ADVANCING PRECISION MEDICINE

Francesca Lake explores the latest goings on in techniques advancing precision medicine

Precision medicine is arguably 'the next big thing' in modern medicine. Various initiatives have been launched and have gathered huge steam and funding in a bid to allow precise medical treatments that will in turn increase treatment success and decrease money lost owing to failures. To name a few, there is the 'Precision Medicine Initiative' (renamed All of Us), announced by Barack Obama in his 2015 State of the Union Address [1], and the 100,000 Genomes Project, announced by then-UK Prime Minister David Cameron in 2013, which focused on sequencing the genomes of patients with rare diseases and their families, and those with cancer, in a bid to improve scientific understanding and thus bring about new medical insights [2]. Funding has, of course, followed and a huge amount of research has been conducted, or is currently underway.

The *BioTechniques* Advancing Precision Medicine virtual symposium was a free-to-attend online event held over 13 and 14 November 2019 that saw a variety of experts discuss the latest in laboratory research, which is helping to drive the development of precision medicine approaches and their adoption into the clinic [3]. The meeting covered a variety of aspects including genomics, big data, microbiomics, wearables and more.

DIVING INTO THE ALL OF US RESEARCH PROGRAM

Stephanie Devaney, Deputy Director of the All of Us Research Program, gave the plenary talk discussing the work accomplished by the program thus far and what is yet to be achieved. Of the participants, 80% are from groups under-represented in biomedical research, a result of All of Us focusing on these groups.

Some particularly interesting aspects of the All of Us Research Program include the emphasis on 'participants as partners', ensuring those providing the data know what data are being collected, what analysis and research will be performed, and how data will be returned to them.

"Traditionally in research studies, going back decades, we have talked about research participants as human subjects," Devaney noted. "We have decided that it really needs to be a bi-directional relationship, in that in order for participants to really want to stay

engaged in this study for as many years as we're asking them to, there needs to be some sort of give back to participants."

Another interesting aspect discussed was the difficulty in ensuring the data are as widely available as possible in order to maximize innovation whilst also protecting the participants.

HIDDEN IN THE GENOME

Our genomics session was begun by Elaine Mardis (The Ohio State University College of Medicine, OH, USA) and focused primarily on oncology. Since Janet Rowley first proved that cancer is a genetic disease(s) in the 1970s and the human genome reference sequence was created, strides have been made in understanding the relationship between genetic variants and cancer, and what that means for healthcare (Figure 1).

What's more, in the last 15 years or so we've moved from capillary technology to next-generation sequencing and, as a result, the cost of sequencing has plummeted from millions to just \$1000 per genome and the time taken has reduced from years to hours. "Of course, all of this high throughput is a great thing, but we really need computational pipelines to be able to tease apart the information that we have and to make sense of it in the context of the individual patient," Mardis noted.

Mardis went on to discuss the particularly tricky example of pediatric cancers. These are often difficult to study owing to their rarity, the increased ethical complications and difficulties in translating adult-approved drugs to children. Essentially, this leads to an 'N of one'.

However, now that some of the differences and similarities between pediatric and adult cancer are better understood, Mardis' team is building a system for cancer next-generation sequencing diagnostics in pediatrics. "We really have benefited incredibly in oncology from the use and development of large-scale resources coming out of cancer discovery," she concluded. "In pediatric cancer we have a little bit more of a difficult path... because of the different nature of genomic drivers in this disease, we're really benefitting from a combination of both DNA and RNA sequencing data and multiple analytical approaches."

Figure 1. A look at the advances in genome sequencing, as presented by Elaine Mardis.

John Quackenbush (Harvard TH Chan School of Public Health, MA, USA) spoke next, looking at the interesting approach of exploring cancer using network medicine. His research centers around the core ideas that biological systems are driven by complex networks, and that network structure is important to understanding system biology. Differentially expressed genes are controlled by regulatory networks, and his group works to develop methods to analyze and compare network topology. “By comparing network topology between healthy and diseased populations what we can start to get a handle on is not just what genes are differentially expressed, but what processes may regulate that differential expression”, he noted. This leads to an understanding of what genes are differentially expressed as well as the how and the why.

This has led to the development of ‘The Methodological Zoo’, a group of models and methods useful for different sets of data that can be gleaned from various experiments and which are named after animals, such as PANDA and CONDOR. He then went on to discuss CONDOR and eQTL analysis in more detail.

Finalizing the genomics session, Jun J Yang (St. Jude Children’s Research Hospital, TN, USA) discussed pharmacogenetics for drug response; specifically how bioinformatics are generally poor at predicting response while high-throughput functional genomics can be extremely powerful. He illustrated this with the case study of *NUDT15* and Thiopurine, where modern techniques allowed a tenfold speed up of discovery to implementation, taking 2 years and 6 months for *NUDT15* compared with *TPMT*, which took 21 years. “This is a particularly exciting time for pharmacogenetics because you can make genetic discovery and transfer that into clinical practice at a really amazing pace,” he noted.

UNDERSTANDING HOST–PATHOGEN & HOST–ENVIRONMENT INTERACTIONS

Rob Knight (UC San Diego, CA, USA) discussed the 3D mapping of microbes and molecules. The human body is, in some ways, more microbe than human – we have around 30 trillion human cells, but 39 trillion microbial cells. This is even starker at the DNA level – for our 20,000, we have an estimated 2–20 million microbial genes. Knight discussed how we are seeing our microbiome diversity deplete, however, while we’re also seeing a rise in some diseases. And that’s not just a coincidence. Knight highlighted how with human DNA you can only classify someone as lean or obese with 57%

accuracy, but with the genes of your microbiome that rises to 90%. His team is now studying environmental bacteria, which are key for both climate and health. One striking example of this is the correlation of Kawasaki disease incidence with wind direction [4]. “The conjecture here is that dust from a particular region of China is carrying with it the causative pathogen of Kawasaki disease,” he noted. He is now working with Jane Burns’ group at UC San Diego to match up microbes in clouds with those on an afflicted child’s fingertips and airways to see if they can identify the particular causative agent.

He’s also now working on water. “Almost nothing is known about how the microbes in the oceans might be getting into the atmosphere and affecting climate,” he explained. “Are those good or bad microbes preferentially? And do they lead to any health impacts?”

The sheer size of the outputs of this research then led to further discussion of big data, which was also a key theme of our next speaker, Michael Snyder (Stanford University, CA, USA). Snyder’s talk highlighted how the current way we do medicine is somewhat flawed, being reactive and based on population-based measurements. However, most ‘healthy’ measurements are really an average of a range, and what is healthy for some might not be for others. His group has been employing various wearables and technologies to perform ‘personal omics profiling’, following a cohort of around 109 people for approximately 6.5 years. “In its most deluxe form we’ll measure 13 or 14 different -omes in people. The genome is just one; we’ll measure all these other -omes as well.” This includes the epigenome, transcriptome, proteome, cytokines, metabolome, lipidome, autoantibody-ome and microbiome (Figure 2).

“We’re literally taking billions of measurements from people,” he continued. “The goal is to try and understand, what does it mean to be healthy? What does the health state look like? How does it differ between different people? How does it change over time?” But where will this lead? “I see a world where people will be getting sequenced before they’re born,” he concluded. “And then together with other deep data profiling, omics of various sorts, as well as wearables, you’ll be able to better predict people’s disease risk, catch disease earlier and treat it before it becomes symptomatic.”

CELLS AS MODELS

David Tuveson (Cold Spring Harbor Laboratory, NY, USA) discussed how organoids are being harnessed for the study of pancreatic cancer. Affecting around 300,000 patients a year in the Western world, it has a low survival rate, with 9% living 5 years [5]. Early diagnosis is problematic, treatment options are limited and often patients are too sick to try a second treatment, so a further understanding of the disease is critical to choose the right first treatment and improve survival. His team has created organoids from pancreatic cancers, metastases and healthy tissues, determining protein and gene signatures, using whole-genome sequencing to compare the models to the primary tumor and performing ‘pharmacotyping’. The different samples have demonstrated a huge level of disparity in drug sensitivities. “This was quite surprising to me, that humans would be this different,” he noted. “We don’t actually measure the amount of chemotherapy that’s in the body of a person when we give it to them. We just give it to them based upon parameters that are set up to limit toxicity, and don’t really study efficacy

in the cancer.” His team is now looking to stratify patients based on organoid signatures.

The organoid theme was continued by Sylvia Boj from Hubrecht Organoid Technology (Utrecht, The Netherlands), who spoke about a new organoid model for cystic fibrosis. “We believe that with this *in vitro* model, we are able to bring patients back to the bench, into preclinical drug development, in order to improve and change the way that until now drugs have been developed,” she highlighted. Her team can now generate organoids from almost any patient, characterizing and stratifying them in a bid to improve treatment.

James Clinton (ATCC, VA, USA) completed the session, discussing next-generation cancer models as part of the Human Cancer Models Initiative [6]. “Cancer cell lines for many specific tissues – pancreas and liver, for example – are really underrepresented,” he highlighted. “I think there’s also increasing realization that many lines have been mis-identified or have been in culture for so long... there’s really no telling how they compare to the original tumor.” He also noted how heterogeneity is missing from existing cell lines, as well as patient history and the lack of relevancy caused by 2D models. The Human Cancer Models Initiative is seeking to change this, and Clinton took us through their goals.

TRANSLATIONAL RESEARCH

For our final session, Heidi Rehm (The Broad Institute, MA, USA) began by discussing a variety of projects that are looking to translate basic research into the clinic, including MedSeq, BabySeq and ClinGen. She highlighted that something underlying all these projects is the need for good standards and data-sharing platforms, for example the ClinVar database, Matchmaker Exchange for rare disease data and newer platforms such as AnVIL and Terra, which are intended to support large-scale genomics. “I would argue that for the best outcomes for all patients, we need to share data on a global scale, and critically evaluate evidence as a collective community,” she noted.

She then focused in on ClinGen, a consortium of people sharing data, developing standards and curating knowledge who work with the ClinVar database, which allows ingestion and sharing of variant-level knowledge [7]. This platform goes on to enable the creation of robust gene-testing panels.

Next, Marni Falk (The Children’s Hospital of Philadelphia, PA, USA) zoomed in on precision mitochondrial medicine, a field where there are no proven effective therapies. Again, big data is critical here, and Falk discussed the best way to collect, integrate, interpret and share relevant data, be it from the genome, transcriptome, physiome and so on, and then report that in a way that is understandable to the family and physician. Falk took us through how her team overcomes these issues, using various systems including some that are actually designed for business. She went on to discuss various initiatives aiming to help develop therapeutics for mitochondrial diseases, including the mitochondrial medicine frontier program [8]. “The goals of this are really to have a continual pipeline from early gene discovery, modelling, therapeutic de-risking and developing of companion diagnostics and translational research to enable us to bring this to patients on a regular basis, specific to each patient,” she explained. “[This] requires us to harness our integrated data systems, a clear registry of patient

Figure 2. Longitudinal personal omics profiling, as presented by Michael Snyder.

genetics, phenotypes and their samples for analysis, as well as development of outcome measures and design and performance of trials that will really be representative.”

Finally, George Patrinos (University of Patras, Greece) discussed how pharmacogenomics are “paving the path to genomic medicine”. “More than 50% of the general population and patients carry DNA variants that affect their response to the majority of the most commonly prescribed drugs,” he noted. This can lead to adverse drug reactions which, in the USA, are one of the leading causes of death [9]. He took us through a number of examples of successful translation of genomic understanding to reducing adverse events (and cost) in the clinic, finishing by discussing the U-PGx project, which is implementing pre-emptive pharmacogenomics testing in real-world clinical settings in Europe [10]. He discussed the various technologies and infrastructure required for the project to be successful in achieving its goal of making pharmacogenomics available to every European citizen.

Overall, the meeting was a fascinating and in-depth showcase of the bedside technology that is enabling precision medicine at the bedside, and this tech feature provides only a superficial insight into what was discussed. We encourage readers to visit the event page to watch the full talks [3] and we will look forward to more advances to come!

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