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Preemptive pharmacogenomics

Working toward bringing timely, individually tailored, precision health care to patients

When it comes to health care, the right prescriptions not only improve patients’ lives—they sometimes save them. So, when a patient requires a medication, a clinician prefers to prescribe it immediately. But that’s not always possible. About 200 of the drugs approved by the U.S. Food and Drug Administration (FDA) note pharmacogenomic (PGx) information—interactions between a patient’s genes and the medicine they need—that should be considered before prescribing that medication. An example is the cancer drug tamoxifen, the efficacy of which depends on an individual’s liver enzyme activity as determined by their particular genetic makeup. Using preemptive pharmacogenomics (PPGx), clinicians can obtain a patient’s genetic information—on all potential markers, or only those that are informative when prescribing medications—in preparation for future pharmaceutical needs. More important, early genetic testing can support potentially life-threatening decisions about the best drug treatment for a patient. The Clinical Pharmacogenetics Implementation Consortium, in providing guidelines to clinicians on using genetic test results in prescribing, assumes that PPGx implementation will grow. Collecting and analyzing that genetic information requires technology designed for the job, and Thermo Fisher Scientific (Waltham, Massachusetts) and some of its partners are looking forward to fulfilling those needs.

Better and safer

“Genetics can cause a person to respond to a drug in a way that was not intended,” says Scott Megill, president and CEO at Coriell Life Sciences, in Philadelphia, Pennsylvania—a company that partners with Thermo Fisher to provide reporting and interpretation of molecular diagnostics tests. Depending on a patient’s genetic makeup, a drug could provide no therapeutic effect at all or even be unsafe.

Ulrich Broeckel, founder and CEO of RPRD Diagnostics, in Wauwatosa, Wisconsin—another Thermo Fisher partner—explains that PGx testing can be done essentially two ways: when requested, on an as-needed basis; or preemptively, so that if a need arises, the patient’s genetic information is already on file. His company focuses on making PPGx testing more widely available so that physicians have information readily at hand to make the best decision for each patient.

PPGx could benefit many—maybe most—patients. About 50 human genes show a high degree of variation that is correlated with responses to medications, but just knowing that a gene varies does not provide meaningful information. “You can’t say that someone who has a variant will always have a problem with a medicine,” says Philip Empey, associate director for pharmacogenomics at the Institute of Precision Medicine, a collaboration between the University of Pittsburgh and the University of Pittsburgh Medical Center. And it’s more complicated than simply identifying whether a gene varies or not. “With some targets, the number of the genetic variant—the number of copies of that gene—is important,” adds Empey.

As in any area of medicine, more data is better. Making more PPGx data available will improve its overall value to health care. For PPGx purposes, genomic data collected from the individual is stored as an electronic health record. When enough data is collected, it can be utilized to improve health outcomes. For this reason, the University of Pittsburgh plans to do PPGx testing on more than 100,000 patients and track the results. “Only with a large study of preemptive genotyping can we determine its clinical and economic value,” says Empey, who is leading this study.

Easier data acquisition

PPGx data collection and analysis starts with a sample, such as blood, buccal swab, or saliva. Then, the genes from that sample must be analyzed. “When focusing on analyzing a targeted set of pharmacogenomic markers, where a rapid turnaround is important, qPCR—real-time [quantitative] polymerase chain reaction—is the better choice,” says Peter Norster, associate director, global market development, applied healthcare solutions at Thermo Fisher. For example, Megill says his colleagues “build specialized panels, such as for cardiac medications, mood disorders, and even a presurgery test” based on qPCR. This technology also makes it easy to add a gene or a section of a gene to a panel, he notes. Thermo Fisher provides a qPCR research solution for PPGx in their OpenArray platform, although other companies are also in that market space.

However, qPCR is not the best method for analyzing large numbers of genes. “When covering all markers—ones that are relevant

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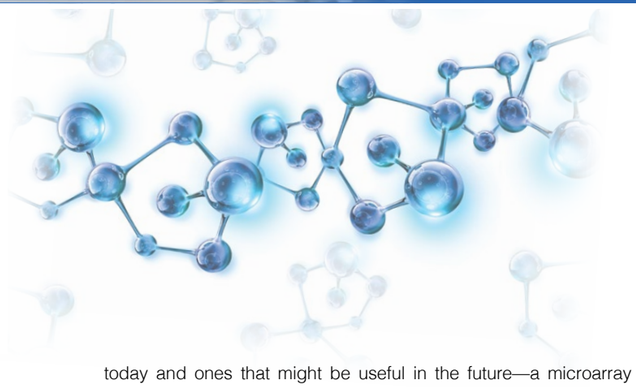

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today and ones that might be useful in the future—a microarray method works better,” says Norster. Working together, RPRD Diagnostics and Thermo Fisher developed the PharmacoScan Solution, which includes the microarray plates and reagents needed for PPGx genotyping. “It covers all of the genes that should be tested,” says Broeckel. PharmacoScan is fully verified and includes highly predictive markers in critical genes such as *CYP2D6*, *CYP2C9*, and *CYP4F2* as well as copy number variation calling. It allows clinical researchers to gain valuable insight into an individual’s ability to process drugs based upon high, moderate, low, or preliminary scientific evidence.

Usable reporting

Collecting the genomic data is only the first step—interpreting the genetic data in a relevant way is also crucial. “You’re looking at targets and placing patients in different categories, such as their ability to metabolize a drug,” says Empey. Most physicians were never taught to interpret a patient’s genetics to predict a drug response. To get the most from existing medicines, genomic data must be combined with medical information, and that need is likely to increase with precision medicine, which aims to find drugs for specific gene targets.

This information can save lives. Megill relates the example of the blood-thinner Plavix (clopidogrel), which is often prescribed after a heart attack or stroke, and is even incorporated into some stents. Nonetheless, 27% of Caucasians and about 50% of Asians poorly metabolize this drug, which makes it significantly less effective for them—all based on variation in one gene that encodes cytochrome P450, a liver enzyme involved in breaking down molecules in the body. With global sales of USD 1.7 billion in 2017, that would be about USD 450 million wasted without PGx testing—and that’s assuming it would fail for only 27% of the general Caucasian population.

Addressing hurdles to PPGx

Given the value of PPGx, it seems likely that it would be frequently applied if more widely available. When asked how often PPGx is used, however, Shannon Manzi, director of the Clinical Pharmacogenomics Service at Boston Children’s Hospital, says, “not often enough.” In fact, preemptive testing is mostly used in very limited circumstances. “Currently, our experience is that outside of a research study or a well-defined standard of care, the vast majority of testing is done after a patient either experiences adverse effects or has a history of nonresponse [to a drug],” says Manzi. So, the first hurdle is that the standard of care isn’t well defined.

The second challenge is that clinicians can’t always access the information as soon as it’s needed. “If the prescriber cannot access the data at the time of prescribing—or in less than 30 minutes—it is not useful,” Manzi explains. “This also applies to the pharmacist at the time of dispensing.” Manzi sees two possible solutions: “Either universal preemptive testing, such as newborn screening—or something real-time—is needed.” Real-time or near-real-time PGx testing is unfortunately not yet possible.

Furthermore, to get the full benefits of PPGx, says Norster, “the information must go into a person’s electronic health record, and that data must be accessible and follow you around,” and be integrated into clinician workflows.

The last challenge is that the entire health care system—including clinicians, patients, and payers—must see the value of PPGx. Experts in the field already see its benefits and envision more in the future. “The key is to raise awareness about the value of preemptive pharmacogenomics,” says Broeckel. In addition, the methods of testing must be easy to use, widely available, and covered by payers. Once all of that is accomplished, every patient’s health record could include the crucial genetic information that would allow faster access to many medications—some of which could be needed at a moment’s notice.

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