What does the term “preemptive pharmacogenomics” mean?

Preemptive pharmacogenomics refers to a clinical practice in which patients have their DNA tested for a number of genetic markers up front, whether they are already taking medications associated with a particular marker or whether those medications might be prescribed in the future. The rationale behind this approach is that having a broad panel of markers available early on has a lifetime of value. There is a cost savings in doing this test as a batch, and it removes the major hurdle of delay in receiving pharmacogenomic test results when a specific need arises in the clinic.

In practical terms, a patient provides a blood sample, which is run across the entire panel of markers. The results are available at any time. Whenever a doctor is considering a new medication, he or she can simply enter the information into the patient’s results portal and find out immediately whether the patient’s DNA has any markers indicating the likelihood of a response or other factors that would inform the treatment decision.

Has the delay in getting results thwarted the potential usefulness of pharmacogenomic testing?

We have learned from implementation projects at the University of Chicago and elsewhere that physicians and patients often do not want to wait days or weeks to get pharmacogenomic test results back when a treatment decision needs to be made. Having a preemptive panel available means the testing has already been done. The physician can identify relevant markers instantly, and that information can be immediately factored into the decision-making process.

So ideally, each patient would have a personal database of pharmacogenomic markers?

Yes, that is the approach we have taken at our hospital. We developed a test panel with hundreds of variants that are potentially important to pharmacogenomic-guided prescribing. In the context of a clinical study, the patient submits a DNA sample at the time of trial enrollment. We create a database for the patient so that any time the patient’s physician is considering a new drug, the system can be queried for pharmacogenomic results.

If a patient is taking a drug for treating gastroesophageal reflux disease and the genetic testing results suggest a poor response to a particular medication, the physician can see a list of alternative drugs that might work better for this particular patient. We provide pharmacogenomic alternatives right in the database, which is another valuable aspect of the preemptive approach. With the preemptive database, the physician can choose the right drug the first time. Without this approach, it could take weeks to find out whether a given alternative drug is suitable.

Could you discuss the work you have done exploring this approach at the University of Chicago?

I am the principal investigator of a study called the 1200 Patients Project that was initiated by the Center for Personalized Therapeutics at the University of Chicago. All of the testing is done in a laboratory approved for clinical decision-making, per the standards set by the Clinical
Laboratory Improvement Amendments (CLIA) in 1988. Conducting pharmacogenomic testing in a CLIA environment is essential if the results are to be used in clinical decision-making, rather than solely for research purposes.

All the patients who are enrolled in the study have consented to the protocol, which does have a strong research component. The investigators need to be able to study how decisions are being made, how pharmacogenomics influences decision-making, whether adverse events occurred that were preventable, and whether the pharmacogenomic information prevented any adverse events. We also want to know what patients and physicians think about having this information available. Is it helpful? Is the database too cumbersome? Does it provide enough information to make educated decisions? Does it slow down physicians caring for many patients in a busy clinic? All of these endpoints are part of the study, which is why consent from both patients and physicians is necessary.

The patient and the physician sign up as a pair, and the testing is done at no cost to either person. The fact that patients and physicians sign up together is an important feature of the study. We thought it would lead to joint decision-making, rather than the physician interpreting the information alone. Pharmacogenomic information needs to be interpreted in the context of everything else that the physician knows about the patient, so it made sense for both parties to enroll in the study together.

**H&O** How is the pharmacogenomic information provided to patients and physicians?

**PO** We have a password-protected online portal. Only doctors enrolled in the project can access the information at this point because we need to be sure that the portal is workable and feasible. Right now the pharmacogenomic information is kept separate from a patient’s electronic medical records, but we are working on integrating the two. When there is a clinical need, physicians log on to the portal to view the patient’s test results. All the pharmacogenomic information is there, including all drugs the patient is currently taking. The physician can see any genetic information relevant to these medications or, as noted above, can query the system about any drugs being considered.

**H&O** What has the feedback been from physicians and patients enrolled in the study thus far?

**PO** The study has been ongoing for about 2 years at the University of Chicago. Among the early-adopter physicians in our clinic, the results have been very encouraging. We have found that they are using the portal, and that they return to it. About 85% of enrolled doctors have used the portal repeatedly, and that rate has been sustained over time. The opt-in rate among patients is about 89%, suggesting that they, too, see value in the approach. Currently, there are approximately 1000 patients enrolled in the study, which is very close to our target of 1200.

**H&O** Do you know whether the pharmacogenomic panels have influenced treatment decisions?

**PO** We study every visit that enrolled patients have with their doctors, so that we can determine how useful the information is to their care. We have seen many instances of physicians changing prescriptions based on our system. Medications have been stopped or started based on the genomic results. The study has not had a strong oncology focus thus far, although there are several oncologists enrolled, and therefore most of our observations are in other clinical areas. For example, a physician saw that the specific proton pump inhibitor the patient was taking might not be effective based on the DNA panel. When the physician raised the issue, it turned out that the patient had noticed that the drug was not helping, so a different medication was selected.

**H&O** Will the project be expanded to other institutions?

**PO** The study is just at the University of Chicago right now, but we are in the planning stages with potential partner institutions. The next phase of this work will likely be a multi-institution project.

**H&O** Could you talk about the mechanics of pharmacogenomics? Why would we have genetic variations related to medications?

**PO** Most of the pharmacogenomic markers we have identified in DNA detect variations in metabolism for certain enzymes. Enzymes metabolize drugs in the body, and sometimes a person has a genetic variant that causes a particular enzyme not to work as well as it does in people without that variant. As a result, the enzyme does not metabolize the drug as well as expected in people, leading to toxicity or alternative responses.

Looking at this question from a teleological standpoint—why did we as a species develop variations that make us react differently to drugs?—we do not know for certain why these variations exist. Genetic variation exists in the human race, and many variants influence susceptibility to disease. Some of these same markers also control drug responses.
**H&O** How common are the variants that have been most relevant so far to pharmacogenomics?

**PO** Across the human population, there are outliers—a small percentage of people with markers that are predictive for a certain enzyme working less well. For most pharmacogenomic markers, approximately 5% to 15% of people carry a given variant.

**H&O** What is an example of a marker-medication association?

**PO** There is a marker in DNA that predicts whether an individual will develop myopathy as a side effect of simvastatin, a statin drug used for controlling cholesterol. Myopathy is painful and can result in hospitalization for patients who experience it most severely. Now we have a genetic marker that can indicate what patients are at high risk for this side effect.

**H&O** Do you envision preemptive pharmacogenomics becoming a routine part of health care?

**PO** The field of pharmacogenomics is becoming increasingly recognized as an important component of clinical practice. Physicians have long known that not all patients respond the same to every drug. Some patients respond, and some do not. Some patients experience severe side effects and some do not. If we can predict those responses, we can eliminate the trial-and-error nature of prescribing medication. When we ask physicians why they want to participate in the 1200 Patients Project, the most common response is that they consider the approach to be part of the future of medicine.

Few institutions are using preemptive pharmacogenomics at present as part of routine care. My vision is that 10 years from now, the approach will be commonplace. For many medications, a doctor will not write a prescription without taking into account the patient’s genomic information.

**Suggested Reading**


