires the following three levels of inquiry:

- Disease
- Variants matching
- Phenotype matching

The WG advised that the matching system should first focus on genetic data, increasingly considering phenotype data and more sophisticated patient matching algorithms, and eventually bringing in pathogenicity evidence. Regarding the genetic level data matching, the initial focus should be on gene level matching, before variant class and specific variant level matching. Consideration will have to be given to the many different types of data available for interrogation (WGS, WES, single genes or single mutations, data quality/veracity, data provided to be queried vs data inputted as a search (which may be fabricated)) each of which will imply a different significance or type of interpretations.

As currently being conceived, use of the matching system will imply mandatory deposition of the input search data for others to search across subsequently. No distinction is then made between these data (which may be fabricated) and any other data, and the problems with this approach have not yet been discussed. Also, a hit is simultaneously alerted to both sources of the matching data, and there has so far been no discussion of whether this is the optimal approach.

Further actions to consider could be:

- To promote access to analytical tools (including data generated from single gene studies)
- To encourage collaboration from other nations (e.g., Saudi Arabia – GenoArabia initiative to sequence 100 000 genomes)
- To access available patient data from IRDiRC members
- To discuss whether and how to expand the Genomic Matchmaker group
- To promote **knowledge** sharing without having underlying data shared (e.g., graphically)
- To include functional and evidence level data in addition to phenotype data

Data sharing from and to the myriad smaller groups in the field

Individual research team, diagnostic labs, and disease specific consortia have a lot of expertise and natural history data on disease patients that will need to interoperate with the Patient Matchmaker system. None of this dimension has yet been deeply discussed.

Some major issues that make it difficult for small groups to engage with these developments could be:

- Technical competence
- Financial resources
- Legal restrictions (or uncertainties)

The Patient Matchmaker project must be designed to encourage and facilitate the involvement of smaller groups and other infrastructures, as sources and users of the system.

As a conclusion to pass on to the Executive Committee, the WG agrees that **genetic level patient matching should be the initial focus of this project, but this must go beyond the granularity of the whole gene, and also fully consider the impact of searching across different types of data (WGS, WES, single genes or single mutations, data quality/veracity, data provided to be queried vs data inputted as a search). Further elaborations of the system should be prioritised in due course, and all of this should be prioritised for funding opportunities.**

Possible deliverables for this WG

- Write a protocol describing priorities (levels and layers) and concrete next steps
- Write a paper about the Patient Matchmaker effort
- Ask RD-Connect to consider organizing a workshop on Patient Matchmaking, to agree common goals and solid deadlines
- Alert the Korean NIH, the Chinese RD Consortium and the Western Australian department of Health about the Patient Matchmaker project, and set up lines of regular communication