From ‘trial and error’ to a targeted approach to medications

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U-M Pharmacy researchers are working to identify genetic variants that impact how individuals metabolize or respond to drugs – which could lead to precise, tailored

treatments

For the most part this is how medicine works: A patient is diagnosed. The doctor recommends a standard treatment. Some patients will do well on that treatment. Other patients will have a hard time managing their condition, or may experience severe side effects. So the doctor picks a new medication to see if that works better. And the cycle continues.

“It’s no different than trial and error,” says Haojie Zhu, Ph.D., associate professor of clinical pharmacy at the University of Michigan College of Pharmacy.

He and colleagues at the College of Pharmacy see a better way. It involves understanding how a patient will likely respond to a drug, based on their DNA, and using that information to select the treatment that’s most likely to work.

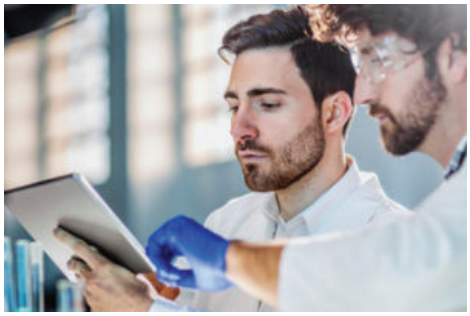
“We want to understand up front what might be the best medication in the hopes it improves efficacy and reduces side effects,” he says.

This approach is called pharmacogenomics: understanding the genetic variants that influence how an individual metabolizes or respond to a drug. Pharmacists hope that discoveries can open the door to testing patients’ DNA and using the results to help guide treatment for diseases such as depression, breast cancer, heart disease, kidney disease and lung injury.

Bringing pharmacists into clinical care

“Discovery has been fruitful in this area,” says Vicki Ellingrod, Pharm.D., John Gideon Searle Professor and associate dean for Research and Graduate Education at the U-M College of Pharmacy. “It’s now time to start putting this into practice. We need to determine the best way to implement this testing. This includes messaging to providers about who to test and how, as well as guidelines for standards of care.”

Ellingrod has started working with family medicine physicians at Michigan Medicine to understand how pharmacogenomic testing could help improve medication adherence and outcomes for



people with depression. Using red flags such as family history can help narrow the number of patients who are tested for variants.

Partnering clinicians with pharmacists will be key to implementing pharmacogenomics testing. Surveys have found that 28 percent of genetic counselors and 13 percent of physicians say they are well-informed and comfortable ordering pharmacogenomic tests. Pharmacists will need to translate the findings and work with clinicians to understand the meaning of a patient's results.

By working with family doctors, Ellingrod hopes that integrating pharmacogenomics into the initial diagnosis will alter the pipeline of patients who need extensive care or who relapse. Not only does this precision approach help target the best drug option, but it might also impact adherence.

"If you tell someone we did a test just for you and we think this drug is going to work best, they might be more likely to take it," Ellingrod says.

Adherence and other issues impact effectiveness

Adherence plays a crucial role in medication and must be considered along with understanding the genetic factors.

"If you don't take your medication, you're not going to get side effects," Ellingrod notes.

"The whole medication use process is complicated. Why someone takes their medication is different for each patient. Some patients will take their medications sporadically, some not at all, some may be taking other drugs they didn't tell their doctor about that might cause interactions," she says.

Even if a patient does take the drug as prescribed, it can be challenging to identify how genetic variants impact drug metabolism among the many other factors that influence how an individual processes a drug – from the disease itself, to the patient's lifestyle and environment.

"These are highly multi-factorial processes. It's difficult to isolate any one factor," says

Daniel Hertz, Pharm.D., Ph.D., assistant professor of clinical pharmacy at the University of Michigan.

Hertz studies pharmacogenomics of breast cancer drugs, where the patient's DNA plays a role in drug metabolism, right alongside the tumor genome that is commonly used to select effective treatment options.

Challenges moving from discovery to implementation

Another key challenge in implementing pharmacogenomics is that most variants are seen in only a small number of people. So who do you test?

"There's no question at all that this approach can make a difference for a subset of patients. For that 1 in 100 or 1 in 1,000 patient who carries the variant, it will make a huge difference. But to test everyone to find the one who has a variant isn't always practical," Hertz says.

Hertz has found a unique way around this. He's working with University of Michigan Comprehensive Cancer Center researchers, who have implemented a program called Mi-ONCOSEQ that sequences the DNA and RNA of metastatic cancers and normal tissue. Hertz is integrating interpretation of pharmacogenomic markers. By using an existing mechanism, there's no additional cost or wait time. When a variant is identified, pharmacists can jump in and partner with oncologists to advise on treatments.

Taking a deeper look

As pharmacogenomics continues to evolve, researchers are also pushing beyond the genome to proteomics.

"Pharmacogenomics can explain some of the variation, but it's not the whole story," Zhu says. He's looking at protein biomarkers to understand whether protein expression levels are associated with response to a particular medication.

His lab has developed a novel proteomic approach to identify genetic variants with the capability of regulating gene expression at the protein level.

It's important because gene expression changes at the mRNA and protein levels are not always consistent. And if the genetic variation does not affect the protein expression, then the variation ultimately doesn't matter.

"Some of the DNA changes we see may not mean anything in regards to drug metabolism or response. What is important is finding variants that will mean something, such as resulting in a different amount of the protein being made, which match with overall function," Ellingrod says.

Zhu hopes that using proteomics will lead to discovery of more functional genetic variations that affect the protein expression, which means more useful genetic variations that can be used to guide precision treatments.

Power in numbers

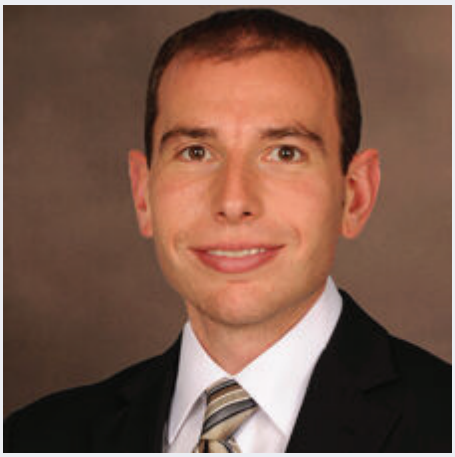
While some diseases, such as cancer, have millions of banked tissue samples that can be tapped for further research and discovery, other diseases are more limited. Additional samples will be necessary to move the field forward, researchers say.

This includes samples from diverse populations. Different genetic factors and variants are at play based on a person's race or ethnicity. Without participation from diverse populations, researchers won't know what those factors are and won't be able to include them in future tests.

"As we implement precision health and have more patients in our health care system with genetic information, it won't just help those patients for whom we're able to guide treatment," Hertz says. "It will also help us as researchers do more discovery and more validation. The faster we can do that, the faster we find additional markers that can help future patients."

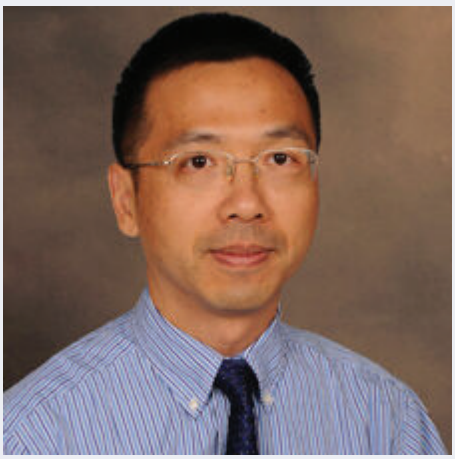
Examples of pharmacogenomics research at the University of Michigan

When it comes to pharmacogenomics, the breast cancer drug tamoxifen is one of the most studied and most controversial. University of Michigan researchers found evidence more than a decade ago that the marker CYP2D6 could predict whether women would respond to tamoxifen. Others have tried to replicate the finding, with mixed results. It's led to a split among the research community and a lack of uptake of CYP2D6 testing by oncologists.



Daniel Hertz has also looked at pharmacogenomics predictors of neuropathy caused by chemotherapy. He has also found an association between CYP2C8 variants and the risk of chemotherapy-induced neuropathy in breast cancer patients. He's also reported a variant in VAC14 that predicts risk of docetaxel-induced neuropathy in prostate cancer patients.

Haojie Zhu's lab was the first to identify a clinically significant variant in CES1, a primary hydrolase expressed in the liver. Many popular drugs metabolize CES1, including ACE inhibitors used to control blood pressure, Tamiflu for influenza and methylphenidate for attention deficit hyperactivity disorder. Most ACE inhibitors show no therapeutic activity until they are converted to active metabolites by CES1. For patients with the CES1 variant discovered by his lab, this function does not happen.



"If you have a loss-of-function variant in CES1, then it could affect ACE inhibitor activation and you would not be a good candidate for an ACE inhibitor," Zhu says. A clinical trial is assessing how CES1 genetic variants affect clinical outcomes in patients treated with ACE inhibitors.

Research in mental health has looked at why an antipsychotic drug routinely causes patients with schizophrenia to gain a tremendous amount of weight. Vicki Ellingrod's lab has identified associations between weight gain or insulin resistance and genetic variants in enzymes that play a role in how the body metabolizes folate. Preliminary results from a clinical trial suggest adding folate supplements significantly reduced metabolic symptoms.

Researchers are using metabolomics—the measurement of small molecules in biological samples—to better understand different patients' responses to septic shock and possibly identify new targets and treatment opportunities.

"Sepsis is a leading cause of death in the U.S. and is a very challenging clinical problem," says Kathleen Stringer, Pharm.D. "Accurate diagnosis is difficult and presently, there is no effective drug therapy. One of the greatest hurdles to finding drug targets for sepsis is the heterogeneity of these patients. By using carnitine to probe sepsis metabolism, we expect to better define this heterogeneity which we expect to unveil drug target opportunities."