Using the genome to maximize therapeutic benefits

How pharmacogenomics is turning “fishing expeditions” into precision care

PICTURED
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Dr. Howard L. McLeod, PharmD admits that when he first earned his degree in pharmacy, he didn’t realize the importance of the genome. After graduating, he went to St. Jude Children’s Research Hospital where he encountered patients that didn’t react as expected to what was considered the “normal” dose of a medication, with potentially fatal side effects. As a team at St. Jude Children’s tried to understand this sensitivity, they uncovered a genetic cause. “[We] found the genomic basis and I realized, the genome is something and I better pay attention to it,” he states. And that began Dr. McLeod’s foray into understanding the interaction between therapies and the genome.

Since that time, Dr. McLeod has used his clinical and research training to examine the spectrum of responses to therapies and the underlying genomic connections. Today, Dr. McLeod is one of the leading authorities on the use of pharmacogenomics—the study of how variations in the genome impact a person’s response to medication—in the clinic.

Andrew Hinton, host of the Illumina Genomics Podcast, had an opportunity to speak with Dr. McLeod about how pharmacogenomics is changing patient care for the better and what needs to be done to integrate pharmacogenomics into routine care in the United States. This article contains excerpts from that conversation. Listen to the interview in its entirety at illumina.com/science/genomics-podcast/ the-impact-of-pharmacogenomics-on-precision-medicine.html.

"In areas like solid organ transplantation, trying to pick out the dose of immunosuppressant that we need to give... We know what dose to give prior to the transplant. You can go straight in with the right dose."

AH: Outside of cancer, what are the primary areas of healthcare that would be most impacted by the implementation of pharmacogenomics?

HM: We're seeing genomics used in a number of other areas. For choosing antidepressants in mental health. For choosing anti-psychotics, also in the mental health area. For pain control. Trying to decide whether [a patient] goes on an opiate medicine and, if so, which one. In areas like solid organ transplantation, trying to pick out the dose of immunosuppressant that we need to give this kidney transplant patient from day one. We know what dose to give prior to the transplant. You can go straight in with the right dose. As opposed to what has been, and still is, in many cases, very much a fishing expedition. We start somewhere. We then try to adapt to it and make sure we get the right therapeutic dose before we harm someone, but that's not always the case. It's allowing some precision to come in, in many different areas of medicine.

AH: How do genes affect drug metabolism, and can one gene affect more than one drug?

HM: Yes. Most medications are administered in the body, as are most anything. Most nutrients that you eat are broken down in the liver. A drug-metabolizing enzyme is typically an enzyme found in the liver. It's sometimes called a P450 based on some of its protein characteristics. These enzymes are responsible for taking a molecule, clipping off a hydroxy group or adding a methyl group, resulting in something that is more easily eliminated from the body, either through the biliary tree or through renal excretion.

The idea that we have these enzymes, and that they can affect certain medications, has been known for quite some time. What we are seeing is that some of these drug-metabolizing enzymes, we've only found one or two drugs they seem to affect, are fairly narrow in their application. Then, there are others that affect many different drugs. For example, there's one protein in the liver that affects about 25% of all of the FDA-approved drugs that are currently available in the United States and most parts of the world. That's an example where understanding the status of a drug-metabolizing enzyme will give you some insight into a quarter of all the medicines available for treating disease, whereas other ones are very narrow in scope.

AH: When we discuss pharmacogenomics, what range of biomarkers are we talking about? How many genes are typically included in interrogation of what you have referred to as "metabolizer phenotypes"?

HM: For the metabolizing genes, you typically have somewhere around eight to ten different genes involved. Those include the so-called P450s, as well as some of the other metabolizing genes such as the UGT family. These are the main genes that will metabolize drugs from an active to an inactive product. Or, in rare cases, from a prodrug, a less active product, into a more active product. For example, codeine, which is a medicine used for pain, doesn't have very much activity until it's metabolized to morphine, a potent pain reliever. There are other medications that also need to be activated by enzymes. You also have transporter proteins that bring the drug from the stomach into the bloodstream, or take them from the bloodstream out into the kidney to get rid of them. The genes that encode these proteins are certainly important.

If you look at pharmacogenomics more broadly, we're typically looking at a panel of somewhere between 30 and 40 different genes that will have impact on either the absorption, distribution, metabolism, or excretion of a medicine. In some cases, they might also be the target of the medicine and influence the outcome.

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AH: Can you discuss the impact that FDA guidance has had on clinical practice? Specifically, where does the data for adverse drug reactions primarily come from in regard to what might be recommended in the clinic?

HM: The FDA has an unusual relationship with clinical medicine. It has a big impact in that the drug company will write the package inserts, the drug administration section, and the information on the pharmacology of the drug. The dosing and different features that are important for the medication will come out of the FDA. Certainly, a lot of the information for trying to decide which drug, at which dose, etc, will come from FDA guidance. But it [the FDA] is not allowed, by Congressional mandate, to practice medicine. It's not allowed to interfere with the practice of medicine and, therefore, it has a line that it tries not to cross in order to allow practice to occur.

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You see important data coming from the FDA, where they've found that a particular gene will be associated with an adverse event and they'll write that into the prescribing recommendations, the package insert. They may even put a so-called black box on the package insert to give an extra warning that in patients with these particular genotypes, you need to use caution when using this medicine or, in some cases, avoid it altogether. But a lot of the adverse drug reaction data will come from the literature. It will come from the insurance companies only paying for certain indications. The national guidelines, from either societies or other learned groups, will influence this. The FDA has a role, but it is not the only one trying to optimize drug safety.

AH: Outside of the FDA, what organizations are influencing guidance for implementation?

HM: The biggest consortium goes by CPIC, the Clinical Pharmacogenomics Implementation Consortium. This is a group of people from about 40 different countries. There are several hundred people involved. Very active in the US, Europe, Asia, and some other continents as well. CPIC asks the question, "if someone had genetic information, should you act on it in terms of drug therapy?" They're not telling you whether you should order a test in the first place, but rather, if you had a whole genome done, or if you had a whole exome done, and you had these results, what should you do? If you had a pharmacogenomics test done, what should you do? It gives some pretty clear guidance on what genes, what genomic variants, what other features should be used in terms of clinical practice.

The Dutch have their own group. The French have their own group. There are several groups in Asia. One group down in South America. All trying to put together some rules, if you will, to give guidance to clinicians as they're going forward. Then, many professional societies have looked at their specific area and had some sort of comment. For example, the American Rheumatology Association had some specific comments on the use of some of the HLA markers for giving allopurinol therapy. They didn't comment on any of the other pharmacogenomics because it wasn't really in their scope of practice, but they did comment on this specific area. We've seen the same thing with the American Heart Association and some of the pulmonary associations, etc. Some of the pediatric-focused associations have also weighed in, and, of course, the American Psychiatric Association and some internal psychiatric associations have also weighed in on the use of pharmacogenetics

in mental health disease. So you see this blurring of lines, but a really nice collaboration between something like CPIC, which goes across all areas of medicine, as well as the individual societies that might be having an impact on just a narrow slice of the diseases that are out there.

AH: Are there any examples of health systems, or nationalized precision healthcare programs, that you find particularly exciting? What can other health systems or nations learn from them?

HM: From a national level, the country that I think has done things the best is the Netherlands. They've implemented pharmacogenomics in a broad way, but they've done it with the input from a number of different levels of practitioner. In the US, it tends to be one group that decides that it's important and tries to convince the rest of them. In the Netherlands, they have the general physicians, the specialist physicians, the pharmacists, the pathologists, all these different aspects of medicine were pulled in to design an approach going forward. So it didn't take an individual champion saying, "let's do this for rheumatology." It was a case where they said, "alright, we're going to go ahead and implement this broadly." Now, that is a smallish country, very different from a country like the United States. We don't have that type of infrastructure. We don't have a ministry of health. We don't have this kind of top-down approach where we could do this for the entire US. It could be influenced strongly by the insurance companies, the FDA, but it's not going to be a situation like in the Netherlands.

In the US, we've seen a number of really strong examples going forward. Intermountain Healthcare is a health system from Las Vegas up into Idaho, with about 30 different hospitals. That's a system where they have now started offering pharmacogenomics more broadly. Certainly, they're doing the cancer part of it, but now the germline part where they're looking for mental health disease, starting to layer out into pediatrics. Now other areas are being developed more fully. You have a similar thing that's happened at the University of North Carolina in Chapel Hill and they're now trying to layer it out to other hospitals in their health system. Atrium Health out of Charlotte and some of the other groups there have started implementing [pharmacogenomics], initially in cancer and now layering it out to many other areas. The Mayo system has done a good job, at their major sites, of trying to have pharmacogenomics be available

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and be preemptive about the approach. There are probably many other examples that I forgot, and they'll be mad at me for not mentioning their system.

It's been an exciting time as we see this thing move from kind of a niche area, for only those people who are in the know, to now more broad application, even for people who don't really understand genomics. That's the beauty of it. We're talking, in pharmacogenomics, about drug safety. You may not know a thing about the genome, but you understand if you need to use a lower dose or higher dose, and you can respond from there. There's a lot more application coming as we see this trotted out into the masses.

Learn more

Pharmacogenomics, illumina.com/HowardMcLeod-TherapeuticBenefits

Illumina Genomics Podcasts, illumina.com/science/genomics-podcast.html

About Dr. Howard L. McLeod

Dr. McLeod is an internationally recognized expert in pharmacogenomics and personalized medicine, having made contributions at the discovery, translation, implementation, and policy levels. He is the Medical Director for Precision Medicine at the Geriatric Oncology Consortium and a Professor at the University of South Florida Taneja College of Pharmacy. Previously, he was the Medical Director of the DeBartolo Family Personalized Medicine Institute at the Moffitt Cancer Center. He also chaired the Department of Individualized Cancer Management, was a Senior Member in the Department of Cancer Epidemiology, and a State of Florida Endowed Chair in Cancer Research.

Dr. McLeod has chaired the National Human Genome Research Institute Electronic Medical Records and Genomics (NHGRI eMERGE) Network external scientific panel for the past decade and was a recent member of both the FDA committee on Clinical Pharmacology and the National Institutes of Health (NIH) Human Genome Advisory Council. Since 2002, Dr. McLeod has been vice chair for Pharmacogenomics for the major National Cancer Institute (NCI) Alliance clinical trials group, overseeing the largest oncology pharmacogenomics portfolio in the world. Dr. McLeod has been recognized as a Fellow of the American Society of Clinical Oncology and the American College of Clinical Pharmacy and was recently ranked #1 USA/#2 World for Pharmacogenomics. He has also been an active Board Member and/or Founder for over a dozen privately held and publicly traded companies. Dr. McLeod has published over 570 peer reviewed papers on pharmacogenomics, applied therapeutics, or clinical pharmacology and continues to work to advance individualized medicine.

Selected publications authored by Dr. McLeod

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