IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Meeting report series

Report of the 1st IRDiRC Diagnostics Scientific Committee

Rockville, MD USA
Thursday, May 10, 2012

Participants

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Action Items for IRDiRC Diagnostics Scientific Committee

- Determine if a list of NIH IRDiRC member activities is available or if one can be developed.
- Talk to the lead researcher of rare diseases at BGI to discuss potential collaboration and to determine their policy on data sharing.
- One of the Committee chairs will determine the exact expectations for this Committee regarding the fall Executive Committee meeting.
- Insert information developed today re: working groups and goals of this Committee into the draft Policies and Guidelines document, and then distribute to Committee members for feedback/review.
- Distribute meeting materials and action items to the Committee members. **Status Complete**
- Collect the list of rare diseases for Canada.
- Add the list of priorities that we developed to the timelines.
- Distribute the list of rare diseases compiled by the CMG to the Committee members.
- Provide the list of all rare diseases generated from matching the lists from GARD, OMIM, SNOMED, GeneTests, Orphanet etc.
- Ask two individuals to join the Genome-Phenome Working Group.

EXECUTIVE SUMMARY

The IRDiRC Diagnostics Scientific Committee held its first in-person meeting on May 10, 2012.

Drs. Michael Bamshad, Kym Boycott and Han Brunner agreed to co-chair the Committee for a minimum of a 1-year term.

Committee members defined the following short-term goals:

- Develop a definitive list of all rare disorders
- Define a set of global QC/QA guidelines/standards for diagnostics
- Determine the availability of cases/families for unsolved disorders
- Define how causality is measured
- Create the Rare Genome/Phenome Project

To accomplish these goals, the Committee identified four working groups and named core group members. The Committee agreed that at least one member of the Diagnostics Scientific Committee should sit on each working group. Committee members are also recruiting members from outside of IRDiRC. The four working groups include:

- Clinical Working Group
- Ontologies Working Group
- Sequencing Working Group
- Genome/Phenome Working Group

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REPORT

1. Presentation of IRDiRC

An overview of the goals and structure of IRDiRC was presented (Attachment 1). Briefly, the scientific Committees (Diagnostics, Therapies and Interdisciplinary) can have up to 15 members. The diagnostics Committee will develop working groups to help move toward the goal of obtaining the appropriate diagnostics and sequencing characteristics for ~6,000 rare diseases over the next eight years. Although working group members don't have to be IRDiRC members or approved by the IRDiRC Executive Committee (EC), it's expected that they will adhere to the standards and policies of IRDiRC.

The goals of IRDiRC include developing 200 new therapies and the means to diagnose most rare diseases by 2020.

What does it mean to be a member of the IRDiRC Executive Committee? Essentially each IRDiRC Executive Committee members are required to provide $10 million in this area of research over a five-year period and to adhere to IRDiRC principals and direction.

An award should be announced soon for administrative support for IRDiRC.

The IRDiRC interim Executive Committee meeting is scheduled for late September 2012 in Paris. The annual meeting is tentatively scheduled for February 2013 in Ireland. Scientific Committee chairs are expected to attend the September meeting to give reports on progress made and to propose how working groups are convened.

2. Goals of the DSC

The group discussed the 2012 goals for the Diagnostics Committee.

- To understand the landscape of genetic diseases – sequencing and characterization efforts
- (Where are we today?)
- To identify and prioritize gaps in sequencing & diagnostics and propose how these gaps could
- Be covered/implemented (Where do we want to go? How do we want to get there?)
- To revise the relevant chapters of the IRDiRC Policy Document
- To define the program for the Diagnostics/Sequencing session for the IRDiRC Conference in February 2013

A list of activities [i.e., any ongoing, funded initiatives already in place (e.g., Centers for Mendelian Genomics)] of current IRDiRC members would be important for this Committee to have available, in part, to create the most effective working groups.

3. Goals of IRDIRC

The group discussed the goals of IRDiRC, specifically, the goal of having 6,000 diagnostics by 2020. Several points were raised and discussed. For example, does 6,000 include the 3,000 or so that already have molecular testing available somewhere in the world, which would leave 3,000. Or is it 6,000 added to the 3,000 solved rare diseases? What is a realistic expectation? This Committee will partly be defining the definitive number of diseases and what is a diagnostic test. It was suggested that this Committee should propose a vision of how this would be done by 2020. There is room to provide this Committee's vision back to the EC in terms of goals and deliverables.

The group concluded that we need a definitive list of rare diseases. There are coordinated efforts among the Genetic and Rare Diseases Information Center (GARD), Genetic Alliance, Orphanet, SNOMED, OMIM, GeneTests and others to standardize nomenclature and to develop a list of rare diseases that all the groups use as a reference. The combined list might be available in a month or so.

Genetic Alliance runs a database, Disease Info Search, on which public users can type in a disorder or disease name and get information that is pulled from all sources (OMIM, NCBI etc.).
The searchable list includes anything genetic—rare and common—all cancers and acquired diseases.

The group confirmed that IRDiRC defines rare diseases to include Mendelian and diseases and complex traits.

4. Brainstorming Session

What can this Committee do? Composition of this group spans gene discovery to therapeutics with a lot of complimentary overlap.

Working groups will work for us to help find solutions to the problems that we are trying to solve. The Committee is focused on goals and direction while the working group will have defined problems to solve.

The Committee will develop policies, guidelines and best practices on how to accomplish our goals, but not necessarily the means by which they get implemented.

How are we defining rare disease? The policy document defines rare diseases in broad terms. We need to come up with a list of rare diseases identify which of those haven't been solved and determine a mechanism to prioritize gene discovery. A clear impediment to maximizing resources is that not everyone knows what is being worked on. The least common denominator would be to only work on those phenotypes that have proven intractable to multiple groups, and decide to work together to solve the disorder.

The group discussed IRDiRC, the EC and the Scientific Committees and the goals of this group in particular. The group agreed that IRDiRC is still developing and emerging, and that the Diagnostics Committee can define concrete goals and priorities today because the goals as defined by IRDiRC at this

point are ambiguous and/or not entirely and clearly defined (e.g., diagnostics for most diseases by 2020). So this Committee can interpret the goals of IRDiRC and further define them.

The group discussed the plans for the rest of this meeting. Basically, the group will work to come up with the top challenges/issues and ways to address those challenges. After these are defined, the group can review the draft policy document and see how it should be changed and/or provide feedback. The group will strive for what will be the most efficient way to solve rare diseases down the road (i.e., the ideal), but will also set goals that are clearly achievable.

5. The group identified three areas in which to focus efforts—phenotypes, gene discovery and diagnostics.

A. Phenotype – if the phenotype isn't correctly defined, genetic analysis is worthless.

Identify all rare disorders, determine which are solved, delineate and prioritize those phenotypes which remain unsolved and coordinate. The Committee needs to set criteria for what phenotypes are included. For example, do we want to include diagnostic conundrums?
IRDiRC requires:

- A list of all rare disorders
- A single phenotype ontology

B. Gene discovery – coordinated phenotype delineation and selection.
Availability of cases/families for all unsolved Mendelian (prerequisite to solving)
Rare Genome/ Phenome Project - annotating the genome with phenotypic information

- Broad data sharing – will be very important to patients
- Phenotype curation
- Experimental/analytical

C. Diagnostics in reality – The Committee needs to come up with rules/standards for how to go from genetic information to writing a diagnostic report where a clinician can say, "Yes, you have disorder X."

Establishing causality – how do you define causality, which is the essence of diagnostics?

- Mendelian
- Complex

Quality of test – if there is a change in sequencing platform then quality standards still have to be changed to keep up with the change in technology.

- Standards – core quality standards

Genome "reference" – will be necessary to define what is 'normal'
Global QA guidelines – need global quality assurance guidelines for all genome-based tests

6. Four Working Groups

Group	Areas of Interest/Priorities Members	Members
Clinical	Phenotype - List of all disorders – 1st priority Gene Discovery - Availability of cases/families – 2nd priority	
Ontologies	Single phenotype ontology	
Genome-Phenome	Rare Genome-Phenome Project	
Sequencing	Gene Discovery - Experimental/analytical - 2nd priority Diagnostics – all areas - Global QA Guidelines – 1st priority - Establishing causality - 3rd priority	

7. Discussions around Committee goals and working groups

The group discussed the idea of setting some minimum criteria for what phenotypes are added to the list. For example, we might only accept samples if there are at least two individuals with the same phenotype. There was no agreement on this point. On the one hand, if you limit what goes in, you may miss discoveries (e.g., disorders caused by de novo mutations). On the other hand, if you don't regulate what goes in, you will slow down the rate of discovery. If resources were unlimited, then we wouldn't limit what goes in, but because interpreting exomes is so much more difficult, particularly with proving causality, we may need to be more particular about what samples we include. One member suggested that instead of regulating the input (how samples get in) we should regulate the output (the data).

Instead make the standard on exome quality and analysis and commitments to sharing the data. Human Phenome Project – annotating the genome with phenotypic information, or annotating the phenome with genotypic information. Researchers need to be able to see if anyone else with this disease has been exome sequenced, or if anyone with this particular genetic variant has phenotype information attached to it.

To interpret individual exome data, we need a genome/phenome database, not necessarily for gene discovery, but for diagnostics. In order to identify the causal variant in a diagnostic exome, you need accessible information on the genes, variants and their phenotypes. You need some way to quickly rule out the non-causal variants. So the primary outcome is the identification of the gene from the disorder

and the secondary outcome is that we can, in the eight years of the project, build tools that will help to interpret diagnostic exomes. It will be extraordinarily useful to have deeply phenotyped groups with which to compare exome data.

Analogous to the Human Genome Project, where if researchers wanted to publish a paper on the discovery of a new gene, they were required to provide accession numbers to show that those data had been submitted to an accessible database. The human genome-phenome project can find ways to encourage/enforce the requirement that they be deposited into this type of database. There are privacy issues surrounding phenotype information, but that is for the working group to address.

Raw data sharing – difficulties include the fact that every country has their own rules and regulations and the quality of the data is extremely heterogeneous. The Committee should state what's ideal, and the working groups will try to work out the logistics. If IRDiRC develops a coherent set of standards, then over time regulatory bodies in the various countries might adopt those. Instead of trying to find a solution that works for all the different systems that are in place now we should work to define a new system. You need people that are playing by the same rules.

The group discussed the idea of drafting a document from the one-line summaries that we've mentioned here that states the challenges, advantages and disadvantages. Why we think this is best for what is achievable in the near term?

To do it right in diagnostics, you have to come back to phenotype and gene discovery; QC also includes education and standards; the way we've been solving things in other fields is by defining what's normal, and then automatically defining what is aberrant. The group agreed that the normal genome is a good reference point. It's an interesting and valid goal for this consortium to try and define as well as we can—knowing that ultimately the goal is not really achievable—the normal genome. That's the only way to identify anything as abnormal.

The group discussed who would support the working groups. Who will coordinate the logistics? It's not clear at this point, but more information should be forthcoming after the contract negotiations for the support contract. The IRDiRC EC has said that the Committee should assemble the working groups and plan the next consortium meeting in February 2013.

There was a discussion about whether or not we should talk to BGI about participating in the program. The major concern is that they don't release data in every case, and anyone that joins the program or participates in a working group needs to accept the IRDiRC model. That said, it would be worth it to have a discussion with them. After some discussions with individuals from BGI since last October, it does not seem that data release issue can be resolved. But, because they are so visible in Asia, and they have access to such large groups of sequenced samples, we should try one more time to talk to them.

8. Working Group Members

Do working group members have to agree to IRDiRC policies? Do they have to be members of IRDiRC? They don't have to be members, and it's not clear if they have to adhere to IRDiRC policies. The group

agreed that for the working groups we should select the best individuals to do the job that would be good team players and would make this work. For that to happen, they'd have to represent the community. There was a lot of discussion about populating the working groups today, but it's difficult to assign people that don't know about IRDiRC, and it'd hard to know if potential members have time to serve on a working group. The group agreed to define a core group of members for each of the working groups now, and add others after we establish goals for the groups. At least one Committee member will be on each working group.

9. Committee Chairs

Drs. Bamshad, Boycott and Brunner agreed to co-chair the IRDiRC

10. Next Steps

- Review the Policy and Guidelines document and find appropriate places in the document to modify or insert information that pertains to what we've discussed today. It's possible that we'll have to suggest ways to re-organize document so our information fits.
- After the revision of the Policy and Guidelines document, send it to Committee members for review, and they will provide feedback by email. Essentially, this will be our way of developing a plan for our working groups, which we will present to the Executive Committee of the IRDiRC.
- The Committee is charged with developing the agenda for the IRDiRC meeting in Spring 2013, and will organize a morning and afternoon session of our agenda items for the 2 ½ to 3 day meeting. The EC, Scientific Committees and Working Groups will attend the meeting.
- One of the Committee co-chairs should attend the IRDiRC EC meeting in Paris in September 2012. Our major deliverable should be the list of rare diseases.
- Formally, ask the EC who our point(s) of contact on the EC are for the Diagnostics Scientific Committee.