The Pharmacogenomic View of Precision Medicine: A Q&A With Howard McLeod, PharmD

HOWARD MCLEOD, PHARMD, *studied pharmacy at the University of Washington in Seattle and clinical pharmacology at the University of Sciences, Philadelphia, and completed a clinical research fellowship in oncology at St. Jude Children's Research Hospital in Memphis, as well as an additional fellowship at the University of Glasgow Beatson Cancer Institute. McLeod was a professor in Glasgow, then in Aberdeen, for about 8 years. For the past 17 years, McLeod has lived in the United States, first in St Louis at Washington University, then in Chapel Hill, North Carolina, at the University of North Carolina, and most recently at the Moffitt Cancer Center in Tampa, Florida. Throughout his career, McLeod has been involved in precision medicine, with an emphasis on practical application of precision medicine in the clinical setting.*

***AJMC®*: You're working on implementing precision medicine. What kinds of technologies are you taking advantage of? Are there any next-generation sequencing technologies?**

MCLEOD: Moffitt is currently the third-largest cancer center in the nation in terms of patient volume. We have implemented precision medicine in a couple of different ways. One has been using next-generation sequencing of the patient's cancer. That has included using both the tissue itself—either at new diagnosis or taking a biopsy of an existing tumor—or liquid biopsies, where we are looking at circulating free-tumor DNA and how we can use that to manage whether patients are still responding. If they are resistant to therapy, what kind of resistance do they have? How do we switch to a new drug? Those considerations are on the benefits side of the risk-benefit equation. We have also started implementing more systematically the use of germline or normal tissue genetics to identify toxicity risks. We started off with the choice of antifungal therapy for our leukemia patients. Fungal infection has been a leading cause of death in leukemia and bone marrow transplant patients because their white cells are suppressed by therapy, so we give them antifungal drugs to prevent that from happening. One-third of our patients will eliminate the antifungal drug too quickly, so we use genetics to identify those people and switch them to either a different, higher dose or to a different drug in the rare cases where patients are extreme eliminators. That is now expanded out. We are doing panels across large numbers of patients, not just in leukemia. We are scaling to a point where every patient at Moffitt will have a germline, a normal tissue genetic panel run to identify excess risk of neuropathies, cardiomyopathies, and other dosing changes, not just for antifungals but also pain control, anti-vomiting medicines, and other classes of medication. We really try to have a broader strategy so that everybody has a chance to benefit from personalized therapy rather than waiting until something bad happens and trying to figure out why.

***AJMC®*: How is this proactive approach helpful in designing treatment pathways at Moffitt, and how might it be transposed to be used in pharmacotherapy optimization in the future?**

MCLEOD: There are situations where there's really only 1 option or where there is an amazing option and a far inferior option, but those are rare examples. Most of the time, you have 2 to 4 very similar options, and you must pick 1. When you have an amazing therapy and the second choice is a not-so-amazing therapy, it would take a lot to not give the amazing therapy. But when you have these essentially equal options, just a feather will tip that scale. It takes a very different type of data because you are not denying someone therapy; you are just choosing from among the buffet in front of you. You have to start with one entrée. Are

you going to pick the one that looks the nicest? Or the one that's more likely to taste great? That is the way we have been looking at this. It's really tie-breaker medicine. How do we choose from among the options that we have? Also, the stakes are high in cancer. If we get it wrong with our therapy, we have a resistant tumor that is harder to treat. If we get it wrong with toxicity, the patient is not able to continue what could be curative treatment, they are now less interested in having active treatment, and we have harmed their quality of life. It is rare that we are talking about an inconvenient rash. What we are talking about is typically a pretty serious problem that we are going to cause. It might be that this is just the price of medicine, but more likely, we can choose a different therapy with a much lower probability of harm and a much higher probability of benefit.

***AJMC®*: What are some of the areas that you are pursuing at Moffitt for maximizing the efficacy of treatment on a patient-by-patient basis? For patients with cancer, what are some of the near-term advances that you can see that use personalized medicine?**

MCLEOD: There are 2 aspects to answering that question. There are the more dramatic examples and the more mundane but highly relevant examples. The dramatic examples are where we are sequencing the tumor patients who have run out of treatment options. We are trying to identify the one-third or so of patients who will have a previously unrecognized treatment option. That data can then allow us to try to treat them, and in some cases, there are very dramatic effects in terms of eliminating the tumor altogether. In other cases, the treatment does not do what it should and the patient is still in peril. Right now, we are sequencing around 120 cancers a week, either to identify FDA-approved options or to look for new options for patients, such as clinical trials. If someone comes to us and they have been treated with all the usual therapies, rather than sticking them on any old trial, we will sequence the tumor, look for something that makes biologic sense, and treat them accordingly. That includes the immune therapies and the growth factor inhibitors (the kinase inhibitors). Then, when we get it right, it is dramatic; we are taking someone from hospice and putting them back to their normal life. But we still have a long way to go before that is every patient's experience. We will give many patients more logical options, but it does not necessarily cure them of the disease. It might buy time, it might allow the family comfort knowing they're going for it, but it doesn't necessarily cure them.

> **"Fungal infection has been a leading cause of death in leukemia and bone marrow transplant patients because their white cells are suppressed by therapy."**

The more mundane side is that all our patients need some level of supportive care. It might be an antidepressant, it might be a pain medicine, it might be a medicine for nausea or high blood pressure. If you are an oncologist and you have done a lot of extra specialty training, you may or may not remember how to treat depression or high blood pressure or hypothyroidism. So if we can have a molecular marker—or any kind of marker for that matter—that will help that busy oncologist manage that "primary care" aspect of the patient, the patient wins, the oncologists do not have to divert brainpower into managing these aspects, and it is good for our health system in general. In terms of broadest impact, supportive-care pharmacogenomics is really efficient because almost every patient needs it. Tumor sequencing is not done for every patient, because there are some people who are doing just fine with the standard treatments.

***AJMC®*: In terms of insurance companies and broad-panel sequencing tests, how has that been a limitation at Moffitt, and how is that likely to change as there is a greater understanding of the importance of genetic testing for patients with cancer?**

MCLEOD: It used to be a big problem. It still is a problem in terms of spending time interacting with the insurance companies, but insurance companies have come to realize that the testing we are doing is a $3000-to-$5000 test that is guiding a $100,000 treatment. Once they had realized we were not using this as an excuse to give expensive treatment but rather to more objectively choose which treatment to give, the insurance companies viewed this in a totally different fashion. It took time and literal interactions with insurance companies so they understood what we were doing; we were not blindly sequencing—we were doing this on purpose, and we had clinical pathways that it fit into. They realized that there is a better chance of value. If they are going to have to do something for the patient, wouldn't they rather do something of higher value? This is my experience at Moffitt now because we interact with the insurance companies, but they have not necessarily rolled that out as broad policy. It will still »

be a while until the insurance companies realize how to use this approach in the community setting. Also, the field has to be using testing appropriately. If we are sequencing someone with a very small ductal carcinoma in situ of the breast, something that barely needs any treatment, that is inappropriate use of technology. There is no added value to sequence data, at least at this point. Whereas if we're taking someone who is fit and wants to be treated, but there are no obvious options, or there is a selection of options, that is the case where we can benefit from sequence testing.

The other thing is relatively recent, about a month or so ago: The FDA approved one of the first anticancer drugs that was anatomy agnostic. Any cancer that has microsatellite instability is eligible for the immune checkpoint inhibitor. That now gets us into the realm where we need to sequence tumors to know whether FDA-approved treatments are relevant. And that has caused the insurance companies to reevaluate what they are doing and try to really get things optimized in that way.

> **"As we look at our value, we use personalized medicine to try to optimize quality and to at least justify, if not reduce, cost."**

***AJMC®*: What kinds of efficiencies can be realized when patients get the right dose of the right treatment at the right time, in cancer and other conditions? How does that shift influence value?**

MCLEOD: Well, the most expensive therapy is the one that doesn't work. If we can optimize our chance at benefit, there is some value right there. If we are going to spend money on therapy, we need to be able to show that it is something that these patients are tolerating and benefiting from. If we are not going to cure the patient, we are buying significant time for them at a high quality of life. We have not focused on things like quality-adjusted life years, but rather we have focused on things like total cost of care. Are we able to show that by identifying patients at high risk for toxicity and switching them to another treatment that has equal benefits but lower risk of toxicity, we can decrease the cost, achieving optimal outcomes with less cost? We have also had some surprises where we end up getting a lot of extra room to treat more patients. We look at our patients, and toxicity is one of the leading reasons why they're getting extra visits, and in some cases, it's averaging around 15 extra visits per patient in the first year to manage toxicity. Toxicity is not well reimbursed, and it is not something the patient wants. It is clogging up our waiting rooms, making it so we cannot treat additional people, which from a revenue standpoint and mission standpoint is important.

As we look at our value, we use personalized medicine to try to optimize quality and to at least justify, if not reduce, cost. It could be that a cost is what it needs to be, but at least we know it is on purpose. It could be that the patients are going to get toxicity, but at least we know that ahead of time and can be ready to manage it. It is a lot cheaper to manage grade 1 toxicity, very mild toxicity, than it is to manage the severe toxicity that requires hospitalization. We have been using this to think about how we manage patients. If we are going to be managing these patients, let's look at it in a holistic fashion. Let's try to reduce things, try to take the things that have been assumed to be part of practice and really question them. Can we reduce the severity, if not incidence, of neuropathy? Part of it has just been a way of changing the culture of our institution, which has been an early-adopter institution to begin with, to really take this on as being normal.

***AJMC®*: How might the evidence-based personalized medicine pathways of care developed at Moffitt Cancer Center be translated and communicated to other treatment centers?**

MCLEOD: We did develop internal versions of pathways. Our pathways are a little bit unique in that they manage the patient's care, so there are things around surgery choices, radiation choices, chemotherapy choices, imaging choices, endoscopies, and all the ways the patient is managed. It allows us to come to a consensus as a group. If there are 4 ways to treat something, those 4 ways will be on the pathway. Anything off the pathway would be quickly identified, and we can either adjust the pathway if there's new data or try to understand what's going on. Insurance companies want to reduce variability, and we can talk to them about our strategy in terms of developing consensus pathways and going forward. It's not just guidelines or suggestions but rather trying to make a more objective decision and then follow up on it. Our pathways right now are available through being licensed, but they are not available for free. There are a number of institutions that have licensed some or all the pathways. It is a lot of work to keep them up, but it has become part of our payer strategy. It has become part of the way we help our community partners practice better. If you are going to have a Moffitt sticker on the door, you are also buying into practicing within the pathways. You have to have a good reason to not practice on pathway. We also build in the molecular sides and try to be as comprehensive as possible.

***AJMC®*: How do you think biomarkers will increasingly become the standards for treatment selection and treatment in cancers in general, rather than anatomical and other traditional ways of staging cancers?**

MCLEOD: I think for surgery and for radiation, anatomy will always matter. For systemic chemotherapy, it will be a long time before we get rid of anatomy in our description. It is going to be hard not to call a cancer rising from the breast a "breast cancer." But in terms of the way we treat it, it is already starting to change. As we understand the molecular drivers, we cannot help wanting to respond to them. That has caused a change in our structure—a change in the way tissue is handled, prioritizing certain markers versus others. If you have metastatic carcinoma, and you have only a brushing or something where you have very few cells, you could make the argument that it is more important to know the molecular drivers than it is the diagnosis. It is rare that we don't have the diagnosis, but from a tissue priority standpoint, knowing what to treat becomes more irrelevant. We are not trying to figure out if it is a breast cancer metastatic to the liver, or a colon cancer metastatic to the liver—we have tissue from the liver cancer that has abnormalities that we can target. And suddenly there is less of a need to know the anatomical origin. We do still try to find that, but you can see the change that's happening with systemic therapy; we want to know what's driving it and how to stop it. It's almost trivial to know where it came from because it's less and less part of the decision on how to treat it.

***AJMC®*: Where do you see precision medicine going in the future? We're seeing the most use of precision medicine and personalized medicine with cancer now, but where might the next frontier be? Or will it continue to be cancer for the foreseeable future? What are some of the growths that you've seen in precision medicine, and how do you see that projecting out over time?**

MCLEOD: There are a couple of areas in which we are seeing a lot of activity in terms of precision medicine. One is in mental health—both at the family medicine level and the psychiatry level. It is more for depression than schizophrenia, but there is activity in both. A lot of patients now get a DNA analysis done for drug metabolism pharmacogenomics prior to the choice of antidepressants. That is definitely an emerging area.

Another area is organ transplantation. Prior to transplant, the transplant surgeons want to know information about both the patient and, when possible, about the donor, to be able to choose the type and dose of immunosuppressant therapy.

There is activity in cardiology, but not necessarily a lot outside cardiac catheterization labs. There are pharmacogenomics going on in the cardiac catheterization lab at many centers, but in terms of treating high blood pressure and heart failure and such, there's not a lot of pharmacogenomics happening currently.

Precision medicine is also emerging in the use of general anesthesia—not for the anesthetic but rather for things like the anti-vomiting medicine. Anesthesiologists don't like risk. They worry about a 1 in 1000 or a 1 in 10,000 event. They're not interested in any patients being at risk for aspiration pneumonia because they vomited while they were still under anesthesia, so there is activity going on in that space to try to choose therapy accordingly. And that affects many different types of patients; surgical patients are usually the largest volume of patients in a hospital. Overall, we are starting to see a lot more activity happening with precision medicine.

***AJMC®*: What do you see happening in the next 5 to 10 years in personalized medicine?**

MCLEOD: In the next 5 years or so, I think a lot of it will be focused around which drug and which dose. Also, expanding on what is already going on further. During the next 5 years and beyond, we are going to see more emphasis on what it is the patient has. And what I mean by that is, "What does high blood pressure mean?" It probably means 20 different things, but right now we just think of it as 1. So as we start getting information, whether it's a biomarker or genetic test, we can now start treating patients accordingly. The same thing applies with depression and other common diseases. There are some areas, like infectious disease, where currently we have a large therapeutic index; we can overdose the patient and it doesn't harm them, but it will kill the bugs. However, as we get more resistance, we are going to start to see more molecular studies there. We will also see more rapid diagnosis through molecular testing. Right now, a well-equipped emergency room can diagnose viral meningitis in 2 hours with a molecular test, whereas the rest of the country will either never diagnose it or will take days to diagnose. We are starting to see rapid turnaround assays for sepsis and other areas that will allow us to make more informed decisions. I think the bottom line is knowing more about the patient and their likely response to treatment and trying to make sure that that happens in a uniform fashion. Informatics is also going to become more important because there's going to be so much data. All of this in the backdrop of an insufficient number of physicians and other health professionals being trained, so it is going to be a really interesting next decade. ■