Colorado Center for Personalized Medicine Biobank Begins Returning Participant PGx Results

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NEW YORK – Researchers at the Colorado Center for Personalized Medicine's (CCPM) Biobank are collecting patient samples in order to analyze genetic data using SNP microarrays to provide pharmacogenetic (PGx) results.

The CCPM has begun returning PGx test results to program participants, and will eventually deliver disease risk and carrier screening results.

Initially launched as a collaboration between the University of Colorado and the UCHealth system in 2014, the CCPM's Biobank collects genetic samples to learn how differences between individuals can affect health and disease. UC Denver Assistant Professor Kristy Crooks joined the CCPM as director in 2015 and now spearheads sample collection and analysis.

Funded by the University of Colorado and UCHealth, Crooks' lab at UC Denver received CLIA certification in 2017 and has since begun recruiting participants to assess drug metabolism, disease risk, and disease carrier.

Patients interested in the project can sign up through UCHealth's "My Health Connection" online portal, followed by a blood draw at a routine appointment with their clinician. According to Crooks, the UCHealth network covers between 1.5 and 2 million patients.

Since launching the biobank in 2014, the CCPM researchers have registered over 100,000 participants, with 50,000 blood samples stored at UC Denver. Crooks' team plans to register between 300,000 and 500,000 patients as part of the biobank's project.

"The 100,000 have agreed to let us de-identify their health information and study in concert with blood samples," Crooks said. "Of those, 50,000 have had a 4-ml blood tube taken, and we've then genotyped about 32,000 in our clinical lab so far."

Crooks explained that her team uses AutoGen's Flex-Star+ to extract DNA from a patient's blood sample due to its automated, high-volume extraction process. While most clinical labs typically extract a patient's DNA from 100 to 200 µl of blood, Crooks' team wanted to extract up to 4 ml per in order to have as much DNA as possible to perform clinical research.

After DNA extraction, CCPM clinical laboratory staff then genotypes the genetic material on a custom Illumina Infinium Multi-Ethnic Genotyping Array (MEGA) chip. The chip allows Crooks' team to interrogate methylation patterns at the genome-wide level, covering more than 850,000 sites.

"We look at about 2.1 million variants on the chip, but of those variants, clinical content is restricted to about 5,000 that could be impactful for health," Crooks said. She pointed out that a large proportion of the SNPs "are useful for pharmacogenetics, as well as pathogenic

or likely pathogenic risks in Mendelian diseases. We can [therefore] build carrier screening panels, especially for some high value things like BRCA1/BRCA2 variants."

Highlighting that the laboratory has clinically validated 173 variants from the Clinical Pharmacogenetics Implementation Committee's (CPIC) list of Level A variants, Crooks said her team can now create panels that could provide pharmacogenetics results for patients.

In addition, using the ClinVar public database, which aggregates information on genomic variants and their relationship to human health, Crooks' team examined pathogenic and likely pathogenic variants to develop disease risk panels. The team identified 1,718 targeted variants on the chip that are high-risk for genetic diseases, such as cardiomyopathies or inherited cancer syndromes.

However, Crooks explained that her group is still determining the best avenue to return carrier and disease risk results back to patients, as the team wants to minimize patients' anxiety and fears when looking over their own reports.

"We started with PGx because we know that even with a small panel, we could give actionable results in up to 95 percent of our biobank population," Crooks said. "Even though most people will not be prescribed the drug of interest, we could study how that often could impact downstream clinical practice and healthcare savings."

Crooks emphasized that the testing services are free of charge to patients who are curious about their genetic results. For example, the team offers a CYP2C19 PGx test, which identifies specific haplotypes and helps the team interpret the participant's ability to metabolize drugs processed by the CYP2C19 liver enzyme.

After learning about their individual drug responses through PGx testing, patients can then separately speak with their clinicians about the potential drug treatment.

Crooks noted that the major hurdles of the project have involved minimizing opposition from clinical practice and managing the large amount of raw patient data after extracting it from electronic health records and MEGA arrays.

In order to improve program enrollment, Crooks' team has reached out to patients and departments at UC Health hospitals through writing formal letters, holding presentations with representatives explaining the team's goals, and partnering with doctors through committees to listen to their clinical concerns.

"A large part of our work is communication, minimizing rumors that get out there and show people that we're approaching this project conservatively, while staying on the cutting edge of technology," Crooks said. "Physicians are really concerned they might get an unmanageable number of phone calls from concerned participants, but we've taken steps to address those issues by providing FAQs on the website and providing numbers to call about their information."

Crooks pointed out that her team also needed to determine how to maintain and parse through enormous amounts of raw patient data to ensure their phenotypic data matches with genotypic data while preserving confidentiality. The CCPM therefore established the Health Data Compass, an enterprise data management warehouse, in 2014, later transitioning the database to Google Cloud in 2017.

The CCPM researchers anticipate increasing the number of PGx results mailed back to patients in the next few months, having delivered about 1,000 tests since the program's launch. Crooks noted that her group is also implementing clinical decision support and best practice alerts for PGx prescribing practices.

"We want to increase [patient] enrollment at a steady pace, as well as explore releasing not only high-value diagnostic results but also carrier screening," Crooks said. "While we're collecting a couple thousand [of samples] a month, we want to up that, so we're looking at marketing strategies to get additional people to agree to participate in the study."

While CCPM is currently collecting whole blood samples, Crooks envisions adding serum as an additional sample type in 2020 to support biomarker discovery. She believes that her team could also potentially examine a wide range of liquid sample types for research, including buccal and urine samples.