# GETTING IT RIGHT

## 10,000 people help answer a basic individualized medicine question

https://www.mayoclinic.org/giving-to-mayo-clinic/philanthropy-in-action/features-stories/getting-it-right

The RIGHT Protocol studies the impact of getting patients the right drug at the right dose at the right time based on their genetic information.

Nearly 1 out of every 3 American adults has high blood pressure. About 70 percent of them take medication for their condition, but only half have it under control. Why? The answer gets to the heart of individualized medicine: Because each person has a unique genetic makeup, everyone responds differently to drugs.

In recent years, individualized medicine, sometimes called precision medicine, has made headlines by predicting the possibility an individual may develop a specific disease — think BRCA1 and BRCA2 genetic mutations linked to breast and ovarian cancers.

But that is just the tip of the genomic iceberg, says Richard Weinshilboum, M.D., director of the Mayo Clinic Center for Individualized Medicine's Pharmacogenomics Program and the Mary Lou and John H. Dasburg Professor of Cancer Genomics.

"When you look at the clinical application of genomics, everyone thinks of cancer — and this is appropriate, because cancer is a genomic disease," Dr. Weinshilboum says. "However, the aspect of clinical genomics that will affect everyone everywhere is pharmacogenomics," or how anindividual's genetic makeup influences the body's response to medications.

How common are these drug-related genomic variations? A Mayo Clinic study found that 99 percent of participants have a "clinically actionable" genetic variant related to just five genes that affect drug response. This means virtually every participant, depending on future health needs, may be prescribed a medication or typical dosage that, at best, acts as a placebo and, at worst, may cause serious side effects.

## Which drug for which patient?

Known as the RIGHT Protocol (short for the Right Drug, Right Dose, Right Time: Using Genomic Data to Individualize Treatment), the study pre-emptively embeds a patient's genetic information in the electronic health record for future use to see if doing so improves long-term outcomes for both the patient and the health care delivery system at large.

The operative word is "pre-emptively." For example, providers today may prescribe any one of four major drugs to treat high blood pressure: diuretics, angiotensin-converting enzyme inhibitors, beta blockers or calcium channel blockers.

"But which drug for which patient?" Dr. Weinshilboum asks. "What we find in high blood pressure is that there's this constant churning in the system before a patient finds the right drug and dose. If we knew at the very beginning who is going to respond to which drug, that would have major financial and health care implications."

In the RIGHT Protocol's initial phase, researchers from the Center for Individualized Medicine sequenced DNA from more than 1,000 Mayo Clinic Biobank participants who also receive primary care at Mayo Clinic. They screened for variants in 84 genes known to influence drug response and embedded information for five genes known to have clinical utility in each patient's electronic health record.

Clinicians treating patients in the study can act on this information with the help of a pharmacogenomic "drug-gene pair" alert system developed by the Mayo Clinic Pharmacogenomics Task Force in partnership with Mayo's Office of Information Knowledge Management. If the clinician prescribes one of 17 drugs — including some blood thinners, antidepressants, cancer therapies and pain medications, among others — the system automatically searches the electronic health record for the patient's genetic information. If it finds an actionable variant, the system displays an alert recommending the clinician consider changing the dosage or drug due to the likelihood of toxicity or lack of drug effect.

"We are really pioneers here," says Suzette J. Bielinski, Ph.D., a genetic epidemiologist and principal investigator of the RIGHT Protocol.

"Until now, pharmacogenomics has been isolated to specialty clinics — HIV, oncology and transplant to name a few. Specialists in these areas deal with therapies on a daily basis that have severe, sometimes deadly side effects, so patients almost always undergo genetic testing before taking the drug. We call this genotyping by indication.

"But in the RIGHT Protocol, what we want to know is how does pre-emptively genotyping patients regardless of their health status impact routine care and what hurdles exist that affect implementation."

## Big picture, bigger sample size

Having developed and tested its systems with the initial 1,000 study participants, researchers are expanding the RIGHT Protocol to 10,000 Mayo Clinic Biobank participants. A sample size of this magnitude will help researchers answer the ultimate, big-picture question: "Does any of this make a difference?"

The Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery is partnering with the Center for Individualized Medicine to help answer that question. The science of health care delivery is a field that combines quantitative and qualitative research methodologies with sophisticated data analysis to define best practices that yield the highest value.

"This is a new enough area that no one really knows if you implement pharmacogenomics widely across the United States, will it be cost-effective?" says Jennifer St. Sauver, Ph.D. She is the epidemiologist guiding this aspect of the RIGHT Protocol and works in the center's Population Health Sciences Program. "Is it worth genotyping all of these patients? Is it possible to integrate into the clinical practice and train clinicians? All of this requires a pretty significant upfront investment in infrastructure."

But in certain cases, it could pay dividends in better long-term outcomes, she says. For patients with high blood pressure, what if getting the right drug and dose the first time lowered the national incidence of stroke, heart attack, kidney failure and other costly conditions? Prevented emergency room visits and hospitalizations? Reduced missed days of work related to health complications?

"There is a tremendous opportunity here," says Dr. Weinshilboum. "The benefits of broadly implementing pharmacogenomics for patients and the health care system need to be tested systematically — and that's what we plan to do."