IT'S CHANGING THE WORLD OF HEALTHCARE. WHAT YOU NEED TO KNOW ABOUT THE MOVEMENT FUELED BY GENOMIC TESTING AND TAILORED TREATMENT.

WHAT IS PERSONALIZED MEDICINE?

By Dawn McMullan

PHOTOGRAPHS BY ADAM VOORHES

YOU GO TO YOUR DOCTOR WITH YOUR SYMPTOMS, AND YOU GET AN EVALUATION, MAYBE HAVE A FEW TESTS RUN.

If you are lucky, you're on your way to a diagnosis and a path to feeling better. How much more personal does it get? In fact, much more. In theory, astonishingly more.

Most often today, your treatment plan doesn't have all that much to do with you specifically. It's identical to what doctors would hand over to essentially anyone with the same condition — your neighbor, the hot dog vendor at Wrigley Field, or the prime minister of Bangladesh.

That's because medicine as we know it revolves around "standards of care," the best courses of prevention or treatment for the general population, or the average person on the street. With breast cancer, for example, those standards mean self-exams and mammograms after a set age and the usual chemotherapy to treat a tumor if one is found. If the first treatment doesn't work, doctors and patients move on to the next one and the next. It's trial and error, with life on the line.

A growing contingent of researchers, some healthcare clinicians, and an increasing number of patients are calling for a more personalized approach aimed as much at preventing disease as it is at tailoring treatment once it's there. Call it what you will — personalized medicine, genomic medicine, precision medicine. It's an approach that emphasizes the ways in which your disease risks are unique and different, just like your other, more obvious characteristics. Those disease risks are based on the predispositions written into your genome at birth, combined with your lifestyle and environment. In the case of cancer, the disease has its own genetic makeup, lending each tumor a unique character with unique tendencies and vulnerabilities.

And perhaps there is, or soon will be, a drug or treatment or tailored combination of the two that will work better for you than it would for someone else.

"The number of targeted therapies in the pipeline for all diseases is increasing dramatically," says J. Leonard Lichtenfeld, deputy chief medical officer for the American Cancer Society. "Personalized medicine in the age of genomics means we're living in dynamic times. The big question right now is 'How do we take all this new information we're gathering and use it for the benefit of the patient?'"

In many cases, the current standard of care may be the safest, most sensible option, but it's also "one size fits all." Sometimes that's perfectly sufficient, but not always. It is in that "not always" category that personalized medicine is making the most headway.

A DECADE OF ADVANCEMENT

Many doctors will tell you they've been doing personalized, patient-centered medicine all along, and they do have a point. Wikipedia defines personalized medicine as "a medical model that proposes the customization of healthcare — with medical decisions, practices, and/or products being tailored to the individual patient." But the definition preferred by the National Human Genome Research Institute is more specific, maintaining that a personalized approach to medicine includes an "individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease." Reaching that goal has been more than 20 years in the making, birthed from an ambitious plan to sequence the first reference human genome. By 2003, scientists had done it; for the first time, they had an essentially complete sequence and map of all the genes in the human body.

"Probably at no time in the history of medical research, going back to the time of William Harvey and the circulation of blood, in the 1600s, has there been more potential and promise for discovery that will benefit mankind in terms of the health of the species as where we are right now as a result of the Human Genome Project," says Scott T. Weiss, scientific director at Partners HealthCare Center for Personalized Genetic Medicine at Harvard Medical School.

Advances in technology have since accelerated the pace of discovery and lowered the cost so much that scientists pushed on from that single reference genome to sequence the genomes of more than 1,000 individuals in all their variations. These days, individual patients — and sometimes healthy people, too — can have their personal genomes scanned or fully sequenced. This knowledge about the basic elements of human genomes and their differences, both common and rare, is central to the concept of personalized medicine. It's changing the field of medicine, even though many of us probably haven't noticed any direct evidence of it at the family doctor's office yet.

A 2013 survey by GfK, a global consumer research firm, found that just 27 percent of people interviewed had heard the term "personalized medicine." Of those, only 4 percent understood what the phrase most often implies: "medicine based on genomic makeup."

AN OUNCE OF PREVENTION

There have been recent, high-profile examples: Angelina Jolie made headlines with a proactive double mastectomy last year after tests showed she carried BRCA1, the same genetic marker for breast cancer that her mother, who died from the disease, carried. The National Cancer Institute puts the risk of breast cancer for those carrying a BRCA1 mutation at 65 percent and the risk of ovarian cancer at 39 percent.

While it's important to remember that genes are not destiny, they do provide information that can lead us to make more informed decisions about our health and healthcare, and, as in Jolie's case, that can change the future.

If you get sick, knowing your genome or the molecular basis of your disease can be an important piece of evidence for doctors seeking the most favorable treatment plan for you. In the case of cancer, genetic tests could lead to successful drug treatment rather than radical surgery. For instance, melanoma can be BRAF positive, meaning the tumor has a specific gene mutation that sets it apart from other melanomas. Your lung cancer can be EGFR or ALK positive. Your colon tumor may be KRAS positive.

Increasingly, doctors will scan not just single genes or a handful, but also complete genomes. The challenge then will be figuring out what it all means and what to do next.

"While personalized medicine is escalating and becoming more common, it's still in its infancy, and there are not yet enough products on the market that have penetrated the consciousness of the average patient," says Edward Abrahams, president of the Washington, D.C.-based Personalized Medicine Coalition. "Patients are not yet asking the question 'Is this therapy going to work for me?' I look forward to the day patients do ask that question."

If you find the idea of personalized medicine more than a little overwhelming, you're not alone. It isn't easy to turn an approach to healthcare on its head.

"I don't think anybody disagrees with the fact that we [patients] are different and we respond differently. But it's hard to make changes," Abrahams says. "You want to see evidence before you're willing to move away from one-size-fits-all traditional medicine. To change it, you have to show that what you're promising is an improvement."

TESTING, TESTING

While more evidence about the promise of personalized medicine is certainly called for, individual stories are already pointing the way. In 2005, Stephanie Haney, now 45, had a pain on her right side that wouldn't go away. It hurt when she coughed or sneezed. She was pregnant, so she didn't investigate the cause, assuming perhaps she'd broken a rib.

Two years later, she was diagnosed with stage 4 lung cancer.

After undergoing chemotherapy, Haney began taking Tarceva (erlotinib) in 2008. But three years later, the drug was no longer keeping the tumors at bay. Prompted by friends and an insistent doctor, she had genetic testing on her tumors, which showed they were ALK (anaplastic lymphoma kinase) positive. This gave her doctor a major clue as to which drugs were most likely to work (or not). Haney was able to start taking Xalkori (crizotinib), designed specifically for ALK-positive lung cancer tumors. She joined a clinical trial for Xalkori in Philadelphia, two and a half hours away. Three years later, her tumors were barely visible.

Haney's journey is emblematic of the ever-growing personalized medicine matrix, wherein spreadsheets will be filled with biomarkers for diseases, if not whole genome sequences, and treatments will be fast-tracked (like her Xalkori) for approval based on clinical trials designed for those who have certain biomarkers or genes.

Researchers have discovered more than 1,800 disease genes

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since the Human Genome Project's completion. There are now more than 2,000 genetic tests for human conditions and 350 biotechnology-based products currently in clinical trials.

Lung cancer treatment is one of the most advanced areas in terms of a personalized medicine approach, with several drugs approved by the FDA or in clinical trials for different lung cancer biomarkers. Unfortunately, but not unexpectedly, Haney found out last October that the cancer had moved to her brain, one of several places lung cancer is prone to migrate. Because Xalkori will not break the blood-brain barrier, she just started another trial drug, LDK378, to treat the brain tumor.

CALEB NOLAN, 8, IS ON TWO BASKETBALL teams. Diagnosed with cystic fibrosis when he was 3 weeks old, he has spent much of his childhood in hospitals, taking many rounds of medicines each day. Like other cystic fibrosis patients, Caleb has a mutation in a gene called CFTR that causes mucus to clog the lungs and obstruct the pancreas so the body can't absorb food.

There are many different mutations of CFTR that lead to cystic fibrosis. Fortunately for Caleb, he has a mutation, G551D, found in 4 to 5 percent of cystic fibrosis patients, for which there is a treatment. Caleb is now on Kalydeco (ivacaftor), a genetically targeted treatment approved by the FDA in 2012 and the first such drug that treats an underlying cause of cystic fibrosis.

Shane Nolan, Caleb's father and a UPS driver, will never forget delivering his son's first shipment to their house. Before Kalydeco, Caleb was on enzymes that allowed him to live with his condition, but life was difficult, and activities such as sports were limited.

With Kalydeco, "Instead of the mucus building up, the medicine is thinning it," Shane says. "Now his body naturally does this. The medicine is preventing damage from the CF. Caleb hasn't been in the hospital since he's been on it [almost two years]. Usually, once kids reach their late teens or early 20s, they have to get a lung transplant. This should prevent that."

The average lifespan of a person with cystic fibrosis is 37. Now, "Caleb could die of old age instead of CF," Shane says.

WHO PAYS FOR THIS?

Caleb was lucky. His insurance paid for Kalydeco from the start. Jolie probably barely registered the $3,000 price tag on her genetic screening, although she did point out in a *New York Times* opinion piece that the price could be an obstacle for many.

When the FDA clearly ties a genetic mutation to a specific drug or treatment, insurers generally do cover the testing and treatment, says Bruce Quinn, senior health policy advisor at Foley Hoag LLP. If you have a family history that calls for it, insurance will pay for BRCA1 testing (in fact, the Affordable Care Act requires it). Where there is no such specific tie, insurance carriers have a judgment call to make.

Patients with cancer are more likely to have their tests covered. "They have an interest in this because they don't want to prescribe drugs that won't work," Abrahams says. "Insurance companies rightly want to see evidence that whatever they pay for works better than what we're used to paying for. But that's a barrier to innovation."

When it comes to whole genome sequences, the uncertainties about outcomes are that much greater, but sequencing is getting cheaper all the time. In January, Illumina, a genetic-sequencing company based in San Diego, announced it had a new system that brought the cost for sequencing a human genome down to less than $1,000. (That's cheaper than Jolie's single BRCA1 test.) This doesn't put a sequencer in your local doctor's office — nor does it cover the cost of interpreting those results — but it does make it feasible for clinicians and researchers to gather the evidence needed to push personalized medicine over the tipping point.

The D.C.-based Personalized Medicine Coalition has made defining levels of evidence that will be acceptable to the Centers for Medicare & Medicaid Services and private insurers a top priority. If a treatment or drug is outside medical guidelines, reimbursement is unlikely.

"Medicine needs to be evidence-based," Abrahams says. "Reimbursement is right up there with research in terms of priorities."

WHO OWNS THE DATA?

With all this data come new questions and ethical and practical challenges about privacy, access, ownership, and more. In many cases, research or clinical trial participants aren't given their results at all. Companies like Myriad Genetics, the primary provider in the United States of clinical BRCA1 testing, have returned individual results to doctors and

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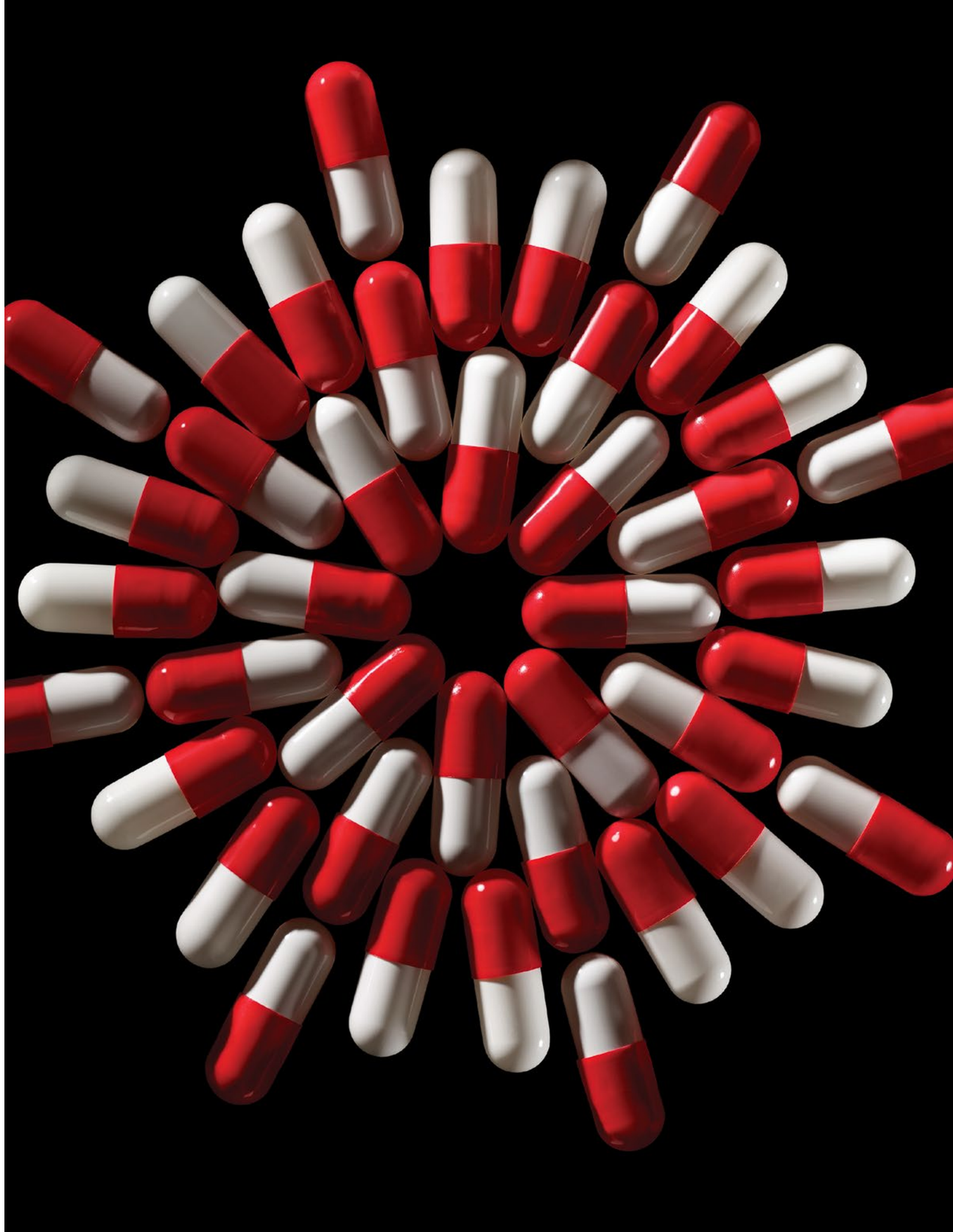
8%
OF THOSE, 8 PERCENT CONSIDERED THEMSELVES "VERY KNOWLEDGEABLE"

4%
ONLY 4 PERCENT WERE ABLE TO ACCURATELY DEFINE THE TERM



patients, of course, but Myriad has kept the bulk of its data as a trade secret.

Weiss, of Harvard Medical School, says patients are and always will be the rightful owners of their personal genetic data.

"This is confidential patient data," he says. "It can be used for medical research, but it's highly unlikely that your identity will be disclosed to some commercial third party in any identifiable way. Academic medical centers may partner with pharmaceutical companies, using their genomic data, but will do it in an anonymous way and only if the patient consents. The patient is going to be in control of what they do here, as they should be."

Laws such as HIPPA (Health Insurance Portability and Accountability Act) and parts of the Affordable Care Act protect the privacy of personal health information. The passage of the Genetic Information Nondiscrimination Act (GINA) in 2008 was considered a major win, too, as it bars employers and health insurers from using genetic information or family history. Still, many people worry about such personal and sensitive information being out there. And genomic data is at the core of personalized medicine.

"You can't do personalized medicine when it comes to genomics without electronic medical records and without the ability to deliver genomic content to providers at their desktop," Weiss says. "We're not really talking about the doctor-patient relationship here. We're talking about the mechanics of how you deliver huge amounts of data to clinicians in the office and at the bedside."

Medicine is getting there slowly but surely. The Obama administration began moving our healthcare system toward electronic records in the summer of 2009. Now more than 50 percent of medical records are available in electronic form.

"We need to get to 100 percent, and just having an electronic medical record isn't enough," Weiss says. "We still have to have software focused on the genomic content delivery to the caregiver."

Ideally, doctors could tap into a single, large database filled with anonymous genetic information — biomarkers tied to patient demographics tied to specific drugs and treatments — to help doctors make decisions about each individual's medical path. But getting there is sure to be a long and bumpy ride, with plenty of detours along the way.

For Daryl Pritchard, director of policy research at the National Pharmaceutical Council, the end game is clear: "The use of that information — whether by a company or by a group of doctors or a provider group — is ultimately going to be advantageous to treating the condition in question going forward. These things will work."

TALK TO YOUR DOCTOR

Starting with a good family history is a smart and simple way to begin a personalized medicine discussion with your doctor, says Geoffrey Ginsburg, director of the Center for Personalized and Precision Medicine at Duke University Medical Center, although it doesn't happen often enough. (Ginsburg is also editor-at-large of *Genome* magazine.) While you're at it, he suggests asking about whether any genetic tests are useful for regulating a dose of a drug, an approach known as pharmacogenomics.

Abrahams recommends asking your doctor the following question: "Do you have the expectation that this drug will work for *me*?"

According to Randy Burkholder, the vice president of policy and research for Pharmaceutical Research and Manufacturers of America (PhRMA), a Washington, D.C.-based trade group representing American biopharmaceutical and biotechnology companies, the most important thing is not being afraid to ask your doctor questions.

"It can be a hard thing to do sometimes, especially when you're seeing a diagnosis," he says. "Asking questions allows you to work with your doctor. The volume of information we can know is so much greater now. Doctors are doing a great job, but they can't be expected to know everything for every patient. As a patient, you shouldn't feel like you're imposing. You should feel like you're helping."

WHERE IS PERSONALIZED MEDICINE HELPING MOST?

Personalized medicine's greatest strides have been in cancer. Consider these statistics on the percent of tumors containing genetic mutations that could be targeted by drugs, as reported by the *Wall Street Journal* in 2011:

- Melanoma: 73 percent
- Thyroid: 56 percent
- Colorectal: 51 percent
- Lung and pancreatic: 41 percent
- Breast: 32 percent

"Cancer is a genetic disease," Ginsburg says. "In many ways, it is the poster child for a disease that has used personalized medicine strategies. It has used them in everything from risk assessment in healthy people — from screening, diagnosis, and prognosis — to selecting therapies based on genetics and the biology of the tumor."

HIV/AIDS is another area where the principles of personalized medicine have made great progress. "The virus mutates differently in each patient," Abrahams says. "Now we can understand the viral load and analyze it, then prescribe the right cocktail of medicine to treat it. This is the progress we've seen taking AIDS from a death sentence to a chronic condition. But that's understanding the virus, not the person."

Other diseases are clearly moving toward more comprehensive personalized medicine strategies, too, including heart disease, rheumatoid arthritis, multiple sclerosis, and infectious diseases. "Also, rare disease diagnosis is now becoming more amenable to personalized medicine strategies through genomics," Ginsburg says.

THE FUTURE OF PERSONALIZED MEDICINE

Abrahams is optimistic about the progress now being made, particularly when it comes to complex chronic diseases.

"At some point, and I don't know whether that will be 10 or 15 years from now, we will reach that tipping point where all medicines are linked to diagnostics, and we'll move out of the one-size-fits-all paradigm," he says. "If we have good answers today with the one-size-fits-all model, I don't think that will change. But most patients are unaware of the limits of our medical knowledge."

Once the evidence is in, many pieces will need to fall into place before personalized medicine becomes mainstream. Payment systems must be flexible enough to account for individual treatment plans based on genetics and other indicators. Regulatory guidelines must adapt to the idea that genetic diagnostics and targeted drugs go together in a treatment plan. Medical schools must include personalized medicine in their curricula. Patient interest and demand are essential, too.

While some patients may be seeing the impact of personalized medicine in some corners already, patient outcomes with today's medicine show plenty of room for improvement. Consider patients with depression, 38 percent of whom do not respond to the first drug they are prescribed. Or patients with asthma, of whom 40 percent do not respond to the most commonly prescribed drugs. Or type 2 diabetes (43 percent), arthritis (50 percent), and Alzheimer's disease (70 percent).

Education will be key. Knowing that tailored treatments are or may be available for various diseases is half the battle. Abrahams looks forward to the day when both patients and doctors will advocate for personalized medicine.

"One day, patients will say, 'I'm not an average patient. I am who I am. You need to understand who I am before you prescribe whatever treatment you plan to prescribe,'" he says. "When that day comes, we'll no longer [have to] talk about 'personalized medicine.'"

We'll know we've arrived when personalized and genomic medicine simply *is* medicine.

Kendall Morgan contributed to this report.

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