Predictive Genomics in action

A spotlight on Dr. Pui-Yan Kwok and the Taiwan Precision Medicine Initiative

His passion is the human genome, his aim is to harness genetics to better predict common diseases, and his dream is to help people live healthier, better lives. And he works on it every day.

Meet Pui-Yan Kwok, MD/PhD. He's a clinician, a dermatologist, a genome scientist, a University of California San Francisco (UCSF) Henry Bachrach Distinguished Professor, the director of the Institute of Biomedical Science at the Academia Sinica in Taiwan, the recipient of the Human Genome Organization (HUGO) 2020 Chen Award for Distinguished Academic Achievement in Human Genetic and Genomic Research, and the innovator behind the Taiwan Precision Medicine Initiative. Throughout his career he has developed tools and strategies to study human genetics including technologies for long-range mapping and assembly of genomes. He splits his time between California, where he leads a world-renowned genetics laboratory at UCSF, and Taiwan, where he is bringing genetics into clinical practice.

During a career that started in the dawn of the genomics era, Dr. Kwok has been an author/facilitator/innovator/early adopter of large-scale genomic studies. One of his most well-known undertakings was a collaboration between Kaiser Permanente and UCSF, where scientists genotyped more than 100,000 Kaiser Permanente members. To this day, it remains a landmark study and a tremendous resource for translating genomics into clinical care.

Today he is focused on two far-reaching goals: first, how to make precision medicine more precise by increasing the diversity of genomic databases; and second, how to sensibly incorporate genetic information into regular clinical practice. In Dr. Kwok's words, "I am trying to replace disease family history as an assessment of risk with more accurate risk prediction based on one's genetic profile. If researchers have a big enough pool of people with known genetic profiles and clinical outcomes to compare an individual's genetic profile against, a risk prediction model can be created to help tailor health management."

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In July 2018, Dr. Kwok helped launch the Taiwan Precision Medicine Initiative (TPMI), a study that will collect the genetic profiles and comprehensive clinical records of 1 million Taiwanese people, or ~4% of the population, by 2022. This study is a partnership between Academia Sinica, the Taiwan Biobank (TWB), and 13 top medical centers across the country. The initiative aims to create a pharmacogenomics database that will enable medication efficacy, guide safety and dosing (right drug, right dose, right time), incorporate early cancer screening for high-risk individuals, and educate and embolden those at risk to make healthy lifestyle choices. Clinical reports and guidelines will be delivered to participants as they become available—a key innovation of the program. According to the TPMI website, over 100,000 participants have joined the study. In Dr. Kwok's words, "Taiwan is an ideal country to launch a large-scale program given the country's comprehensive health system, years of using electronic health records, and a population of people with a relatively homogeneous genetic background." With the collection of clinical and genetic information, TPMI will establish a rich database that will aid in reducing costs, increasing lifespan and healthspan, and fueling innovative research within the Taiwanese biomedical industry.

The launch of the TPMI initiative is among a surge of national population genomic initiatives all over the globe. These efforts are critical, especially when the overwhelming majority of samples in genomic research studies so far are from people of European ancestry. As of 2016, according to an analysis by Alice B. Popejoy and Stephanie M. Fullerton, 81% of the 35 million samples collected for large-scale genomic studies were from people of Northern European descent. This was an improvement from a 2011 study when the number was as high as 95%.

The importance of improving ethnic diversity of genomic databases beyond primarily people of European descent is exemplified in the Taiwan population and the efforts of TPMI. Dr. Kwok explained that type 2 diabetes in the United States (US) has a phenotype that is vastly different from diabetes in Taiwan. In the US, type 2 diabetes is typically associated with higher body weight, but in Asian countries people with type 2 diabetes are generally thin and eat lower amounts of sugar (compared to the US), indicating there are other factors leading to the disease. In Dr. Kwok's words, "There are really different genetics involved. We may never find the genes but we can identify the high-risk group and profile them."

The same parallel is seen with lung cancer. Dr. Kwok continued, "In Taiwan there are many more women who have lung cancer at a young age who are not smokers. This is very different from the US or European experience. Taiwan women with a family history of lung cancer get low-dose CT scans early. Knowing ahead of time facilitates strategies to detect cancer at an early stage, where surgical resection is curative."

In short, we need more representative baseline genomes across the globe that capture the variant differences within and between populations. Dr. Kwok professed, "When we have a big enough cohort of individuals to compare the genetic profile against, we should be able to identify people at high risk for any disease. However, genetic risk is not everything. We also know there are environmental, developmental, and personal lifestyle influences. We should put them all together. Genetics is not the only thing."

Dr. Kwok also discussed the number of challenges that had to be overcome to launch TPMI. These included funding the project, generating public interest, recruiting participants, sensibly planning for return of results, and making the right technology choice. The latter two topics were a focus of in-depth discussion.

Enabling participants to have access to their interpreted data and information was critical from the onset. Dr. Kwok explained, "People are very eager to get the results back, but we are very conservative. We don't want to give them either false hope or false risk." The information provided back from TPMI could unveil important health information that has both positive and negative implications. Dr. Kwok provided an example of a type of stroke called CADASIL. He explained, "[CADASIL] is not the type of stroke that causes one major catastrophic event but rather these are tiny strokes involving small blood vessels in the brain. For individuals with this diagnosis in Taiwan, 70% have one mutation in the *NOTCH3* gene. That is a huge association, and that particular *NOTCH3* gene mutation is considered the cause of the disease. However, screening of the population found that 1% of the people in Taiwan have that mutation but the vast majority of them (~99%) do not have stroke symptoms, so there is a big discrepancy between the people who have the mutation versus the number of people who actually get the stroke pattern."

The concern then becomes how you inform people without causing undue harm, mental burden, and extra cost to the health system. People get diagnosed with CADASIL after dementia or other stroke symptoms have already taken hold. If caught early, there are inexpensive ways of delaying the onset like early screening and treatment. However, there is a need to match the phenotype to genotype and understand why different people with the same variant profiles can have different outcomes. Fortunately, large-scale genetic studies enable researchers and clinicians to perform in-depth analysis of complex, multifactorial diseases. Dr. Kwok summarized, "The goal is to manage everyone's risk the best we can to prolong a healthy life."

Disease risk isn't the only category of results that will eventually be returned to participants. Personalized pharmacogenomics reports, carrier status for rare disease mutations, blood type, and HLA type will also be delivered. The hope is for participants to use this information as a nudge toward lifestyle adjustments (e.g., exercise, food choices, weight management) and better health management (e.g., screening, well visits, changes in drugs or drug dose).

The first step toward launching TPMI was the construction of a set of reference genomes representing the Taiwanese population. This was done using long-read sequencing and mapping techniques on 154 samples from Taiwanese individuals. Whole-genome sequencing data was obtained from 1,500 people through the work of TWB. The data were combined to generate a set of key markers that represented the genetic makeup of the Han Chinese people as well as markers associated with disease risk, rare genetic disorders, and adverse drug reactions. This information was used to create a custom single-nucleotide polymorphism (SNP) array on the Applied Biosystems™ Axiom™ platform, which was then used for participants of TPMI.

TPMI
台灣精準醫療計畫
Taiwan Precision Medicine Initiative

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When considering technology choices, Dr. Kwok explained, "We required [a genomics] technology that was the most accurate, easily customizable, and cost-effective. And for the lab we needed the easiest protocols to run the workflow." Once these were defined, a custom genotyping option was the clear choice. Dr. Kwok engaged with Thermo Fisher Scientific on their custom Axiom microarray platform. In his words, this platform is a "mature, cost-effective, customizable technology." He continued, "When looking at common diseases there are many genes involved, so sequencing isn't as effective because we are trying to interpret one person's genome against a common disease caused by multiple genes. The need is to leverage the common alleles and focus on risk, not disease-causing mutations." In terms of a specific design content, it was critical to include actionable risk variants with a high allele frequency (~0.5%), mapping SNPs to capture population data to generate polygenic risk scores, and an abundance of copy number variation (CNV) probes across the genome. The design that TPMI used was population-specific given the homogeneous makeup of Taiwan. For countries that have populations of mixed ancestry, a generic array with different ancestral markers may be more useful.

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Given Dr. Kwok's longtime experience with population-scale genotyping studies, he is an expert resource for national initiatives, health systems, and academic research organizations that want to embark on precision medicine initiatives. Regarding technology choices, Dr. Kwok advised that when considering the three aspects of precision medicine—cancer, rare genetic disease diagnosis, and common disease risk—you need to choose the best-suited application. For cancer, sequencing is needed to identify the somatic changes that drive the cancer. Sequencing is also important for rare genetic diseases because you're hunting for rare variants. Common disease is a different scenario. As there are multiple genes involved, it is more fruitful to look at genetic profiles and not individual markers. For common disease, sequencing everyone is costly when a genotyping test can be done at 1/30th of the cost. Instead of sequencing 1,000 people with current technology, you can obtain genetic profiles of 30,000 people by genotyping. It is also important to capture clinical data and pair it with the genotyping information—in Dr. Kwok's words, "You cannot have one without the other."

Dr. Kwok summarized that enough people should be included in the study to capture the diversity of the group. In Taiwan, for example, the genomes of approximately 1,500 people out of a population of 23 million were sequenced to capture the diversity. Then you can design a custom genotyping array and merge it with good clinical data for a large group. Once you have that, then the rest of the population doesn't need clinical data; they just need the genetic profile to match against the database.

Dr. Kwok concluded by describing how TPMI is reimagining health care and improving the lives of the Taiwanese people. From an impact perspective, the intention is to develop disease risk models and work with medical societies to formulate patient care guidelines. Dr. Kwok explained, "I'm envisioning something similar to finding out your BMI [body mass index]. For BMI, you can enter information on a website, and out comes your BMI. We can do the same thing. You have a genetic profile and then you enter your lifestyle information and an algorithm spits out a bunch of scores for you for a range of diseases, and furthermore, guidelines that doctors can follow." He continued, "We are already building this. It is almost like a search engine in the background. Every time a genetic profile is produced, we will put it into the patient's medical records and match up the guidelines. If someone needs to be screened for colon cancer at age 40 rather than 50, the information will be in the medical record so the doctor knows to discuss colon cancer screening earlier because of an increased risk." Pharmacogenomics information and warning labels on pharmaceuticals will also be readily available so the prescribing doctor understands which medicine to use, along with the proper dosage based on genetic background. According to Dr. Kwok, "The doctor doesn't have to explain the mechanisms behind the guidelines, they can just follow the medical society recommendations." Patients will also have access to this information online.

Dr. Kwok's personal hope with TPMI is to find the people who are at high risk for cancer and develop new methods of screening. "If we can move people from stage 3 or 4 to stage 0 or 1 so the cure rate is 95% rather than 30%—that would be a dream come true."

Find out more about Predictive Genomics at
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