Study applies drug-gene testing to improve patient care

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In a newly published study appearing in *Genetics in Medicine*, investigators from Mayo Clinic and Baylor College of Medicine found that targeted genomic information can play an important role in drug

prescribing practices.

The results from the "Right Drug, Right Dose, Right Time: Using Genomic Data to Individualize Treatment" (RIGHT 10K) study strongly suggest that preemptive testing could benefit nearly every patient at some point, particularly when the testing extends beyond DNA variants already known to influence drug metabolism.

"Genetic differences can affect how a person processes and responds to medications," says Liewei Wang, M.D., Ph.D., the Bernard and Edith Waterman Director of the Pharmacogenomics Program and Director of the Center for Individualized Medicine at the Mayo Clinic. "The right drug matched to a person's genetic makeup may maximize the drug's therapeutic benefit, but the wrong drug or dose may make a medication ineffective or even fatal." Dr. Wang is the co-first author of the study.

The RIGHT 10K study recruited 10,077 long-term Mayo patients and used their stored samples from the Mayo Clinic Biobank to isolate DNA for the study. The Mayo Clinic Biobank is a collection of samples, including blood and blood derivatives, and health information donated by Mayo Clinic patients. Seventy-seven genes known to be involved in drug metabolism or transport were sequenced, with results from 13 genes placed into the patient's electronic health record (EHR), together with an interpretive report and best practice alerts for 21 drug-gene pairs.

"We found that nearly all of the participants could have benefitted from receiving preemptive pharmacogenomics data and the interpretation report, depending on the drugs their clinician might prescribe," says Dr. Wang.

Benefits of implementing preemptive sequence-based

drug-gene testing

Researchers chose to apply targeted DNA sequencing to capture less common genomic variants that could by themselves, or in combination, have significant clinical relevance. The participants' outcomes identified many clinically actionable drug-gene variants and rare unclassified variants in the genomes of every patient.

"If this kind of testing is performed at all, it is generally confined to testing specific DNA nucleotides already known to impact drug efficacy or toxicity. Here, we used a targeted sequencing approach to capture both common, known variants, together with the more numerous, but in most cases, uncharacterized rare variants that may impact drug prescribing practices," says Steve Scherer, Ph.D., a professor in Baylor College of Medicine's Human Genome Sequencing Center and Department of Molecular and Human Genetics. "In time, a number of these rare variants will be reclassified into the 'known' category." Dr. Scherer is a co-first author of the study.

Further key findings include:

- Greater than 99% of study participants carried a clinically actionable variant within the 13 genes written to their EHR.
- 79% had three or more of these variants.
- Each participant, on average, was found to have at least another three predicted harmful rare variants in these genes.

Testing and reporting of predicted phenotypes included two critical but highly polymorphic and complex testing targets: CYP2D6 and the human leukocyte antigen (HLA) region. CYP2D6is involved in the metabolism or processing of up to 25% of all drugs marketed. The HLA region is involved in several of the most severe adverse event episodes observed to date.

Based on the sequencing data, 2,782 clinically actionable eConsults were sent to primary care health care professionals who accepted 54% of the pharmacists' semiurgent eConsult recommendations.

"The research suggested potential benefit if drug-gene data were available at the time medications for those patients were prescribed," says Richard Weinshilboum, M.D., co-corresponding author of the study. "Most of these patients had been on their therapy regimen for some time, so their drug therapy might have already been altered in response to either the occurrence of an adverse reaction or lack of efficacy."

Implementing pharmacogenomics into clinical care

This study is a testament to what can be accomplished by large collaborative efforts, according to Richard Gibbs, Ph.D., Wofford Cain Professor of Molecular and Human Genetics and Director of the Human Genome Sequencing Center at Baylor College of Medicine. Dr. Gibbs is a co-corresponding author of the study.

"Our center has a long history of translating genomic research into clinical application, and together with the Mayo Clinic team, we have shown that pharmacogenomics can be successfully used in clinical care," Dr. Gibbs says.

Dr. Weinshilboum says this study is a steppingstone in developing the foundations necessary to use DNA sequencing in helping to guide clinical care. Key components in the successful implementation of this study included pharmacogenomics education programs for medical staff, information technology support to build and implement the data pipelines and integrate with the EHR, and test reports that were quickly understood by clinicians. According to Richard Sharp, Ph.D., a co-author of the study, it will also be critical to provide genetic education

and support to patients who receive pharmacogenomic results. In a companion study, Dr. Sharp and his team in Biomedical Ethics are examining patient understandings of pharmacogenomic results.

What's ahead for pharmacogenomics?

The researchers state that the future of pharmacogenomics will almost certainly include machine learning-based predictive algorithms that use clinical and genomic information with other data types.

"Pharmacogenomics will extend well beyond genotypes for the small number of genes included in the 21 drug-gene pair alerts we studied," explains Dr. Wang. "I believe pharmacogenomics promises to become a standard component of clinical practice that will help the health care team optimize pharmacotherapies for all patients."

More information: Liewei Wang et al, Implementation of preemptive DNA sequence–based pharmacogenomics testing across a large academic medical center: The Mayo-Baylor RIGHT 10K Study, *Genetics in Medicine* (2022). DOI: 10.1016/j.gim.2022.01.022

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