US$1,000 **DIAGNOSTIC COST** of sequencing an individual's genome today, down from US$100 million in 2001

THOUGHT LEADERSHIP

MEDICAL MARVEL

Treating diseases on an individualized basis—the promise of precision medicine—is partly a data challenge.

BY ROB PRESTON

Speaking at a recent conference on "precision medicine," Genentech Executive Vice President Michael Varney asked the audience a rhetorical question: What is the worst thing a doctor can do to a patient?

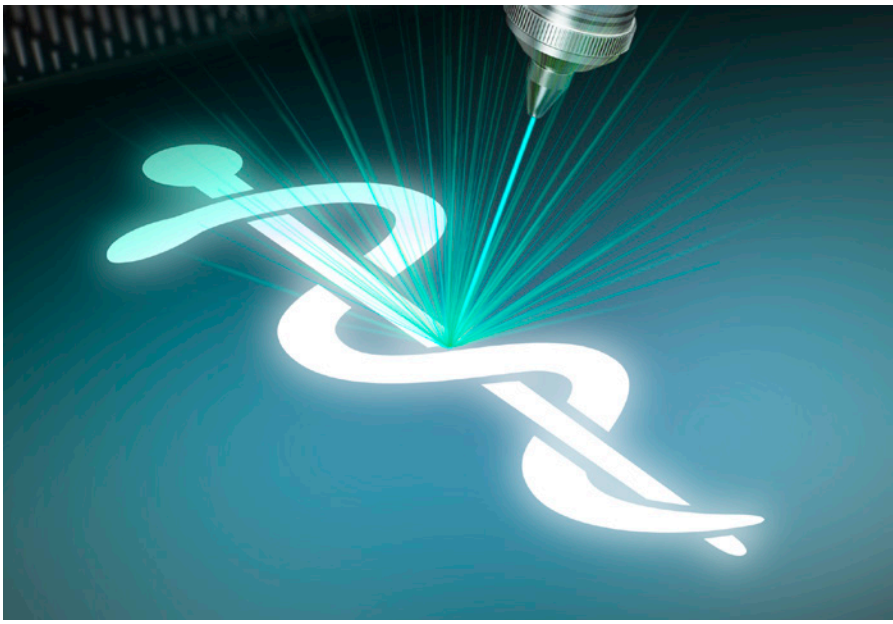
His answer: Give a treatment that has no chance of working.

Yet today that practice is far too common, not because of negligence or indifference, but because of inadequate or incomplete information about a patient's specific condition and viable treatments at the point of care.

It's a costly waste of time and resources for all involved, especially for the patient whose condition fails to improve or deteriorates, Varney told attendees of the conference, held at Oracle headquarters in late February 2016. The consequences are all the more serious when highly intrusive, even toxic treatments such as chemotherapy don't work, he noted.

The broad objective of precision medicine is to improve the efficacy of treatment programs by taking into account each patient's individual variability in genes, environment, and lifestyle, as well the specific variant or mutation of the disease or other condition he or she has contracted. Tapping into vast amounts of clinical data—from patient genome sequences to health records—precision medicine practices inform drug development and help determine how those drugs affect different people in different ways. And if making treatments more precise can also help reduce the US$2.7 trillion cost of US healthcare, which now accounts for a whopping 17.7 percent of GDP, all the better. "These breakthroughs aren't going to help if they're just for the rich," Varney said.

Precision medicine has been around for a couple of decades, but mostly in the realm of research labs and academic journals. It has moved into the clinical world over the past few years as pharmaceutical companies have climbed onboard (precision medicine already accounts for 42 percent of all drugs in development) and



I-HUA CHEN

the diagnostic cost of sequencing an individual's genome has plummeted (from US$100 million in 2001 to about US$1,000 today and expected to drop to a few hundred dollars within a few years). "One day soon genomic sequencing will become just like any other lab test a physician will order," says Jonathan Sheldon, global vice president of healthcare product strategy at Oracle, who holds a PhD in molecular biology/biochemistry and has been involved in precision medicine for the past 20 years.

ONCOLOGY AND BEYOND

Today, the beachhead for precision medicine is oncology: the prevention, diagnosis, and treatment of cancer. Almost every form of cancer can now be treated with drugs developed with specific patient and tumor biomarkers. Precision medicine treatments for colorectal cancer, for example, have increased survival rates for that disease by 15 percent.

Precision medicine is a natural fit for treating infectious diseases as well, as doctors seek to

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shorten the all-too-common "diagnostic odyssey" with those diseases, says Joseph DiRisi, chairman of the Department of Biochemistry and Biophysics at the University of California–San Francisco (UCSF) School of Medicine.

At the precision medicine conference hosted by Oracle in February, DiRisi offered the real-life example of a 14-year-old Wisconsin boy admitted to the hospital with a mysterious case of meningitis. Following weeks of extensive tests and procedures (including a brain biopsy and medically induced coma) that failed to reduce the brain inflammation or isolate its cause, the boy's doctor contacted UCSF, where a lab team generated millions of distinct DNA sequences from samples of the patient's cerebrospinal fluid and blood.

Using a UCSF-developed analysis tool, the team compared the patient DNA to samples in the GenBank database maintained by the National Center for Biotechnology Information, discovering a linkage to a type of bacteria native to the Caribbean, where the boy had been on vacation. Armed with that data, the doctors treated the boy with basic penicillin, eliminating the infection and leading to the patient's discharge from the hospital's intensive care unit in three weeks.

PRECISION MEDICINE ENTERS CRITICAL WORKFLOWS

As precision medicine moves from the research labs onto the front lines of patient care, doctors need timely access to the latest clinical and genomic information. And they need an easy way to discuss best treatment options for individual patients with a range of third-party experts.

Those experts include researchers who uncover genetic biomarkers and molecular pathologists who identify the actionable biomarkers for a given condition. Clinicians then evaluate the resulting data and advise on treatments. What those experts have lacked, however, is a scalable and secure way to collaborate.

Enter Oracle Healthcare Precision Medicine, software that addresses the data aggregation, knowledge sharing, data normalization, and workflow issues that restrict the timely creation of patient molecular profiles. Key benefits of the software include support for genomic testing, ranging from gene panels to whole-genome sequencing; accelerated test throughput via streamlined lab workflows; consistent report design and simplified clinical action planning; auditability for regulatory compliance purposes; and integration with electronic medical records systems.

Early adopters of the new software include major medical centers. "We're initially working with the molecular pathology, medical genetics, and clinical genomics guys, because they're the people who are interpreting this data and liaising with the physician in front of patients," says Jonathan Sheldon, global vice president of healthcare product strategy at Oracle.

Most major medical centers first tried to build their own precision medicine workflow systems over the last 10 years, Sheldon says. "They came to Oracle because they realized that they couldn't maintain it and they couldn't ensure that it was going to be scalable as the data grew," he says. "A lot of them would rather buy the infrastructure and the platform and then focus on all the great science they can do on top."

More so than with most forms of cancer, speed of diagnosis is critical with infectious diseases, DiRisi said. The workflow developed by the UCSF lab reduced the time between sample collection and actionable diagnosis to about 48 hours, ultimately helping the medical team in Wisconsin save the boy's life. "If you have a data-driven diagnosis up front, you're not guessing about what it could be," he said. "We should be treating all of these things as data."

GOVERNMENT BACKING

Precision medicine is now becoming a government priority as well. During his State of the Union address in January 2015, President Obama set aside US$130 million for the National Institutes of Health to build a 1-million-participant group, called a cohort, that will support precision medicine research for a range of diseases, as well as US$70 million for the National Cancer Institute to conduct cancer-specific genomics research. Enrollment in the cohort is expected to begin this year.

Elsewhere, a 100,000-person genome-sequencing project started in the UK will focus on patients with rare inherited diseases, cancer, and infections. And science journal *Nature* reports that China could be finalizing plans for a 15-year, 60 billion yuan (US$9.2 billion) initiative that could span hundreds of projects to sequence genomes and gather clinical data to fight cancer, heart disease, and other common diseases in that country.

"These things are moving slowly, but at least they're pointed in the right direction," says Steve Rosenberg, senior vice president and general manager of Oracle Health Sciences, who sees Alzheimer's and Parkinson's disease as two of the next frontiers. "So a slow pace is a good thing, because in this particular case we don't understand exactly how all of this is going to happen."

For societies to realize the full potential of precision medicine, they need to mesh it with the broader movement toward population health, Oracle's Sheldon says. That alignment may seem contradictory, he acknowledges, given that population health is about defining and treating large groups of people, while precision medicine is about treating individuals. "But actually it's highly synergistic, because precision medicine gives you the molecular tools to accurately dissect the disease and the phenotype to a level of granularity where you can start to manage clinical and financial risk at a population level," Sheldon says. "So being able to understand the individual means you can extrapolate up to the population in a meaningful way."

There are still myriad challenges. Among them are creating smooth information workflows

among researchers, pathologists, and clinicians (see the "Precision Medicine Enters Critical Workflows" sidebar); standardizing descriptions of genomic and other relevant data; isolating clinically actionable information and creating individual diagnostic reports; scaling the supporting IT infrastructure and ensuring it interoperates across the public and private sectors; and funding all of this heavy lifting.

Consider just the IT challenges. In its raw form, whole-genome sequence data takes up 500 to 600 gigabytes of storage per sample. Multiply those numbers by just one 1-million-patient cohort, and you start to grasp the magnitude.

"And remember: It's not just the genomic data that is really important," Sheldon says. "It's also all the context that sits around it. So you need to be looking at clinical data, claims data, image data, remote-patient monitoring, and self-reported data. It just goes on and on and on."

Meantime, all of that data needs to be shared over broadband networks, and internally it needs to be queried and analyzed in a timely manner. A lot of this genomic data also needs to flow back into clinicians' electronic medical records systems, which weren't designed for that purpose.

Another major challenge is educating doctors in community hospitals—not just in the major medical centers—about precision medicine best practices and outcomes. Those doctors can be resistant to change. "One of the promises of this whole genomic movement is to try to bring that care to the patients who need it as opposed to just the medical centers that want to do it," Oracle's Rosenberg says.

And let's not forget that precision medicine is a business, so one of the big ongoing challenges is reimbursement. Leaders at the US Centers for Medicare & Medicaid Services are still considering which of these tests to pay for, as are those at commercial payers such as UnitedHealthcare, Blue Shield, and Aetna. "From an industry perspective, we've already done the big research to understand better which genes are linked to which disease," Sheldon says. "But it's only really now that we're starting to look at the financial impact of changing that care pathway because of that genetic test. And you need to do those studies in order to justify reimbursement."

STILL QUESTIONS ON COST

The theory is that because drugs and other treatments typically work only 20 percent to 40 percent of the time, precision medicine will eliminate plenty of wasteful spending. But the jury's still out on the cost savings. Lots of new drugs that ultimately don't work represent no advance, noted Paul Markovich, CEO of Blue Shield of California, at the Oracle-hosted conference.

Dr. Michael Seiden, chief medical officer of McKesson Specialty Health and the US Oncology Network, agrees, saying there's no evidence yet that precision medicine has "bent the cost curve down." Dr. Seiden is more positive about precision medicine's progress in other areas, giving it a grade of A for the speed and cost of genome sequencing and an A- for the "unbelievable" scientific discoveries.

But he gives precision medicine only a B- or C+ for improving patient outcomes, because the number of conditions whose outcomes can be significantly improved by targeting specific mutations is still relatively small. For every positive story, such as the diagnostic sleuthing that led to the successful treatment of that Wisconsin boy, there are cases where such sleuthing leads to a dead end or conditions prove unresponsive to precision medicine treatments. Some question whether the medical community should focus its scarce time and money elsewhere—on getting people to lose weight and stop smoking, for instance—rather than on complex and still expensive targeted treatments.

The biggest challenge may still be the ever-evolving science of precision medicine—keeping up with disease mutations and variations, and matching effective treatments to individual cases. The healthcare industry can always overcome the technology limitations, Dr. Seiden said, but the scientific limitations are far more daunting. He compared the situation to space travel: We have the rocket technology for manned travel to the stars; the really hard part is keeping a person alive for the centuries-long journey.

One thing is certain: The precision medicine field has evolved tremendously from its hopeful beginnings. Says Oracle's Sheldon: "Some people are still a bit in denial by saying, 'Oh, it's still mostly research. We don't understand a lot about all the variations you can see in the genome.' But the reality is we are making therapy decisions based on whole-genome data or gene-panel data, so it's here already. All that's going to happen is we're going to be doing much more of it, and our clinical accuracy will increase as the knowledge-base necessary for interpretation grows." □

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ACTION ITEM

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