Mylynda Massart at the UPMC Matilda H. Theiss Health Center

PRECISION MEDICINE FOR THE MASSES

MYLYNDA MASSART BRINGS GENOMICS TO PRIMARY CARE

BY ELAINE VITONE

PHOTOGRAPHY BY JOHN ALTDORFER

A few years ago, Mylynda Massart was mentoring a young man who was struggling with depression. To add insult to injury, his trial-and-error search for the right treatment was *itself* a series of unfortunate events, one awful side effect after another.

Distraught, the mentee blurted out: *It's the 21st century. Why can't we just look at my genetics and know what to prescribe the first time?!*

And that, in a nutshell, is one of the biggest frustrations in medicine right now, for both patients and physicians.

In some specialties, precision medicine is already the standard of care. Genetics guide therapy for cancer, for example, as well as many rare diseases treated by medical geneticists. Sadly, in primary care clinics—the front lines that see most patients most of the time—we're just not there yet.

But it *is* coming, says Massart, an MD/PhD assistant professor of family medicine at Pitt, who teaches genomics and precision medicine to Pitt Med students as well as practicing physicians.

Researchers are optimistic that the table is finally set to build an understanding of the enormous variability of sickness and health, of disease progression and remission, of response to treatment and its opposite. Scientists hope to clarify the interplay among genes, environment, and exposure. The reasons why one identical twin can get a chronic disease and not the other.

Massart told her mentee that he was justified in his anger. And in fact the research on his very question—which depression meds are right for which patients—was looking promising, but still not ready for prime time in clinical care.

Today, more than 200 medications, which are used in treating dozens of diseases, have some genetic considerations. For some, there's an indication right on the FDA-approved product labeling. And yet most frontline clinicians have no idea this is the case. Massart knows because she asks them to venture a guess when she gives talks. Most docs guess 20, maybe 30 tops. When she tells them the answer, it's like a bolt of lightning.

"They're all shocked. *Two hundred?!* They're all pulling up their phones and clicking on the FDA site," says Massart, who is 5'2" and likely to be spotted with her pink backpack as she ferries to and from three clinical and academic offices. She's a self-described storyteller by nature. (It's a Jewish gene, she says with a smile and a shrug.)

The science is evolving faster than practicing physicians can keep up.

And with the advent of genetic testing from companies like 23andMe, which deal directly with consumers rather than providers, patients are showing up at doctors' offices with genetics reports. The physicians are confronted with questions for which their training never prepared them. (See our Tough Questions discussion starting on p. 12 for more on this.) So referrals to genetic counselors—of whom there is a dire national shortage—are growing. Patients can wait several months to get in, and a lot of very scary Google results can show up in the meantime.

As one of only a handful of primary care physicians in the country with training in genetics, Massart is uniquely qualified to straddle these two worlds and begin what will likely be a long, hard effort to bridge them. And here at Pitt/UPMC—which established the UPMC Genome Center, the Pharmacogenomics Center of Excellence, and the Institute for Precision Medicine—she feels she's at exactly the right place and time to do it.

This summer, Massart and Philip Empey, PhD assistant professor of pharmacy and therapeutics in Pitt's School of Pharmacy and associate director of the Institute for Precision Medicine, will open a primary care clinic for precision medicine. It will serve as a testing ground for new services for patients, as well as for new educational tools to help other physicians and pharmacists provide these services.

And a lot of education is needed, Massart says. Physicians need to understand what's covered in health risk reports from companies like 23andMe and how to explain those results to patients. They need to understand the FDA guidelines regarding direct-to-consumer test results—what they can and cannot do with information from those reports, when to order repeat testing, and what labs to order them from. Also, they need to know where to store genomic data in the electronic health record and then how to integrate those data into patient care.

At the new clinic, some patients will come for a visit or two to address a specific concern. Some will stay for their long-term primary care needs at this multidisciplinary clinic. Some will be referred to the appropriate genetics services (neonatal genetics, pediatric genetics, oncology genetics, etc.).

Lucas Berenbrok, assistant professor of pharmacy and therapeutics, will be on-site offering his expertise in pharmacogenomics, or how genetics contribute to medication response.

Massart and her team see triaging genetics cases appropriately—and teaching other primary care docs to do the same—as one of their most important charges.

To help other clinicians catch up, they'll build teachable moments into every interaction with referring physicians: souped-up consultation reports, recommended readings, and FYIs on deeper-dive materials that they're creating, like precision-medicine lectures and online courses.

Massart strongly believes genomics is something that primary care docs can pick up. They're already trained to do 70 to 80 percent of pulmonology, cardiology, endocrinology, and so on, she says. "We know where our boundaries are and when we need to phone a friend, . . . whether it's calling for guidance or actually referring the patient to that specialist."

She aims to *be* that friend—and eventually work herself out of that job.

The clinic doesn't have a name yet. For now, it's in a temporary home in the UPMC Matilda H. Theiss Health Center, the site of Massart's family medicine practice. "There are some messages on that phone over there with some early referrals," she says in her office on a recent spring afternoon. "Our hope is to officially launch around July."

The new clinic is a dream realized for Massart, who is 47. Her career has been a kind of timeline of historic moments in the pursuit of bringing precision medicine to the masses; everything seems to have been building to this.

Massart got her BS in cell biology from the University of Illinois, then went on to grad school in biochemistry and genetics at the University of Utah, which was one of many sites where the Human Genome Project took place. Massive, room-sized sequencers were housed in her adopted haunt, the Eccles Institute of Human Genetics, with its prominent double-helix staircase.

By chance, Massart fell in with a new crowd, geneticists. The first of these fast friends was a genetic counselor who reached out with an invitation for Massart to participate in a study that was recruiting among Salt Lake City's Ashkenazi Jewish community, of which Massart was a member.

That community, which largely retained shared genetics over time, was ideal for study. Ashkenazi Jews became central to many ground-floor findings in genetics.

A University of Utah faculty member, Mary-Claire King, had identified the breast cancer genes *BRCA1* and *BRCA2*. A start-up called Myriad Genetics formed around subsequent research in which Massart participated. That work further characterized the genes' associated mutations, which affect about 1 in 40 with Ashkenazi Jewish ancestry. (In the general population, it's 1 in 500.)

BRCA was kind of a signpost moment for precision medicine, Massart says.

It was the first oncogene to go commercial in a big way. For the first time, people could see the coming storm. "I think that just gave so many people a sense of having some power and control over a disease that we feel so powerless against," says Massart.

Meanwhile, Massart's new friends were inviting her to shadow them in their clinics and sit in on case conferences. She found their collaborative process riveting. These genetic counselors (experts in both the science of genetics and the psychosocial aspects of counseling) and medical geneticists (often MDs who diagnose and treat diseases with significant genetic components) would discuss the histories of patients and their families, review photos, and plot out pedigrees on the whiteboard. Together, they'd come up with a diagnosis and a plan.

"They were brilliant," Massart says. For the rest of grad school, she snuck over to watch them in action every chance she got. "I would set up an experiment that needed to go for two hours and run down through the hospital."

Kathryn Swoboda, a neurologist, medical geneticist, and University of Utah fellow who was joining the faculty, hired Massart for a postdoc position in her lab. Through Massart's first two years of medical school (she started her MD after completing her PhD), they characterized a very rare disorder called alternating hemiplegia of childhood (AHC). With cases so few and far between, studying these children meant traveling the world.

The pair grew close with these families as they documented the children's symptoms (episodic paralysis and stiffness and unusual eye movements) and collected blood samples to bring back to Utah. Years later, Swoboda helped lead the international collaboration that identified the gene for AHC.

In the second half of med school, which Massart completed at Oregon Health and Science University in Portland (she'd transferred there to be near her grandparents), she was sure she was going to be a medical geneticist. That went out the window when a couple of things happened in 2004.

First, she fell in love with primary care. That clinical rotation was filled with a little bit of everything and everyone, from babies to 90-year-olds—basically, paradise for Massart, a people person. And her attending could tell. Three weeks into her clerkship, he and his partner sat her down and said, *Mylynda, this is an intervention. You are not a specialist. You are a primary care doctor, and you just need to accept it.*

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Then, that same week, her pink flip phone rang. An emergency department physician was on the line, calling from Italy. One of the kids in Swoboda's registry had checked into the hospital with influenza, and the doc was terrified of messing up. He had to know: What did a child with this infection need in the context of this rare disorder?

Did they tell you I'm only a medical student? Massart said. *I'm not a doctor.*

They did, he said. *But this is such a rare disease. And the family gave me your name. They said you're one of only three experts in the world.*

Massart gave him the best advice she had (treat him as you would any other child, but keep an eye on his lactic acid), then got back to her evening routine. It was her toddler's bedtime. After tucking Noah in for the night,

she sat down at her computer to write a paper due the next day. She doesn't remember what the assignment was, exactly. But she does remember what came out of her reeling mind and onto the page:

A treatise on why genetics belong in primary care.

Genetics have context, she realized. Genetics are part of a broader picture—a person, a life, a family. And though the term *precision medicine* wasn't part of the lexicon at that time, medicine was clearly moving to the molecular level. "And we were never going to have enough geneticists in the world to handle the magnitude of health issues that involve genetics," Massart says.

Massart and her young family moved to rural Idaho in 2009. For five years, she practiced family medicine with a focus on genetics. It was gratifying from the start. To her knowledge, there was only one genetic counselor in the entire state, and zero medical geneticists. It was very if-you-build-it-they-will-come, says Massart. "I just showed up, and these genetic cases just started walking in the door." First, a man with cystic fibrosis. Then, a brother and sister with a rare genetic disorder. Then, a woman with some printouts of data from a little start-up called 23andMe.

In 2013, Angelina Jolie went public with her own *BRCA* status and subsequent decision to undergo preventive double mastectomy. From then on, genetic testing start-ups—both consumer-facing and physician-focused—seemed to sprout up like weeds, says Massart. She thinks Myriad Genetics paved the way for these companies, which quickly mounted aggressive marketing campaigns. Representatives fanned out to doctors' offices. TV and social media ads turned science terms into household words.

Now, patients come to see Massart with health reports from these companies all the time. "Patients are taking ownership of their health care more than ever before," she says. "They really want to understand this."

The 1960s *Star Trek* reruns were a staple of Massart's childhood. Through her teens, her family taped *Next Generation* on VHS so they could watch together when her dad got home. And she's propagated the Trekkie gene in her own offspring, she reports. "Last night we watched the season five finale of *Discovery*."

The tricorder-wielding doc of the future was pretty much what Massart thought she was slowly working toward during her training. Like, wave a device across the patient, and *beep*, diagnosis. Or at least: Type-type, click-click—maybe even scan a fingerprint—and *beep*, medical record, complete with DNA data. And that thinking was, *ahem*, logical, given the times. At the 2000 White House press conference announcing the completion of the Human Genome Project, the effort's leader, Francis Collins, called our newly sequenced genetic code "the book of life." By many scientists' predictions, DNA would directly inform treatment by the end of the aughts.

We've since learned that the genome is no open book. Genetics, environment, and exposure riff off of one another in complicated ways. To better understand this perplexing interplay, the National Institutes of Health launched the Precision Medicine Initiative in 2015. Its primary charge: to build a 1-million-participant study called All of Us, which would include both genomic data and electronic health record data over time—at least 10 years, and hopefully longer.

All of Us recruitment launched right here in Pittsburgh, led by Steven Reis, MD associate vice chancellor and Distinguished Service Professor of Medicine, who directs Pitt's Clinical and Translational Science Institute. When he met Massart, he recognized she was a natural fit for All of Us Pennsylvania, both because of her background in genetics and her work in underserved communities. (Massart is medical director of the UPMC Matilda H. Theiss Health Center, a family medicine practice in Oak Hill.) To make research as relevant as possible to as many Americans as possible, diversity in the All of Us cohort is key; Massart leads the statewide effort to help it live up to its name.

Prescribing for depression and many other maladies is like throwing a dart at the dartboard, says Massart. "Most of the time you don't hit the bullseye with that first drug. . . . We're pretty much shooting blind."

So back the patient comes a few weeks later. Then, the physician must consider: Is the problem that this is the wrong dose, or the wrong class of antidepressant altogether? The dart-throwing can go on for months, and in that time, a lot can happen.

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"I share the story of my own family," says Massart. "My grandmother committed suicide during that time. That's the worst possible outcome, right? But there are many other negative outcomes. People lose their marriages. They drop out of school. They lose their jobs. They may start [abusing] drugs and alcohol."

It's not yet possible to look at genetic test results and know exactly what to prescribe—but we're getting closer, says Massart. For now, physicians can rule out at least some of the many medication options. Throwing fewer darts can mean less suffering.

In the world Massart's young Trekkies will inherit, she hopes fewer people will wind up sick in the first place. That's the ultimate mission of precision medicine.

So Massart is doing all she can to get primary care docs up to speed. "I want them to be far ahead of the game—preventive and proactive," she says.

Steady as she goes. ■

Philip Empey

JUST DOING IT

More than 200 FDA-approved medications already have genetic considerations in their labeling. But the tests required to find out if you can safely take the drug can be expensive. This is one reason why frontline doctors haven't yet caught up with the rapidly evolving science known as pharmacogenomics, or "how DNA contributes to medication response," explains Philip Empey, who leads Pitt's new Pharmacogenomics Center of Excellence and is Mylynda Massart's cofounder at the new primary care precision medicine clinic.

To prove pharmacogenomics is worthwhile on a broad scale—in terms of improving patient outcomes, or saving costs, or getting people to the right meds faster—it has to be systematically implemented, then its use needs to be tracked and fine-tuned. In other words, to prove it's worth doing, you have to do it.

To help nudge precision medicine out of this classic chicken-and-egg conundrum, the Pharmacogenomics Center of Excellence recently launched a five-year, 150,000-participant study. Through a partnership between Pitt Pharmacy and the Clinical and Translational Science Institute, volunteers across Western Pennsylvania will undergo a panel testing for more than 4,600 genetic variants in nearly 1,200 genes.

Of those 1,200 genes, 13 have shown an especially high level of clinical utility and are now relevant to prescribing practices for some 40 medications. Results from related genetics tests will be incorporated into the UPMC electronic health record, which is getting an upgrade to help guide physicians through genomics-based prescribing practices. For example, if a doc tries to prescribe a drug that the patient's genetics suggest wouldn't do diddly to help, a warning window will pop up on the screen.

When physicians or pharmacists in the UPMC system see one of these pop-up windows, Massart explains, they'll also see an option to click and read more—maybe a paragraph or so—and then get back to their patient. "And then, . . . in the evening or on a break or at lunch, they could watch perhaps a 15 minute CME video, and learn even more in-depth."

Test results for those 13 genes, by the way, will be accessible for patients in the UPMC system.

Empey believes pharmacogenomics will make a difference for at least some patients. Determining which patients is what this study aims to do. *—EV*