ONE SIZE DOES NOT FIT ALL, BUT TAILORING IS NOT SO SIMPLE

BY MICHAEL FITZGERALD

TRYING ON PERSONALIZED MEDICINE
The man in the exam room is in his early 40s. A salesman. He has two kids under 13 and metastatic melanoma that has spread to his lungs and his lymph nodes. Not long ago, his doctor, Ahmad Tarhini, would have had a grim conversation with him. There was little hope for a patient with stage 4 melanoma. Chemotherapy could shrink tumors but not prolong his life by much. Perhaps 10 percent of patients at this stage responded to a drug called interleukin 2, which sparks the immune system to fight off cancer. Some patients were helped by experimental drugs in clinical trials, yet there was no way to tell what drug would work for whom. But it’s now June 2014, and Tarhini can have a somewhat more upbeat conversation. He would not mention the word “cure” just yet to patients in this situation. But he does tell the man: “There are effective targeted and immune therapy options that are proven to prolong life and were recently approved by the FDA. Also, there are new medications and combinations of existing medications being tested in studies, and the preliminary data are very encouraging.

“The patients using them are still being followed by researchers, but we are seeing long-term survival.”

Tarhini, an MD/PhD and associate professor of medicine in Pitt’s Division of Hematology/Oncology, walks his patient through some options. He tells the patient his melanoma is driven by a mutation of the BRAF V600E gene. The same mutation is found in about 50 percent of melanoma cases. He could be given a drug that targets this mutation and shuts it down and effectively stops the cancer. (Ipilimumab is approved as a monotherapy but is also available in combination with other drugs in clinical trials.) Those who respond well to ipilimumab have what Tarhini calls “durable” responses, living longer than patients who take existing targeted therapies. Some have lived for a decade. One catch: It only shrinks tumors, so far, in about 1 percent of patients; yet about 20 percent of patients have survived for years with it. Another catch: Some patients experience severe side effects with ipilimumab. Tarhini doesn’t know how the salesman would do with this immune therapy. But his cancer is slow-moving, so it could be worth trying.

The salesman’s case gives a glimpse of the targeted therapy. Since 1975, five-year survival rates for breast cancer in the United States have gone from 76 percent to 90 percent in 2007.

The sequencing of the entire human genome in 2003 created tantalizing potential for researchers to match treatments for any given disease to individuals. The National Cancer Institute started The Cancer Genome Atlas project in 2006, with the goal of sequencing the genomes of different cancers to establish the DNA aberrations that cause them. (By the way, Pittsburghers helped build this atlas; the University of Pittsburgh Cancer Institute is one of its largest contributors.)

UPMC expects a five-year, $100 million investment in high-powered computing, data warehousing, and analytics will help its doctors and Pitt researchers evaluate treatments and develop new ones while bringing down the cost of care. (For more on how that massive undertaking is progressing, see p. 24.) In the meantime, a number of Pitt physician-scientists are helping build a future for personalized care through other avenues, like the National Institutes of Health’s SPORE, or Specialized Programs of Research Excellence (Pitt has three of these), as well as genomic and tissue databanks built by research consortia.

We can expect the history of personalized medicine to read like a Russian novel, revealing complex (biologic) interrelationships. This is just the first chapter in what’s likely to be a tome.

Yet patients like the salesman already have more options.

Melanoma patients and their doctors started having more hopeful conversations after August 2011, when the FDA approved vemurafenib. Vemurafenib was a first-of-its-kind targeted therapy for late-stage (stage 4) melanoma in tumors with the BRAF V600E mutation. BRAF V600E causes a part of the protein pathway, the communications link from a cell’s nucleus to its surface, to either be permanently on or off. Vemurafenib could flip that switch in cancer tumors, inhibiting growth and encouraging cancer cells to die off.

Oncologists now routinely sequence late-
stage melanoma tumors, looking for the BRAF mutation and others, says John Kirkwood, the Usher Professor of Medicine, Dermatology, and Translational Science and director of the melanoma and skin cancer program at Pitt. (He directs the skin SPORE, as well.)

BRAF and the other mutations account for about 70 percent of late-stage melanomas. Kirkwood hopes we’ll soon get a better harness on immunotherapies like ipilimumab, which spurs a specific part of the immune system’s arsenal, cytotoxic T lymphocytes, to go after melanoma cells.

If you’re the salesman, you also have to think about ipilimumab’s side effects. For many patients it causes colitis, a swelling of the colon. Symptoms include diarrhea, sometimes so extreme patients die from it.

In June, Tarhini presented preliminary results from an ipilimumab trial in which 60 percent of patients taking the medication suffered some form of colitis in response. Fourteen percent had grade 3 or higher colitis, with more than eight bowel movements a day.

The patients did not have a history of colitis, inflammatory bowel, or autoimmune diseases. In Tarhini’s preliminary results, 86 percent of the patients who experienced any grade of colitis (18 of 21) had a mutation in one gene.

Tarhini says the study suggests that genetic profiling that may predict which patients are likely to benefit from ipilimumab.

A lot of money needs to be raised for a larger trial. Being part of the NIH SPORE helps, but does not cover all the costs.

Interpreting data is already a huge part of his work, but Tarhini expects the new UPMC data analytics initiative, in combination with new technology, will make sequencing faster and significantly cheaper.

The salesman decides to start with immunotherapy and see how it goes.

He’ll join an NIH-funded national study, led by Tarhini, that tests ipilimumab in combination with interferon-alpha. Samples collected on this study will allow the validation of Tarhini’s preliminary biomarker findings.

Lung cancer treatment is also being transformed by genomics. Burns’ office in the Hillman Cancer Center is crammed with papers on the subject. Knowing what mutations lung cancer patients have completely changes how they can be treated—about 60 percent of lung cancers have driver “oncogenes” that are identifiable, says Burns.

“If you have metastatic lung cancer, when you walk in the door, we’re sequencing your tumor,” he says.

One driver linked to a mutation is EGFR (epidermal growth factor receptor), for which several targeted treatments have been developed, notably gefitinib and erlotinib. Similarly, crizotinib was approved after a phase 1 clinical trial produced a 70 percent success rate in patients suffering from lung cancer driven by a genetic alteration called ALK-translocation. Patients who have mutations for which targeted treatments are available can sometimes live years with their disease, as opposed to 12 months or less for patients without these targetable mutations.

Such improvements in outcomes led 16 cancer centers, including the University of Pittsburgh Cancer Institute, to form the Lung Cancer Mutation Consortium, an industry-funded group researching treatments for 14 common genetic alterations in lung cancer. Burns’ ongoing research has focused on KRAS, a mutation responsible for 25 percent of all lung cancers but so far resistant to treatments.

Burns thinks the sorts of analytics tools being deployed at UPMC may lead to innovations in care, like helping to identify the right markers exist for patients who might suffer side effects from ipilimumab. The drug costs $30,000 a dose; a course of treatment is four doses. No one wants to give it to a patient who might suffer a potentially fatal reaction. Yet Tarhini needs to see data from many more patients for a statistically valid conclusion about what he considers culprit genes.

His other recent gene-expression profiling study of the melanoma microenvironment, had 34 patients and cost $22,000. In April, he reported on a preliminary gene expression signature based on the microenvironment of the patients who might suffer a potentially fatal reaction. Yet Tarhini needs to see data from many more patients for a statistically valid conclusion about what he considers culprit genes.

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The pancreas is also largely isolated from exterior disease, it can be linked to one of two sources. Each works. "You want to know from a molecular standpoint exactly how to apply knowledge of these markers in clinical settings. To advance that cause, Whitcomb has proposed the Genomic Resources to Enhance Available Therapy (GREAT) study. Its main goal is to combine clinical information with genetic information from 1,000 patients with pancreatic diseases for clues regarding what phenotypic or genomic characteristics lead to specific diseases. Included in the plan are detailed medical histories, as well as tissue and blood samples. Whitcomb’s team will then look for patterns in the data. This information will inform follow-up studies for devising new types of treatment.

Whitcomb has done small studies to see how the analytics program will work. One preclinical study looked at how to manage genetic information. Researchers sequenced the genomes of 70 pancreas patients and 70 liver patients and moved that information into a database. They wanted to figure out how best to format the data; see how easy it was to get it into and out of the database; and demonstrate they could protect patient privacy. For the GREAT study to become reality, Whitcomb has to get past the Institutional Review Board, which approves all patient research. He is hopeful that will happen soon.

In July, Whitcomb and colleagues published a study in *PLOS Genetics* that he says will offer new clues for treating some of his patients. Whitcomb’s group showed that many people with idiopathic pancreatitis have an alternate form of cystic fibrosis. “We would love to steal treatments designed for classic cystic fibrosis to help our pancreatitis patients,” he says. “This is personalized medicine.”

On a summer day, after flying into Pittsburgh at 12:30 a.m. from a conference in Israel, Whitcomb made time for a lunch meeting with this reporter. Over a Pittsburgh Salad at the University Club, he drove home his main point: He sees the GREAT study as a template that researchers and clinicians can use to mesh data and care.

“You want to know outcomes for your patient and start making some predictions about what treatment is going to be effective.”

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**If the research yields answers, Slivka might be able to recommend certain patients have their pancreas removed immediately, rather than enduring years of procedures that ultimately do little for them.**

Pitt’s David Whitcomb thinks medical scientists should be looking to the pancreas as a guide to tackling chronic conditions. He is. The organ looks complicated; it’s both an endocrine and exocrine gland, meaning it produces hormones like insulin that go straight into the bloodstream and digestive enzymes secreted via ducts.

“It turns out that the pancreas is the best organ to work on for developing new models of personalized medicine because it is very simple,” says Whitcomb, an MD/PhD, chief of Pitt’s Division of Gastroenterology, Hepatology, and Nutrition, Giant Eagle Professor of Cancer Genetics, and professor of medicine, of cell biology, and of human genetics. His own work looks at the exocrine part of the pancreas, which has only two classes of cells—acinar cells, which make enzymes, and duct cells, which squirt them out. These cells do only one thing, says Whitcomb, “and we know from a molecular standpoint exactly how each works."

That means when a person has a pancreatic disease, it can be linked to one of two sources. The pancreas is also largely isolated from external factors, unlike, say, the lung or kidney. Here’s the thing. The organ’s anatomy might be straightforward, yet in terms of what Whitcomb and other GI specialists know at the moment, nothing about figuring out who will get diseases of the pancreas seems “very simple.”

Five to 10 percent of people in the general population have pancreatic divisum, in which the two ducts that are supposed to merge to form the bile duct instead stay separated. This group faces a higher risk for chronic pancreatitis; yet the majority of people with pancreas divisum never suffer from anything. Some suffer severe pancreatic reactions as a result of passing gallstones, smoking cigarettes, or drinking alcohol—the pancreas becomes inflamed and scars. Others drink or smoke heavily and suffer no pancreatic disorders. Some have extreme pain in reaction to even mild scarring, others have little pain. Whitcomb says a pancreatic disease can have multiple factors involved, none of which is enough to cause the disease on its own.

Whitcomb thinks answers will come through computer modeling and simulations and applied analytics. “This is what every other science has gone to except for medicine,” he says. By using big data sets and information on individual patients, Whitcomb believes scientists can help identify people who are likely to suffer from severe pancreatitis or severe pain, diabetes, or fibrosis. Because the number of potential variations is so large, tens of thousands of patients will need to agree to participate in research studies to help identify causes. Yet (thanks to efforts Whitcomb has helped lead), scientists have some genetic markers; the challenge now is to figure out how to apply knowledge of these markers in clinical settings.

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Prediction demands description, says Adam Slivka, who is an MD/PhD, associate chief of clinical services in the Division of Gastroenterology, Hepatology, and Nutrition, and a bear of a man. He's voluble and excited about the potential of personalized medicine; he also thinks about the challenges. Consider how you might describe pain.


 Somehow, these different definitions of pain, of a feeling, need to end up as a quantitatively searchable item in a database for studies like GREAT that will lead to more individualized care. “It’s not all computer-science, flat-file database type of input,” Slivka says. And correlating qualitative phenotypic data, like pain measures, with genotypes “is really hard.”

In his homey office in UPMC Presbyterian, with its three small fish tanks and loads of family mementos, Slivka says the term “personalized medicine” suffers the same issue as “pain.”

“Ask 20 people what it means, and you’ll get 10 different answers,” he says.

Yet assessing pain in a way that is consistent across physicians and can be made searchable in a database is something Slivka and Whitcomb intend to do.

“People don’t appreciate what it takes to make a history meaningful for a database so that we can get to the point where we can [determine] how genetic variables correlate with what the patient’s telling you,” says Slivka.

He points out that doctors will need to ask questions that aren’t part of their routine right now. The GREAT study initially proposed an 11-page form for each patient visit. Slivka might see 25 patients on a typical day. Those 11-page piles are above and beyond the normal documentation doctors have to do just to get paid; and Slivka says they would have probably doubled the time spent entering records. Whitcomb says he’s significantly shortened the form now and put it into UPMC’s electronic health record. “It can take as little as 2 minutes,” Whitcomb promises.

Slivka is on board with Whitcomb’s GREAT study because he believes it will yield new insights into what causes pancreatic conditions and how to treat them more effectively.

For instance, for pancreatic pain, he has seen studies that show giving people pancreatic enzyme supplements doesn’t help them. Yet Slivka says that some patients seem to respond well to such enzymes. The studies lumped together different types of pain and pancreatic dysfunction. He hopes that using genetic information will show that certain types of patients do benefit from enzyme supplements.

He also hopes there will be a clear genetic reason why some people develop pancreatitis so severe that the organ eventually has to be removed. Right now, there’s no way to tell who will respond to preventive procedures and who won’t.

If the research yields answers, Slivka might be able to recommend that certain patients have their pancreas removed immediately, rather than enduring years of procedures that ultimately do little for them.

In Slivka’s clinic in the UPMC Digestive Disorders Center, standard-issue talismans of hope fill the walls of a patient room: efficient-looking medical instruments, an optimistic print of a flower, a chart mapping out an organ system. Inside this particular room sits a mother and a patient (not yet 20) who has suffered from intestinal pain her entire life. She has been referred from another doctor, who suspects a gallbladder ailment.

In an ideal world of personalized medicine, Slivka would know the young patient’s genetic makeup. Slivka would also have access to records showing whether procedures like endoscopies and CT scans had been performed, and what they found, even if those patients were not part of the UPMC system (which digitized its medical records years ago). But we have not reached that world yet. In this room, there is no genetic code in the patient’s chart, and no history except comments Slivka must elicit from mother and patient.

To question after question, the patient says, “Sometimes.” How does that get entered into a database in a way that is meaningful? What about the vague memories of what previous procedures revealed?

Slivka also says ethical issues are bound to come up in patient care. At conferences he gets into debates with doctors about doing a disservice to patients if he sequences their genomes. Some argue he will cause them to be discriminated against by insurers. (A federal act prohibits health insurers from discriminating based on genetic data. See p. 24 for a discussion of such issues.) Slivka says a long-term problem for personalized medicine research is how to take data that’s been blinded and open it up, so that when a clinical study concludes, doctors can go back and help patients who were part of it. Whitcomb hopes to show how to do this in his GREAT study.

Slivka also predicts that personalized medicine will be difficult to reconcile with medical insurance practices. Insurers, he says, “want efficiency, mass scale. Personalized medicine is almost the antithesis of that.” He knows that personalized medicine should save money by avoiding unnecessary tests and procedures. “But the onus is going to be on us doctors to prove it,” he says.

Still, he thinks the future will be better for patients like the one he’s just seen. He can say that she does not have a gallbladder problem. But he can’t say what the issue is. He can’t even say whether genetic sequencing will yield a treatment for her. But “it may help us stop unnecessary testing. Look what that patient’s been through,” he says, “CT scans, five scopes,” and he gestures with his fingers going down his throat.

Such patients are black boxes, he says, “You don’t know what’s wrong with them. You’re hunting for answers to try different treatments that might help them. But if I’m going to do an ERCP [endoscopic retrograde cholangiopancreatography, the scope he referred to above] on you, cut open your sphincter, or put a stent in your pancreas, all those things [can] have complications.”

He hopes that analytics will give him a better way to see what ails them. Getting there will take longer than he or anyone else would like.

When considering the complexity of the human system and the challenges of tailoring care, Berg, of Pitt’s Institute for Personalized Medicine, notes, “I’m feeling very humble.”