DREAM INN, SANTA CRUZ
DECEMBER 4, 2016:

CIFAR GENETIC NETWORKS AND PERSONALIZED MEDICINE WORKSHOP REPORT

BREAKING RESEARCH BARRIERS

CLINICAL OPPORTUNITIES AND CHALLENGES

THE ROLE OF PUBLIC AND COMMERCIAL INSTITUTIONS
On December 4, 2016, Fellows from CIFAR’s program in Genetic Networks held an introductory workshop with other clinical, academic and industry leaders to explore the challenges and opportunities in integrating genetic interaction based research into the field of personalized medicine. Workshop participants approached the topic from three perspectives: breaking research barriers, clinical challenges and opportunities, and the role of public and commercial institutions in genomic medicine. The following report summarizes the key discussion points raised during the workshop.

SESSION 1: BREAKING RESEARCH BARRIERS

Steve Scherer, CIFAR Fellow, The Hospital for Sick Children
Mike Cherry, Stanford University

SESSION SUMMARY

There is a strong intersection of genomics and clinical medicine. Currently, 70% of all admissions to the Hospital for Sick Kids in Toronto has some form of a genetic disorder and with the accessibility to genomic screening technologies, it is becoming increasingly common to see both genotype and phenotype characteristics in clinical case reports. While genomics has been proving is worth in providing us with new information on diseases, such as clinically relevant variants, challenges still remain.

From a practitioner perspective, the meaning behind the sequence of a patient’s genome is still not well understood and the lack of consistency in how genomic data is captured and reported on across disease types has posed issues in integrating the information into medical records. It is also not common practice within research papers to provide guidance to health care practitioners for how to best use genetic findings, further limiting their integration in the clinic. From a technical perspective, whole genome sequencing, while advantageous in many respects, still has a number of drawbacks including lack of suitable control data, poor affordable cloud storage and computation fees, and the need to use other technologies to extract additional genomic data (e.g. deletions, duplications, etc.) in order to get a comprehensive picture of the disease state needed to explain a particular phenotype.

It was highlighted that the standardization process by which genomic data is captured and described in the literature is a critical issue, particularly considering the work by international and cross institute collaborations (e.g. Personal Genome Project Canada). Canada’s Genomics Enterprise, a national genomic tools network for life science research, was mentioned as an organization starting to take steps towards addressing this standardization need.

The need to make genomic sequence information publically available, such as through cloud-based databases, was also seen as an important step towards greater uptake and accessibility of the data by research and clinical communities. The MSSNG project, an effort to sequence the genomes of 10,000 individuals with a family history of autism, was one example of a project using such data-sharing practices. It was also highlighted though that these databases, particularly those developed by the academic community, need to be developed in a manner that is relevant to needs of clinicians in order to best support the clinical evaluation of a phenotype in light of other clinical data.

This effective coupling of genetic and clinical data was seen as essential component for advancing the field of personalized medicine particularly in relation to medical management, the development of care pathways and pharmacological intervention. Enabling opportunities for collaboration amongst physicians and scientists was viewed as an additional mechanism for fostering this genetic and clinical data integration.

Standardization was again raised as a core need by the academic and clinical sectors. The Gene Ontology (GO) project, a cross model organism database that helps connect model organism data to human disease, was noted as an industry best practices as all gene annotations are cited in a common language.
Other databases such as the Encode project and Regulome are also taking steps to standardize how data is curated and annotated to create uniform queries. Another database discussed was ClinGen (Clinical Genome Resource) given that it is working in an evidence-based fashion, using clinical data and published data supporting the role for genes and gene variants in disease, to standardize its database to improve variant interpretation and help better inform clinical decision making. It was noted that many commercial clinical labs could also benefit from such an approach to aid not only in the reproducibility of research but also to better inform clinical management of disease.

The session closed with a call for the development of a gene variant database that would describe variants for which we currently know the function of but for which have not been seen in the clinic. Linking such a database to other functional and clinical databases would improve the ability of gaining a systems level view of a given gene.

SESSION 2: CLINICAL OPPORTUNITIES AND CHALLENGES

Rahul Deo, University of California, San Francisco
June Carroll, University of Toronto

SESSION SUMMARY

Genomics is gradually being integrated into primary care however the sector is experiencing the “building the bridge as we walk on it” issue. This is because not all primary care physicians have a uniform level of understanding of its importance and limitations or in their degree of integrating such data into their practice. The strongest level of integration has been seen by physicians in hospitals, where the majority of genetic testing occurs, and particularly by pediatricians given new born screening procedures. This too has created a skewed view of its relevance or value to medicine more broadly. However, family physicians are increasingly being exposed to genomic data, particularly with the advent of whole genome screening, as prenatal screens reveal secondary findings (i.e. findings that do not relate to the diagnosis) that then must be addressed.

It was highlighted that another issue emerging for physicians is direct to consumer genetic testing provided by private companies. Here, consumers are provided with genetic data, much of which physicians are ill-equipped to address, either due to lack of literature related to the findings or lack of genomic education and training on how to interpret the results. Filling such gaps could better inform the genotype-phenotype connection.

The need for tools to understand the role of gene variants in human disease was highlighted through a case study on inherited cardiomyopathy. As a condition in which a number of genes have already been attributed, the role of variants in the disease however is currently not well understood. This knowledge is necessary particularly given the role of pleiotropy, in which a mutation in one gene can have functional effects in multiple genetic diseases. It was noted that more data is needed to effectively and accurately interpret variant data and that perhaps a patient’s own phenotype data could be used in this regard.

Despite these challenges, a number of opportunities were presented that would create a stronger integration of genomics into primary care. Among them included having researchers generate evidence of the utility of genomics in medicine beyond prenatal or breast cancer screening, conduct pilot projects with primary care physicians, sit on expert panels evaluating the application of genomics in primary care practice, and develop primary care guidelines based on best evidence. Enhanced genetics training amongst primary care physicians was also noted as an area for greater attention. GEC-KO, the Genetics Education Canada Knowledge Organization, was cited as one tool that is helping address this knowledge gap.
SESSION 3: THE ROLE OF PUBLIC AND COMMERCIAL INSTITUTIONS

Michael Paterson, Institute for Clinical Evaluative Sciences
James Lu, Helix
Robert Nussbaum, Invitae

SESSION SUMMARY

The lack of integration of genomic data and clinical decision support into medical records was raised as a limiting factor for advancing the field of personalized medicine. For example, in Ontario, the Institute for Clinical Evaluative Sciences, which collects data linked to an individual’s Ontario Health Insurance Plan number (e.g., medical visits, prescriptions, etc.), has the power to perform long-term population-based studies. However, the lack of clinical detail as well as lab-based data associated with these findings has hindered a more comprehensive understanding of clinical findings. It was recommended that approaches to integrate genomic results and clinical decision support be done in a manner in which the data is primary care physician friendly.

A picture of the broader applications and implications of genomic data was also illustrated by case studies on Helix, a personal genome company, and Invitae, a diagnostic company. As noted previously, concerns were raised about how the increase volume of data generated by direct consumer genome sequencing would impact primary care including the need for secondary testing and the associated costs. This issue further illustrated the sentiment for enhanced education and awareness amongst physicians. Comments were also made on how genomic testing provided by companies needs to have clinical validity, clinical utility, analytical validity and address social, legal and ethical implications.

DISCUSSION SUMMARY

Following the plenary talks, discussions focused around three core themes for how to advance the integration of genetic interaction-based research into the field of personalized medicine: potential research opportunities for the Genetic Networks program and the larger community doing fundamental research, the integration of research data into the medical system, and opportunities for breaking down silos between academia, industry and the health care sector.

From a research perspective, it was clear that there is still a need to better understand functional data and to generate and catalogue the data in a standardized fashion. Using model organisms as in vitro platforms for understanding gene function was noted as a core activity that should continue and data resulting from such studies should be integrated, where relevant, into other commonly used databases. Comments were also made about the critical need to raise awareness of related genes and functional variants identified through genetic interaction studies. Discussion also centered around complex traits and the need to better understand how specific gene variants function in combination to generate or increase the risk of presenting with a disease.

Creating opportunities to ensure genetic-based data is transferred into the hands of those that can use the data to better inform their own decision making, such as the medical community, was also a primary topic of discussion. Participants cautioned however that communications to the medical community, and public more broadly, be positioned in a way to not over promise what genomic medicine can provide, ensuring clear messaging about what the field has to offer and what the limitations are. It was noted that it is not just providing access to data that is a necessity but also doing so in a manner in which it is understandable and useful to a physician. Developing decision supports for a physician and providing information that a clinical lab can use to better understand variants were two suggestions provided that could help address these concerns.
Discussions also centered around how to break down silos between the academic, medical and business communities. It was recognized that using model organisms to develop a fundamental understanding of the pathways and genetic interactions that contribute to the development of disease needs to now feed into studies to explore the effects in human cells and into medical data more broadly. It was noted that work by the Genetic Networks program is already starting to build on program-generated knowledge through yeast studies to map the synthetic lethal interactions in human cells. It was recommended that research also build on some of the work of the program by examining pairwise interactions in non-essential genes as there is a potential to increase the number of targets than can be achieved through studies focusing just on essential genes.

One initiative cited that is supporting the integration of research and practice is the Rare Diseases: Models & Mechanisms Network - a network established to catalyze connections between people discovering new genes in patients with rare diseases, and basic scientists who can analyze equivalent genes and pathways in model organisms. It was suggested to build on this work that a research team be organized to establish full vertical integration across genetic and medical data for a specific disease as a proof of concept for medical genomics.

Participants continued emphasized the critical need to expand research exploring the impact of genetic interactions in human cells given that pairs of genes can drive 10 fold changes in phenotype than a single gene on its own, particularly for complex traits. Using priors from yeast genetics to find pathways that are enriched in genetic interactions to cause a phenotype and doing so in unbiased ways in human populations was a recommended approach.

In closing, participants explored the idea of holding a follow-on workshop and which voices would need to be at the table. Suggestions included economists, researchers exploring machine learning approaches for clinical validation of genetic variants, and pharmaceutical company representatives specialized in target identification, rare diseases and Mendelian disorders. It was also suggested that a future workshop include case studies showing the impact of data integration on our understanding of human disease.

**APPENDIX 1: WORKSHOP PARTICIPANTS**

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<tr>
<th>Name</th>
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<td>Charles Boone</td>
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<td>June Carroll</td>
<td>University of Toronto</td>
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<td>Mike Cherry</td>
<td>Stanford University</td>
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<td>Amy Cook</td>
<td>CIFAR</td>
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<td>Michael Costanzo</td>
<td>University of Toronto</td>
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<td>Rahul C Deo</td>
<td>UCSF</td>
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<td>Rebecca Finlay</td>
<td>CIFAR</td>
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<td>Douglas Fowler</td>
<td>University of Washington</td>
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<td>Sharon Hainey</td>
<td>CIFAR</td>
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<td>Sriram Kosuri</td>
<td>UCLA</td>
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<td>James Lu</td>
<td>Helix</td>
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<td>Jennifer McKelvie</td>
<td>CIFAR</td>
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<td>Chad Myers</td>
<td>University of Minnesota</td>
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<td>Robert L Nussbaum</td>
<td>Invitae</td>
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<td>Aimee Park</td>
<td>CIFAR</td>
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<tr>
<td>Michael Paterson</td>
<td>Institute for Clinical Evaluative Sciences (ICES)</td>
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<td>Jasper Rine</td>
<td>UC Berkeley</td>
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<td>Frederick Roth</td>
<td>University of Toronto</td>
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<tr>
<td>Stephen W Scherer</td>
<td>Hospital for Sick Children</td>
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<td>Joshua M Stuart</td>
<td>UC Santa Cruz</td>
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APPENDIX 2: AGENDA

CIFAR Genetic Networks: Personalized Medicine Workshop  
Sunday December 4, 2016  
Dream Inn, Santa Cruz, 175 W Cliff Dr Santa Cruz, CA. (831.200.4466)

AGENDA

8:00-9:00  Breakfast - Beach View Room

INTRODUCTION TO WORKSHOP - SURF VIEW ROOM
9:00-9:15  Fritz Roth

SESSION 1 – BREAKING RESEARCH BARRIERS
9:15-9:45  Steve Scherer
9:45-10:15  Mike Cherry
10:15-10:45  David Botstein
10:45-11:05  Coffee Break - Surf View Room

SESSION 2 - CLINICAL OPPORTUNITIES AND CHALLENGES
11:05-11:35  Rahul Deo
11:35-12:05  June Carroll
12:05-1:25  Working Lunch with discussion of research elements missing

SESSION 3 - THE ROLE OF PUBLIC AND COMMERCIAL INSTITUTIONS
1:25-1:55  Michael Paterson
1:55-2:25  James Lu
2:25-2:55  Robert Nussbaum
2:55-3:15  Coffee Break - Surf View Room

SESSION 4 – DISCUSSION
3:15-4:00  How can we limit dangers of personalized genomic medicine?
4:05-4:45  Breaking barriers between research/clinical/commercial services
4:45  Adjourn