

MEETING REPORT

The future of genomic medicine is here

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Abstract

A report on the 6th annual Future of Genomic Medicine conference, held at the Scripps Seaside Forum, La Jolla, CA, USA, March 7-8, 2013.

On his flight over to San Diego to lead the Future of Genomic Medicine (FoGM) conference, Dr Eric Topol (Scripps Translational Science Institute, USA) used a heart monitor device attached to his smartphone to diagnose a distressed passenger with atrial fibrillation. Already, mobile technologies such as this one are beginning to transform medicine, and genome sequencing, with its rapidly decreasing costs, is no exception. As we get closer to mini-sequencers and what George Church (Harvard Medical School, USA) termed 'wearable sequencing,' a future of genomically informed medicine becomes possible. The FoGM conference integrated the patient-oriented perspective of genomic medicine, along with cutting-edge technologies and data integration, and developing methods and models in the aim of clinical utility.

Patient-oriented genomic medicine

It is becoming increasingly clear, at this and other conferences, such as the Cold Spring Harbor Personal Genomes meetings, that genomics can have a profound role in guiding diagnoses and treatments. A major theme of this year's conference was the patient perspective and their reaction to having their genome sequenced in a clinical setting. The conference started with a direct perspective from the parents of Lilly Grossman, a patient with a lifelong undiagnosed disease, marked by tremors and sleepless nights. After having her full genome sequenced by the Idiopathic Diseases of Man (IDIOM) study, led by Topol, mutations in *ADCY5* and *DOCK3* were able to

putatively explain her phenotype, and suggest a possible treatment, which provided a few weeks of regular sleep. While the result was not a conclusive answer, it provided hope for the patient and her family. Howard Jacob (Medical College of Wisconsin, USA) agreed, stressing that even in the absence of clinical utility (if a diagnosis is not actionable), the personal utility of having a diagnosis is important to the patient and the patient's family. Jacob suggested a consumer-driven economy for personal genomics, and that even though variants and annotations are subject to change as technologies and interpretations improve, involving patients in the process can be an effective way to deal with these changes. Misha Angrist (Duke University, USA) mirrored these sentiments, drawing parallels to open-access publishing: subjects should have the right to their own data and to see results of the studies that use their data. Randy Scott (Invitae, USA) outlined his and Invitae's mission of bringing genetics to the masses by building databases and infrastructure for managing genetic information. The books that were handed out to participants reflected this mission, between AJ Jacob's *Drop Dead Healthy*, a foray into taking control of one's health, as well as the book by myself (Konrad Karczewski, Stanford University, USA) and Joel Dudley (Mount Sinai School of Medicine, USA): *Exploring Personal Genomics*, a handbook to understanding and interpreting personal genetic data.

While much of these opinions on patient perspectives were anecdotal, Cinnamon Bloss (Scripps Translational Science Institute, USA) presented hard data on the perceptions of both patients and physicians, and the differences therein, through surveys of families. Parents of patients and their doctor agreed that the doctor was knowledgeable about genetics, but the parents were much less satisfied with the doctor's explanations of the results. However, Bloss noted that the majority of patients, parents and physicians were interested in receiving secondary findings, regardless of age of onset or actionability and desire for these results increased with actionability for all three groups.

Going beyond SNPs

Another major scientific theme of FoGM this year involved the expansion past somatic variants (SNPs) to other technologies that could be integrated to inform

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diagnosis and treatment. In addition to getting his genome sequenced, Michael Snyder (Stanford University, USA) tracked a number of omics technologies over time, including his transcriptome, proteome and metabolome, and used this information to track the onset of diabetes concurrent with infection. Since every patient is unique, an 'N of 1' study, followed longitudinally over time, provided him with interesting observations of altered physiological states (such as infection) compared with his healthy state.

While Snyder's analysis was aimed at comprehensive profiling of a healthy individual, Elaine Mardis (Washington University in St Louis, USA) suggested a similar approach for cancers, where sequencing RNAs in addition to DNA would inform predictions of peptides binding with HLA class I. Such an analysis would prioritize antigens that could then be used for personalized immunotherapy. Eric Schadt (Mount Sinai School of Medicine, USA) used similar data types to discover personal cancer drivers and create patient-specific networks that could suggest personalized cancer treatments.

George Weinstock (Washington University in St Louis, USA) and Michael Eisen (University of California, Davis, USA) both brought the microbiome into the mix. Weinstock described efforts to sequence neonatal microbiomes to predict antimicrobial resistance, and discussed a future of fecal transplants and microbiome-based acne treatments. Eisen shared the optimism that the microbiome will become important for human phenotypes, but cautioned against overselling and being careful between correlation and causation, which becomes difficult for large numbers of hypotheses whose outcomes may be linked to their causes. Additionally, we already have a high demand for genetic counselors, but additional data types may bring similar demands, as Eisen called for microbiome counselors.

Scaling up and towards unified models

Finally, a conference of this nature would not be complete without a call to arms for developing methods and models that will ultimately enable physicians to use genomic information in a clinical setting. Daniel MacArthur (Massachusetts General Hospital, USA) cautioned that consistent calling of exomes and genomes is of utmost importance for variant accuracy. He laid out the challenges for scaling up to variant calling of more than 26,000 exomes, but presented one solution in reduced

BAMs, a compressed format, that then can be used for joint variant calling to increase accuracy. From this dataset, MacArthur was able to catalog tolerated protein-coding variation. David Goldstein (Duke University, USA) used such tolerated variants to identify genes that were likely to be functional and focused on these to narrow genetic factors for epileptic encephalopathy.

Peter Visscher (University of Queensland, Australia) described models for predicting complex traits from genotype, which will become increasingly important for sequencing of healthy individuals and prioritization of disease risks. Atul Butte (Stanford University, USA) brought this message back to the clinic, using likelihood ratios, which doctors already use, to combine variant risk information into a unified risk factor. While six gigabytes of genetic data may seem overwhelming at first, Butte reminds us that there is a specialty that routinely analyzes gigabyte scale data: the radiologist. All that are needed are the proper tools.

Conclusions

The consensus among speakers at FoGM this year was clear: the genome has an important role in the clinic. With the price of sequencing dropping to costs amenable to regular clinical use, the question now is not if, but how, genomic information will be integrated. There is a coming onslaught of 'big data' that will improve individual healthcare and enable genomic personalized medicine. Challenges still remain, including establishing a patient-centric view of genomic data, which is tied to educating the public and encouraging participation in personal health, as well as standardizing models to most accurately identify causal variation and portray disease risk. As these and new challenges arise, it will take a concerted effort of physicians and scientists to bring forth a future of genomic medicine.

Abbreviations

BAM, Binary Sequence Alignment Map; FoGM, Future of Genomic Medicine; HLA, human leukocyte antigen; SNP, single nucleotide polymorphism.

Competing interests

The author declares that he has no competing interests.

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