Still, many experts picture a future when many of us will be comfortable—and happy—getting assistance from health care chatbots.

"There are lots of situations where people don't understand the significance of some symptoms, and they either overreact or underreact to something important," says Fraser. "And there's potential for these types of tools to help patients."

"But they've got to be developed in a very rigorous way," he continues, "and be evaluated in a series of stages from a lab-based approach just using existing patient data through clinical observational studies to real randomized-controlled trials. And you can't just rush into trying to diagnose whether the patient has malaria, meningitis, a heart attack, a pulmonary embolism, or a stroke, for example, without ensuring that the system is designed to be usable and rigorous and safe for that population."

Fullam sees an immediate application for triage of patients and making sure the right patients get the right provider: "In the long run," he says, "adding medication data to chatbots could significantly improve diagnosis and triage suggestions."

—Howard Wolinsky

Precision Medicine in Primary Care: Bespoke. Genetic and Genomic. And Maybe Not Ready.

With genomic sequencing on the rise and patients having more say about their treatment, two hot areas—predictive genetic testing and pharmacogenomics—promise to extend "personalized" medicine beyond cancer care. But will this precision improve outcomes and pay for itself?

Say "precision medicine" and people think of personalized cancer treatment. But this innovation has already begun to revolutionize primary care too—even though the jury is still out, in many cases, on whether it makes a clear difference in outcomes.

Just what precision (alias "personalized") medicine is isn't always spelled out precisely. But usually it is discussed as prevention or treatment that takes into account individual differences among patients, most often genetic differences. Some people expand the concept to consider individual differences in environment and lifestyle.

> Pharmacogenomic results **could end some of the trial and error** with drugs

In adult primary care, two subsets of precision medicine have attracted the most attention recently: predictive genetic testing and pharmacogenomics.

Predictive genetic testing is what it sounds like: A genetic test that forecasts a person's chance of getting a disease. The term is also applied to germline genetic tests that provide some indication of the predisposition being passed down to offspring. Proponents see predictive genetic testing for certain inherited conditions as a way to unearth risks in people who can then get early treatment or take preventive steps to head off serious and possibly costly conditions. Actor Angelina Jolie put BRCA testing as a predictive genetic test into the public consciousness with her announcement in 2013 that she underwent a double mastectomy after testing positive for a BRCA mutation.

Pharmacogenomics studies show how a person's genes can affect his or her response to medications. Ideally, pharmacogenomic (sometimes called pharmacogenetic) results could end some of the trial and error with drugs and help providers and patients choose the most effective drug right off the bat.

Testing the testing

Where federal dollars are concerned, precision medicine has already stepped out of the cancer box. In 2015, President Barack Obama committed $215 million to precision medicine research, including a genomic study

of more than a million Americans to extend precision medicine from cancer to other diseases. A year later, the 21st Century Cures Act expanded this funding to $1.5 billion over the next 10 years.

Aided by a multibillion-dollar genomic testing industry, some providers have started testing precision medicine beyond oncology. In 2018, Geisinger Health System in central Pennsylvania made a splash by announcing that it would add DNA sequencing to routine primary care. A small number of other hospitals are starting to monetize these tests. In August 2019, STAT reported that a handful of academic medical centers, including Brigham and Women's Hospital and the Mayo Clinic, have started elective genome sequencing clinics for generally healthy patients willing to pay hundreds, sometimes thousands of dollars in cash for a genetic workup.

> Not surprisingly, **payers have been reluctant** to cover sequencing tests of various kinds

Skeptics see carts preceding horses; solid evidence that routine genetic testing results in better outcomes is lacking. As one genome-sequencing clinic leader conceded in the *STAT* article, such testing can lead to expensive follow-up testing. Not surprisingly, payers have been reluctant to cover sequencing tests of various kinds.

Regulators have breathed life into some kinds of testing and poured cold water on others. Last year, 23andMe was the first testing company to get FDA approval to market a direct-to-consumer genetic test for three (of the more than 1,000 known) BRCA gene mutations linked to increased risk of breast, ovarian, and prostate cancer. But in April 2019, the agency issued a warning letter to Inova Health System in Northern Virginia to stop marketing pharmacogenomics tests it claimed could predict patients' responses to antidepressants, opioids, and other drugs. The FDA said it was unaware of data to support these claims.

A survey published two years ago in *Clinical Pharmacology and Therapeutics* found that clopidogrel, a blood thinner, was the medication most commonly tested for a drug–gene interaction, followed by simvastatin and warfarin. Nearly 40 academic medical centers and community health systems testing ways to implement pharmacogenomics in clinical practice were surveyed.

Evidence—or the lack thereof

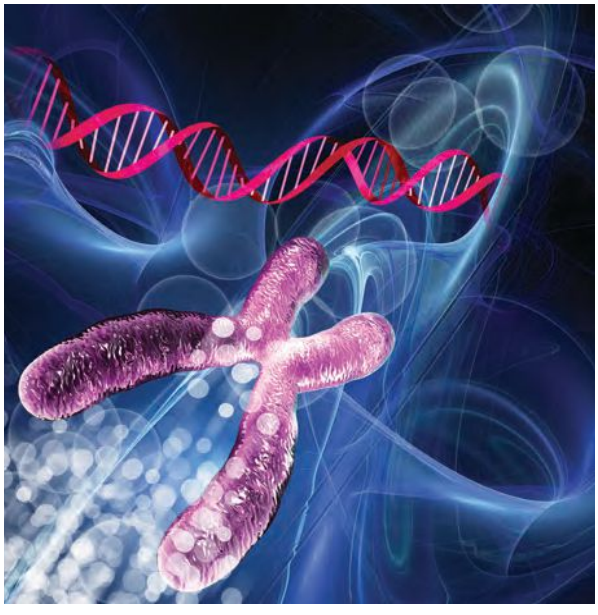
Some evidence suggests that traditional screening methods may not identify everyone at risk for certain inherited conditions. In a study published in *Science* three years ago, researchers at Geisinger and Regeneron (which manufactures Praluent, a drug used to treat familial hypercholesterolemia) found that only about one in four people carrying the familial hypercholesterolemia gene variant met the Dutch Lipid Clinic Network criteria (widely used diagnostic criteria) for genetic testing. Still, evidence for the clinical utility of many pharmacogenomic or predictive genetic tests is pretty scanty at this point.

"Right now, for the average primary care provider, there are a relatively limited number of situations where pharmacogenomic testing is clearly beneficial to outcomes in a way that's dramatic," says Greg Feero, MD, a faculty member at Maine Dartmouth Family Medicine Residency and a former senior advisor to the director of the NIH's genomics research division.

For predictive genetic testing, there are a few notable exceptions—hereditary breast and ovarian cancer, Lynch syndrome, and familial hypercholesterolemia—if certain criteria such as family history of the condition are met.

> ... many primary care providers are **uncomfortable evaluating and addressing** genetic risk

The CDC has designated genomics applications for these conditions as Tier 1, the highest tier on its evidence-based ranking system of genomic applications by their potential for a positive public health impact.



Source: GettyImages

In a 2017 editorial published in *American Family Physician,* Vinay Prasad, MD, and Adam Obley, MD, of Oregon Health and Science University said that rigorous meta-analyses haven't yet shown that genotype-guided dosing for warfarin, clopidogrel, or antidepressant selection is better than usual care. Prasad is a well-known critic of what he sees as the proliferation of medical treatments and therapies without good evidence behind them. "We need to know on a broad scale that [these tests] improve outcomes for patients, and don't just reassure physicians they're choosing a better drug," Obley tells MANAGED CARE.

Kathryn Phillips, *a health economics professor at University of California–San Francisco*

Prasad and Obley also argued in their editorial that without further proof of improved outcomes, routine genetic testing could just fuel more inappropriate care. Guidelines carve out clear boundaries for who should get tested because there are scenarios in which the risks and benefits of preventive measures aren't known, they said, noting that the U.S. Preventive Services Task Force advises against genetic testing for BRCA mutations in women without a family history of BRCA-related cancers.

A small pilot study suggests that genetic testing in primary care may not lead to improved outcomes. In 2017, *The Annals of Internal Medicine* published the first randomized trial of whole-genome sequencing in primary care. Gene variants were found in 20% of the participants whose genomes were sequenced. But six months later none of them had improved outcomes.

The test "produces lots of information," says Obley, who wasn't involved in the study. "But it's not clear that any patient was managed differently in a way that improved their health."

Will insurers pay the bill?

Without evidence supporting the clinical utility of routine pharmacogenomics or genetic testing, most payers are unwilling to cover them. Some exceptions exist, such as employers that offer routine genetic testing as an employee benefit. In a blog post published in 2018, Color Genomics touted Visa and the German software company SAP as customers. Medicare covers pharmacogenomic testing of two gene variants that predict warfarin responsiveness for beneficiaries enrolled in a randomized, controlled clinical study that meets certain standards.

Susanne Haga, *associate professor of internal medicine at Duke University School of Medicine*

The high cost of genetic testing has been cited as another reason insurance coverage is limited, but payers may not budge even as testing gets cheaper. "The cost of doing the test itself has been declining quite rapidly," says Kathryn Phillips, a health economics professor at University of California–San Francisco who researches personalized medicine access, quality, and reimbursement. She has disclosed in recent studies that she is a paid consultant for Illumina, a DNA sequencing company. But she says "it's hard—and it's going to take longer—to figure out where to use genetics in primary care in healthy populations, and [for insurers] to pay for it."

The current state of evidence and bleak reimbursement prospects haven't deterred early adopters from embracing precision medicine in primary care. For Megan Mahoney, MD, chief of general primary care at Stanford Medicine, precision medicine begins with going after data on key determinants of health—not just genes, but also environmental factors, social determinants, and health behaviors.

> Guidelines **carve out clear boundaries** for who should get tested

In a yearlong pilot of 50 patients—more than half of whom were at risk for cardiovascular conditions—Stanford Medicine care teams created personalized care plans to prevent and manage chronic illness. The plans leveraged data from several sources, including genetic-risk assessments and genetic testing for the three CDC Tier 1 conditions and remote monitoring devices.

Before the pilot, which ended in 2018, Stanford did not offer routine genetic testing in primary care. So far, that hasn't changed. But Stanford is making the genetic-risk assessment tested in the pilot available to its primary care providers, hoping it can increase screening rates for the Tier 1 conditions, says Mahoney. Studies show that many primary care providers are uncomfortable evaluating and addressing genetic risk. Five patients in the pilot discovered through the genetic risk screening that they're at high risk for breast cancer, demonstrating that this type of tool can help to identify previously unknown risks.

Post-pilot, Stanford is also offering patients with poorly controlled blood pressure connection to a Bluetooth-enabled blood pressure cuff and health coaching as part of a larger study. Genetic testing has dominated the discussion of precision medicine in primary care, but Stanford's experience shows that it isn't the only way to tailor preventive care to individual patients' needs.

Even if clinical utility is ultimately shown, folding precision medicine into primary care will likely follow the path of many new developments in medicine: There will be some early adopters, but most practices will have a wait-and-see and depends-on-the-reimbursement attitude.

Educating doctors on how to interpret, use, and communicate genetic testing results to patients will be one of the biggest hurdles. "They'll be learning on the job," says Susanne Haga, associate professor of internal medicine at Duke University's medical school, who leads educational activities in genetics and genomics for the Duke Center for Applied Genomics. An obstacle course of other possible barriers awaits: the limited number of certified genetic counselors, concerns about privacy and genetic discrimination, and the potential for the lack of diversity in genomic data sets to exacerbate disparities in care.

Still, Haga sees the convergence of three factors that will force the health care system's hand and usher in precision medicine in primary care: patients' increasing ability to influence decisions about their care, the declining cost of testing, and a critical mass of people, numbering in the millions, who will have had their DNA sequenced in genome programs such as Geisinger's or several national genomics research initiatives.

"It's coming," she says, "one way or another."

—Sarah Kwon

Lab Benefit Managers Seek To Stem The Rising Tide of Genetic Tests

As genetic testing gets more costly and complex, health plans call on yet another intermediary for help in curbing excessive utilization. But is adding a new middleman really the answer?

There are more than 140,000 genetic tests currently in use, and lab companies launch more than 15 new ones every day. The tests themselves have become more intricate as next-generation sequencing (NGS) technology has become common.

Using NGS, labs can find variances in 50 or more genes in one panel of tests. Because of the way billing codes work, the more genes a lab can pack into a panel, the more it can bill. While seeking variances in more genes may provide useful clinical information, ambiguity in how these panels are described and billed can confuse health plan billing systems because billing codes and coverage policies generally are organized gene by gene.

What's more, health plans' claims-adjudication systems fail to identify the specific test that was performed, making it difficult to determine coverage and pay a fair rate, according to Concert Genetics, a Franklin, Tenn.,-based tech company that helps health plans to address these problems.

That complexity—along with the difficulty payers have capturing the data needed to make efficient payment decisions based on medical necessity—has fostered the growth of laboratory benefit management (LBM) companies. LBM programs have come into their own since the turn of the century. Today all of the nation's largest health insurers either have an in-house department to manage the tests or contract with an outside LBM.

LBM services typically include programs to educate physicians and other health care professionals about genetic tests. They also develop lab networks, test formularies, and design coverage policies. Some will also provide utilization review and prior authorization services.

> LBMs could wind up **erecting barriers** to care

But some see LBMs as the introduction of yet another middleman into American health care that, in the name of management and efficiency, winds up adding an extra layer of cost and profit making. Insurers will need to answer the question of whether these companies can meaningfully improve the management of genetic testing—and whether the flood of results from these and other types of lab tests improves outcomes.

One recent investigation doesn't instill much confidence. In a *Health Affairs* blog post last October, Kathryn A. Phillips, a health researcher at the University of California–San Francisco, and Patricia A. Deverka, director of value evidence and outcomes at Geisinger, looked