The impact of pharmacogenomics on precision medicine

Dr. Howard L. McLeod discusses what can happen when medicine and genomics collide

PICTURED
DR. HOWARD L. MCLEOD,
MEDICAL DIRECTOR, PRECISION MEDICINE AT GERIATRIC ONCOLOGY CONSORTIUM
PROFESSOR, UNIVERSITY OF SOUTH FLORIDA TANEJA COLLEGE OF PHARMACY
PRESIDENT AND CHEIF MEDICAL OFFICER, PHARMAZAM

Why does a medication effectively "cure" one patient while having little to no effect, or worse, an adverse effect, on another? The answer may be found in our genome. Pharmacogenomics research aims to understand the phenomenon of how genetic variations affect responses to medications. Ultimately, the goal is to improve patient outcomes. Pharmacogenomics can have a profound impact in the clinic, providing vital information for primary care physicians and specialists as they choose a therapy regimen and prescribe dosage.

Pharmacogenomics data "should be readily accessible and standing guard for your optimal care, whether you're an outpatient or inpatient, or seeing a specialist or a generalist, pharmacy, or nursing," states Dr. Howard L. McLeod, PharmD. As the Medical Director for Precision Medicine at Geriatric Oncology and President and Chief Medical Officer of Pharmazam, Dr. McLeod is one of the leading advocates for moving pharmacogenomics into routine practice. "This is the kind of data you want sitting there as a safety net, ready to help the patient, just when they need it."

While there are some processes in place, we still have a ways to go to achieving a true presence for precision medicine. Andrew Hinton, host of the Illumina Genomics Podcast, had an opportunity to speak with Dr. McLeod about his thoughts on pharmacogenomics and the future of precision medicine. This article contains excerpts from that conversation. Listen to the full interview at illumina.com/science/genomics-podcast/the-impact-of-pharmacogenomics-on-precision-medicine.html.

"We have examples where extreme toxicity can be detected ahead of time because of the genome... it certainly is important for drug development, but it's also important clinically for drug safety and for choosing the most effective drug."

Andrew Hinton (AH): How did you end up working in the field of pharmacogenomics?

Howard McLeod (HM): I first got a degree in pharmacy and after that some clinical pharmacology training, I knew that there would be some things that would be important, and some things that would not be important, in medicine. One of the things I thought would definitely never be important is the genome. I thought that was just something that wouldn't be relevant. And, very soon into my training, I had a little girl who nearly died from the therapy for her leukemia. As we dug into why she had such a horrific outcome compared to other people, we found a genomic basis. Then it happened again with an adult who was receiving chemotherapy. We found the genomic basis and I realized that the genome is something that I better pay attention to.

AH: Can you describe the scope of pharmacogenomics and what it covers in the clinical realm?

HM: Pharmacogenomics is the collision between a medication and the genome. Certainly, knowing about the genome can be important for choosing a therapy during drug development. It can be important for choosing a therapy in the clinic. It might be as simple as understanding what dose of a medicine to prescribe, or it might be as complex as deciding whether a high-tech, difficult-to-administer medicine is given to someone, or whether an alternate is decided. We have examples where extreme toxicity can be detected ahead of time because of the genome. We have ways to help choose from amongst a number of different therapeutic options in the clinic.

On the outside, it's also thinking about the policy pieces of it. How do we use the genome to understand when you should use a generic medicine versus a branded medicine, with differences in cost and access? It certainly is important for drug development, but it's also important clinically for drug safety and for choosing the most effective drug.

AH: You've described the implementation of pharmacogenomic information into the clinical flow of medicine as a "low-hanging fruit," but also commented that a number of barriers need to be overcome in order to routinely use pharmacogenomic variant data in improving drug prescribing. Can you expand on these statements?

HM: Certainly. One of the reasons why I feel that pharmacogenomics is a so-called "low-hanging fruit," in the scope of other genomic applications, is that we already have a drug safety mechanism that's in use on a daily basis. If you go to a practitioner, you'll

have a medication review. There will be software already in place, an electronic medical record, to look at drug–drug interactions, drug–allergy interactions, and a few things like that. The concept of trying to understand a patient's level of risk and apply it on a routine basis is already in place. It's now layering in the pharmacogenomics aspect of it. It won't really change the workflow. It will just be additional signals that come in through that same role. That is the heavy lifting. That's also the barrier.

Our electronic medical records are primarily systems designed for scheduling and billing purposes. We try to use them for the practice of medicine, but they are not really ready to do most of the things we need. We can store information. We can take a pharmacogenomic panel. That data can be stored as a PDF somewhere within the electronic medical record, but it's very difficult to then have decision support actively tell a prescriber don't prescribe this medicine, use this other one instead. Or don't use this dose, use the other dose. That sort of thing is the heavy lift. The pathway is there, it's just figuring out how to construct it so that this data is routinely available and applied readily. This is not the kind of data you want anyone thinking a lot about. This is the kind of data you want sitting there as a safety net, ready to help the patient, just when they need it.

"If you go to a practitioner, you'll have a medication review. There will be software already in place, an electronic medical record, to look at drug–drug interactions, drug–allergy interactions.. The concept of trying to understand a patient's level of risk and apply it on a routine basis is already in place."

AH: Historically, pharmacogenomics has been used for single-gene, single-drug interactions and that's still how much of it is reimbursed. What will it take for us to move to polypharmacy medication management of comorbid patients?

HM: We're at a time when there is an inflection happening. There used to be the old joke that pharmacogenetics means one gene and pharmacogenomics means you're looking at more than one gene and trying to amplify things. What we're seeing now, is that several of the insurance companies, United Health, Palmetto Health, one of the CMS MACs, are now reimbursing at a higher rate if you have certain indications and you have a larger panel done. Whereas if you don't have these particular disease indications, or you have a smaller panel, you either won't be reimbursed at all, or it will be at a much smaller reimbursement rate. This change in reimbursement, based on the panel size and the clinical indications, is certainly making a difference. We still have a way to go before insurance companies and other payers really understand the value of preemptive testing. The idea that you could spend the same amount of money to have a whole array of tests, excuse the pun, for an individual patient, and then be able to use that as needed, on a just-in-time basis, is still escaping many of the insurance companies. First of all, they're not used to preventive-type services. Secondly, they're a little wary that they're going to pay for something, and then the patient will move to a different carrier and they'll lose the value from there. But we're not seeing employers and other groups understanding that we can offer this as a benefit.

"This change in reimbursement, based on the panel size and the clinical indications, is certainly making a difference... we're seeing a little bit of a shift where insurance companies are coming in and starting to pay, but also employers, especially the self-insured, are starting to realize that we need this safety net if we're going to keep our employees happy."

This could be something that our patients can use, our employees can use. It might be a reason why they stay with our company. It certainly is a reason why we can save some costs for individual folks. So, we're seeing a little bit of a shift where insurance companies are coming in and starting to pay, but also employers, especially the self-insured, are starting to realize that we need this safety net if we're going to keep our employees happy.

AH: Will true pharmacogenomic clinical implementation require immediate integration to the electronic health record for collaboration between the pharmacist and the specialist?

HM: The ideal system doesn't exist, but it [pharmacogenomic data] should be readily accessible and standing guard for your optimal care, whether you're an outpatient or inpatient, or seeing a specialist or a generalist, pharmacy or nursing, or whoever. That may happen someday, but it is yet to happen anywhere on the face of this earth. I think the approach that is more realistic is integration into the electronic health record, but also integrating into the other records that are currently used. You might have an electronic health record in your particular institution, but pharmacy also has a pharmacy management electronic system that they use. Pathology has PathNet of some version that they use. Radiology has their own thing. They [should] all feed into the electronic medical record and interact with it, but they allow the specialist activities to occur in that way. I think that we're going to see some use of that where pathology and pharmacy are working together between their aspects of electronic medical record so that they can get the testing right, they can get the action right, and then feed that forward into some aspect of the electronic medical record. It will end up being maybe a two- or three-part process as opposed to a one-part, one-size-fits-all approach. This now allows steps to be taken without disrupting the entire electronic medical record system. This sort of thing is starting to happen. We're also seeing other approaches where you can use an app of some sort that will basically sit on top of the electronic medical record so that as you go in to prescribe, it can intervene, provide a pop-up box that says, "try this drug, this dose," as opposed to it having to happen within the electronic medical record.

From a functional standpoint, as a practitioner, you wouldn't even know the difference. In terms of how it's written and constructed, it allows the big, hard-to-move electronic medical record to do its thing, while the more agile apps are being layered on top. We're seeing that start to happen now and that's certainly making some serious progress.

And then there are some movements out there to have the patient be more in control. One approach, the one I'm involved in (full disclosure), is called Pharmazam. It allows the patient to be in control of their drug information, pharmacogenetics, drug–drug interactions, etc., and then share it with their practitioners as needed. The beauty of this, is that it allows patients to put in the over-the-counter medicines, the minerals, or whatever else they might be taking, that often don't get captured in the electronic medical record. It also allows patients to share the information immediately with any specialists they may see in the same way in which they share it with their primary care physician, etc.

Patients that are 55 and older will have eight different specialists, on average, that they see over the course of a year. There is no electronic medical record that can feed all of those different places. Typically, you're going to need some other approach. I think one where the patient is driving it is a really exciting approach that can serve this purpose. The patient is being tasked with being responsible for this anyway. Now it allows them to do it without having to go to medical school or something like that. It's an exciting time as these are all applied.

"There are many opportunities to bring in all this new science, especially polygenic risk scores, and it's exciting to place it within the grasp of a community physician, or an academic physician, neither of which may want to learn all that much about genomics."

AH: Are you seeing research studies currently combining pharmacogenomics and polygenic risk scores? What is the real benefit to academic and community physicians?

HM: For the last few years, there's been research on polygenic risk scores for disease risk of various types. That's been very exciting. It certainly could be a way of reaching people that would not be obvious with our current tools. We're now starting to see some of these also happen for pharmacogenomics. One of the first studies in heart failure is now in press and available in the literature and there's others that will likely be coming. That's really an exciting development because we know some of the pharmacogenomics information. We know what to do in the case of a patient that has certain drug-metabolizing variants, etc, but we don't really know all of their risks. A polygenic risk score may allow that to open up even further.

From a practical level, if you just give a community physician a bunch of genomic information, there will be a few of them that say, "oh great, thank you very much," and most of them will say, "why have you just made my life harder?" But, if you feed it to them in very practical terms, so it says this person has a heightened risk of this adverse event or has a lower risk

"The idea that you have your entire genome done as soon as possible in your lifespan and have that information available to help you with choices around drugs, choices around polygenic risk scores, choices around disease, is very exciting."

of this other adverse event, that allows them to immediately assimilate it into the way they practice medicine and not have to really change anything. You're going to get much better intake with this approach than if we try to make it super fancy and super different and super special. We're seeing some effort now to do very high-quality science, but then bring it down to a very simple level. For example, one of the groups that I've worked with has these molecular reports with a short executive summary that you can read in 30 seconds or less. That can be used by a busy clinician going from room to room. Whereas a full genomics report that we normally give is just not going to be digested in the proper way. There are many opportunities to bring in all this new science, especially polygenic risk scores, and it's exciting to place it within the grasp of a community physician, or an academic physician, neither of which may want to learn all that much about genomics.

AH: What excites you about genomics in the future and where do you see precision medicine in 5-10 years?

HM: One of the things that's exciting to me is this movement, what I call a movement from portrait to landscape. We've been looking at individual genes with individual drugs, individual genes with individual diseases, and that sort of thing and we still have a lot to learn about when a gene variant causes, or doesn't cause, a particular endpoint. But we are now at the point where we can start looking at panels and start to come up with rules for what we do when we look across someone's entire genome. The idea that you have your entire genome done as soon as possible in your lifespan and have that information available to help you with choices around drugs, choices around polygenic risk scores, choices around disease, is very exciting. You're looking across the person, not only a rheumatic disease, not only at cardiology. That to me is a really exciting pivot. We're not leaving any of those behind. It just means that we have to be able to apply it more broadly and that's exciting to me.

We also have the technology to do that. We can now sequence someone's genome in a very small amount of time, for a reasonable price. You can have your whole genome done, at clinical grade, for less than the cost of a CT scan. The idea that you can get this information and apply it is really very exciting. You can see precision medicine starting to really take this up, where it's not just for the one cardiologist who happens to be interested in it, but it's for the internist. It's for the primary care physician. It's for the person who is looking broadly across this patient. It's going to be exciting to see this all laid out.

Learn more

Pharmacogenomics, illumina.com/HowardMcLeod-PrecisionMedicine

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

Roden DM, McLeod HL, Relling MV, et al. Pharmacogenomics. *Lancet*. 2019;394(10197):521-532. doi:10.1016/S0140-6736(19)31276-0

Hicks JK, McLeod HL. Probabilistic medicine: a pre-emptive approach is needed for cancer therapeutic risk mitigation. *Biomark Med*. 2019;13(12):987-990. doi:10.2217/bmm-2019-0228

Knepper TC, McLeod HL. When will clinical trials finally reflect diversity?. *Nature*. 2018;557(7704):157-159. doi:10.1038/d41586-018-05049-5

illumina®

1.800.809.4566 toll-free (US) | +1.858.202.4566 tel | techsupport@illumina.com | www.illumina.com

M-GL-00081 v1.0