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Gene Machine

Matthew Herper, 01.17.11, 6:00 PM ET

Flash of life: Jonathan Rothberg holding one of the silicon wafers from which his DNA-decoding chips are cut.

The machine that could change your life is a compact device, only 24 inches wide, 20 inches deep and 21 inches high. At a glance you might mistake it for a Playskool toy--or, better yet, the Apple II computer, which sparked a revolution. Indeed, this gizmo, developed in a drab office park overlooking a duck pond in Guilford, Conn., could have as dramatic an impact as any technology since the personal computer and help kick off a market that one day could be worth perhaps as much as $100 billion.

Take a closer look. On the right side is an 8-inch touchscreen, on the left a dock that allows data to be downloaded to an iPhone. Below that is a row of four test tubes, marked with a circle, an X, a square and a plus sign. These symbols represent the four basic chemical letters, or bases, the body uses to form DNA--guanine, cytosine, adenine and thymine.

Audaciously named the Personal Genome Machine (PGM), the silicon-based device is the smallest and cheapest DNA decoder ever to hit the market. It can read 10 million letters of genetic code, with a high degree of accuracy, in just two hours. Unlike existing DNA scanners the size of mainframes and servers, it fits on a tabletop and sells for only $50,000, one-tenth the price of machines already out there. For the first time every scientist, local hospital and college will be able to afford one. If the PGM takes off and regulators let him, your family doctor could buy one--and so could you, if, say, you wanted to see how fast that thing growing in your fridge is mutating.

Invented by engineer and entrepreneur Jonathan Rothberg, such desktop gene machines could transform medicine, agriculture, nanotechnology and the search for alternative fuels. Using DNA sequencing, Rothberg says, doctors in the not-too-distant future will finger genetic weak spots in tumors and treat cancer patients with customized drugs. (This is already happening at some cancer centers.) Kids born with rare diseases will get large portions of their genome decoded to pinpoint the cause, eliminating guesswork and misdiagnoses.

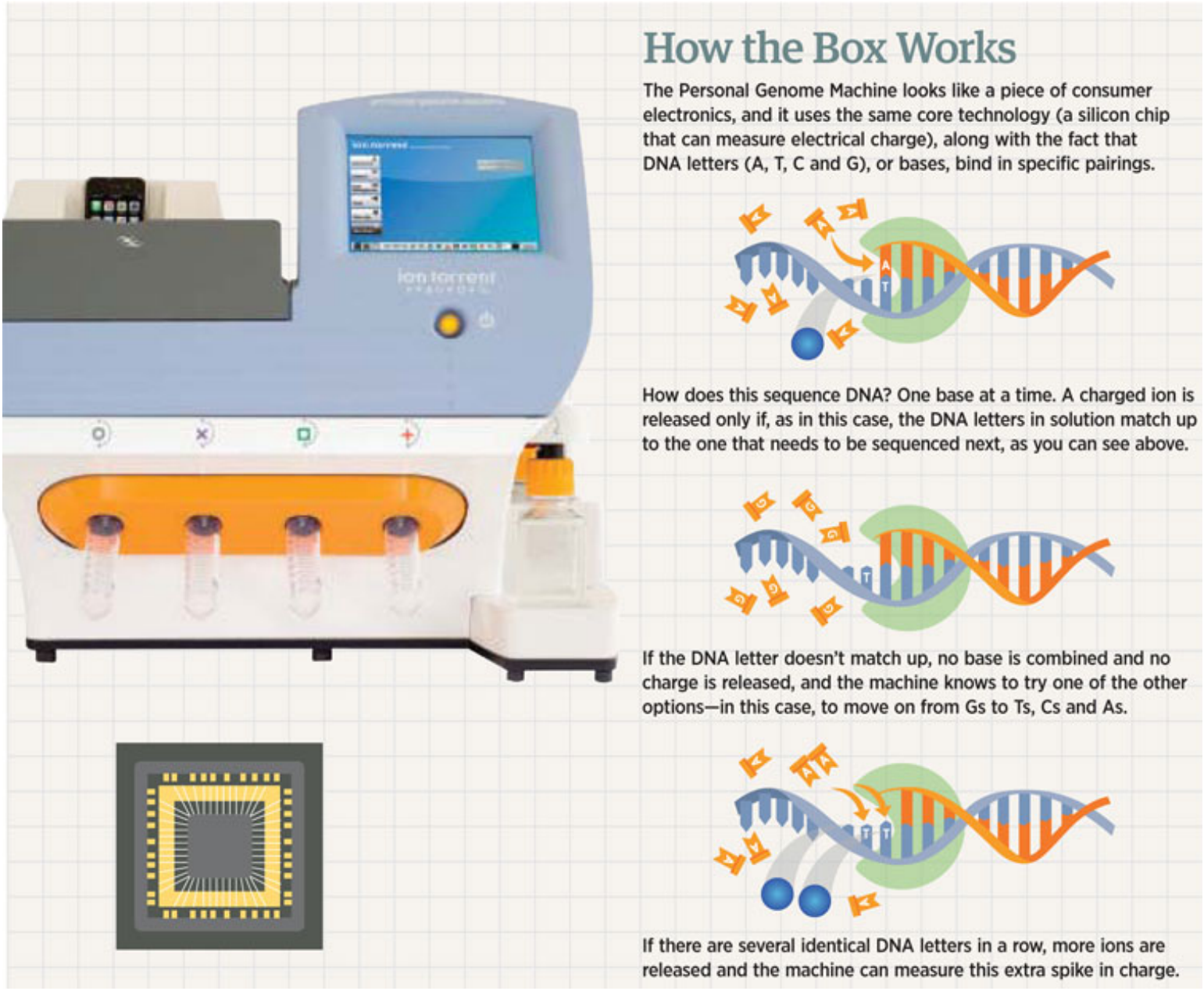
Outside the lab, rescue workers in the Third World might use portable gene machines to trace bacteria or viruses causing waterborne epidemics. Airport officials could take genetic samples from travelers to track infectious bacteria and viruses before they become outbreaks. Engineers can use DNA readers to concoct designer microbes to grow future fuels. DNA sequencing will help farmers breed supercrops that grow faster, resist pests and drought and need less fertilizer. Synthetic biologists might harness bacteria to make laundry detergent, clothes, furniture, even concrete that self-heals cracks.

"Sequencing is going to affect everything," says Rothberg, 47. "This is biology's century--just [as] physics was the foundation of the last century." Citing the $100 billion medical imaging industry, he boasts, "I believe sequencing will be that big."

There's substance behind the bravado. An engineering geek with a flair for marketing, he has founded four genetics companies. His current startup, Ion Torrent, created the PGM just three years after Rothberg dreamed up the idea; a soft launch took place Dec. 14. The device has at least one big believer: Life Technologies, a $3 billion (sales) lab equipment maker, was so impressed that it bought his company for $375 million (plus milestones worth another $350 million or so) this fall, before the machine was done. "He has wonderfully romantic ideas and pulls together dream teams of people and doesn't let anyone get in his way," says Kevin Davies, who has a doctorate in molecular genetics and is author of The $1,000 Genome (Simon & Schuster, 2010).

You think you've heard this before, don't you? Genomics has certainly been overhyped--and so far failed to deliver on its promises. Many intelligent people have relegated the idea to the dusty corner shared by hopes for cold fusion, world peace and World Series rings for the Chicago Cubs. When scientists first mapped the human genome a decade ago, they bragged it would lead to cures for Alzheimer's, heart disease, schizophrenia and more. It hasn't happened. Drug approvals have gone down. The search for the genetic roots of heart disease, diabetes and other common ills has yielded surprisingly little useful information for the average person. Even 23andMe, the high-profile consumer gene-testing company cofounded by Anne Wojcicki, the wife of Google's Sergey Brin, had to lay off people last year.

The problem, Rothberg says, is that technology simply hasn't been powerful enough to decode the genetic secrets lurking behind diseases like cancer, lupus and autism. As you may or may not remember from high-school biology, there are 6 billion chemical letters that make up the DNA double helix at the center of every cell. Some of it is probably genetic gibberish; a lot of functions are waiting to be discovered. But scattered throughout that DNA are 20,000 genes, the recipe books that tell the body how to make proteins such as insulin, muscle, hemoglobin, brain tissue, bone, clotting factor--virtually everything in our bodies. A single wrong letter hidden deep inside a gene can boost the risk of colon cancer or diabetes.



Finding the errors that cause disease and distinguishing them from numerous harmless genetic variants is turning out to be an immense data-crunching challenge. But the technology to meet that challenge is also improving at an extraordinary rate. It took government researchers a decade to decode the first human genome at a cost of $3 billion to taxpayers. In a virtual tie with private efforts by gene maverick Craig Venter, the race was finally finished in 2001. Now you can get an accurate reading of a person's entire DNA sequence for only $10,000 in a few weeks. Nearly 3,000 people have gotten such scans, mostly as part of research studies. The number could soar to hundreds of thousands by 2012, say sequencing experts. "What is possible now . . . even a few years ago would have been unthinkable," National Institutes of Health director Francis Collins said in a recent speech.

Despite the steady drone of genetics studies in top medical journals, most scientists still don't have access to DNA-decoding technology. Existing sequencers are like computer mainframes in the 1960s. They cost $600,000, take a week to yield results and need scads of technicians to run them. Half of the 1,400 DNA-sequencing machines in the world reside at just 20 big academic and government research centers, according to Goldman Sachs.

Rothberg's machine could change all that through speed of analysis and wider dissemination of tools. He says that only 400 labs are currently doing this sort of genomics, and he wants the PGM to open the field to 4,000 research groups that

are not participating. That will multiply the number of minds working on genetics problems and unleash lots of experiments that now languish on the sidelines. "I can create a fanatical user base, and people will start coming up with more and more applications for the technology," says Rothberg. "The demand is going to be enormous," predicts UC, Davis researcher Jonathan Eisen. "You're going to see a huge number of people buying it." George Church--a Harvard gene researcher, sequencing pioneer and Ion Torrent adviser--predicts the PGM will be "like an iPad" for geneticists. Everyone will want it "big-time, even if there are warts."

But as of now it's still a small-time business. Right now the market for DNA sequencing hardware is $1.5 billion, mostly through sales to scientists. Medical gene tests and other molecular diagnostics generate another $2.6 billion, according to PricewaterhouseCoopers.

How do you get from a $4 billion business to a $100 billion one? Rothberg's answer is that, like radiology, there will be armies of trained physicians using specialized machines, as gene scanning hits the medical mainstream; that gets expensive very quickly. Here are the assumptions--admittedly very speculative--for what could happen in 20 years:

- Cancer is the biggest near-term market. Today treating a cancer patient costs hundreds of thousands, sometimes millions, of dollars. Some breast cancer patients already get a specialized gene test to help determine what treatment is right for them. If similar gene tests become routine for all 4 million cancer patients in the U.S. and Europe, as many oncologists expect, this alone could be a $20 billion market. Some patients might be sequenced multiple times as a tumor spreads and mutates. Total so far: $40 billion.

- Another $10 billion market could come in scanning kids and adults with unexplained symptoms for rare inherited diseases or other genetic risk factors. A whole new medical specialty may sprout up to interpret the complicated data produced by gene scans and tell patients what it all means, another $10 billion. Now you're up to $60 billion.

- Tracking the movement of infections in hospitals, airports and public places like shopping malls to identify microbes and prevent them from becoming epidemics--that has to be a $10 billion industry. Running tab: $70 billion.

- If costs drop low enough, affluent people may start getting their genomes--or those of their newborn children--on a thumb drive as a precautionary measure. If 50 million people a year do this at a cost of $2,000 per test, that would bring the tally to $80 billion.

- The market for sequencing genes in agriculture, resulting in better mate selection in the livestock industry and for optimal seed selection to get maximum yields is, perhaps, a $5 billion market. Total thus far: $85 billion.

- Numerous other industrial applications, such as searching for designer biofuels, designing new enzymes for laundry detergent--and doing other things that haven't even been imagined yet could easily add another $15 billion over time. Et voilà: $100 billion.

Race to the Future

NEW, POWERFUL DNA DECODERS ARE A FAST-GROWING MARKET, ACCORDING TO GOLDMAN SACHS. HERE IS A RUNDOWN OF THE PLAYERS.

COMPANY	POSITION/BATTLE PLAN
ILLUMINA San Diego, Calif.	The leader. Lowered cost of sequencing a human genome below $10,000. It has 63% market share of next-gen sequencers and is betting on new technologies to maintain its lead. Annual sequencing sales: $450 million.
LIFE TECHNOLOGIES Carlsbad, Calif.	The comeback? Once the only maker of DNA sequencers it now has only a 17% share of next-gen machines, though it still sells older models. Can devices like the Ion Torrent Personal Gene Machine help it grab back the cutting edge?
COMPLETE GENOMICS Mountain View, Calif.	The factory. The company sells DNA sequencing at a bulk rate from a single, giant complex. It counts Pfizer and Eli Lilly as customers and says it can sequence 400 genomes per month.
PACIFIC BIOSCIENCES Menlo Park, Calif.	Speed reader. PacBio is the first sequencer to read single molecules of DNA. It is fast and potentially useful for infections and cancer, but some experts worry the error rate is too high. PacBio says the errors average out.
OXFORD NANOPORE Oxford, U.K.	The next wave. Its device reads a single molecule of DNA in a way that could become very cheap. It is still at least three years away, but its alliance with Illumina could be a powerful marketing advantage.
ROCHE AND IBM Basel, Switzerland and Armonk, N.Y.	The giants. Roche has the first of the new sequencers (the one invented by Rothberg); this 454 sequencer has 18% market share. Its next bet is on "DNA transistor" technology from IBM that could be fast and cheap.

SOURCES: GOLDMAN SACHS ANALYST ISAAC RO; COMPANY STATEMENTS; FORBES REPORTING.

"'We've gone faster than anybody thought we could," says Illumina Chief Jay Flatley. He says he'll continue to dominate the competition.

Have we mentioned the ifs? Like all potentially disruptive innovations, gene sequencers could fizzle. Their success depends on unpredictable events: how fast the technology improves, how quickly researchers can make medical discoveries based on the new machines and--most critically--whether drugs can be developed to treat diseases. Gene test prices could drop, becoming a low-margin commodity like medical blood tests (cholesterol, blood sugar and so on), which, at a few bucks a pop, are a $40 billion business. Ultimately Rothberg's machine may not win. Like the Commodore 64 home computer that dominated in the 1980s and disappeared soon after, the PGM could be quickly eclipsed.

Rothberg faces three formidable hurdles. First, the market for sequencing is dominated by Illumina of San Diego, whose big machines have helped make most of the major discoveries so far--and competing won't be easy. Next, a novel (and faster) approach could leapfrog the Ion Torrent device. Finally, sequencing could ultimately be a bust if it proves tough to find genes linked to disease, or improved cancer diagnoses and hoped-for improvements in manufacturing drugs.

At least a dozen venture-backed companies are competing for the title. Pacific Biosciences in Menlo Park, Calif. raised

$200 million in an October initial offering on top of $370 million of venture funding. Its machine is due in early 2011 and will be the first to scan a single DNA molecule. Nearby, in Mountain View, Complete Genomics (whose November IPO raised $90 million) is betting that DNA scanning will become a service industry like pathology where everything is sent to giant centralized labs.

Like early PCs, Rothberg's gizmo has limitations. It won't compete immediately with the monster machines from Illumina because it can decode only a tiny fraction of the human genome at a time. The first version of the PGM can read a modest 20 genes at once. This may be enough for many smaller jobs, as when a doctor wants to test a tumor for a small number of disease-causing genes and whether a certain drug is likely to work on a particular tumor, or if an infectious-disease researcher wants to verify which strain of microbe is present in a saliva sample or water source.

Illumina Chief Executive Jay Flatley claims the PGM poses no threat. "We've gone faster than anybody thought we could," he says. Indeed, his machines can crunch a thousand times as much data as the PGM. "That has relegated everybody else to niche markets." More proof: Illumina's shares are up 700% over five years. His team is working on many next-generation technologies that could render Ion Torrent obsolete, including one that will read a single DNA molecule. That's huge. Right now detection isn't able to do this and instead requires thousands of copies of molecules to be made.

But Rothberg's secret sauce is rapid scalability. Because his gene machine is the first DNA decoder to rely on silicon transistors, it should improve performance very quickly; he says an upgrade, due out in the first half of 2011, will be ten times as powerful as the original. He explains he is building on the $1 trillion already spent on microchip R&D and manufacturing. "Once you move to a semiconductor device, obviously taking advantage of Moore's Law"--that you can double the number of transistors on a chip every 18 months-- "things get cheaper and they become ubiquitous," he says.

He vows to have a machine by 2012 that will decode in two hours all 20,000 human genes that code for proteins. (This is roughly 3% of all DNA and will still be far behind Illumina, which can do all the DNA twice.) Eventually, he hopes to create a machine the size of an iPad. "There isn't a technology that we will not pass in a very short period of time," he says. "It doesn't matter how far ahead they are."

Behind the swagger lies a serious mission. Rothberg's 14-year-old daughter, the oldest of his five kids, has a mild form of an inherited disease called tuberous sclerosis complex, a relatively rare disorder (50,000 or so Americans have it) that can cause benign tumors in the heart, kidney, skin, lungs, eyes and brain, where seizures can occur. Gene scanning might help nail the causes so that drugmakers can find a cure. "All motivation forever has been personal," Rothberg says, "because we all want to affect the people we love," adding: "If it [were] just intellectual, I would have a company now doing artificial life . . . making non-DNA."

Rothberg grew up in New Haven, Conn. in a family of science-oriented entrepreneurs. His father, a chemical engineer, owns a company that makes high-performance adhesive for tiles. As a kid Jonathan went on sales calls with his dad. In college at Carnegie Mellon, where he majored in chemical engineering, he idolized Steve Jobs and went to hear him speak. He still has a 1982 Time magazine cover story on the Apple founder.

He founded his first company, Curagen, in his basement in 1991 soon after getting a doctorate in biochemistry from Yale. It was one of the first biotech firms to automate the search for new genes with robots and easy-to-repeat experiments.

The timing was great. Just a few years later Craig Venter started making headlines for his gene-sequencing work--giving biotechnology a lofty place alongside the dot-com boom. Curagen went public in 1999. By the next year it had a market cap of $5 billion, bigger than American Airlines. In 2001 Curagen notched one of the biggest biotech deals of its time, a $1.5 billion agreement with Bayer to develop drugs for obesity and diabetes.

Like most of its high-flying genomics peers, Curagen was soon in Icarus free fall. Its lead drug to treat chemotherapy side effects failed, and the Bayer deal yielded nothing fast. Investors started to bail. Rothberg got pushed out in 2004. In 2009 drug developer Celldex Therapeutics of Needham, Mass. bought the remnants of Curagen for just $95 million.

While still at Curagen Rothberg realized that better technology was needed to make genetic medicine a reality. When Noah, his second child, was born in 1999, he had to be sent to the neonatal intensive care unit because of breathing troubles. Noah turned out to be fine, but Rothberg was frustrated that doctors didn't have a rapid test to ensure his son didn't have an inherited disease. Sitting in the hospital waiting room, he thought about the similarities between gene sequencing and microelectronics. Existing DNA sequencers, he reasoned, used clunky technology akin to computers based on vacuum tubes. He thought he could do better. He infuriated his wife by spending most of his paternity leave working on the new technology that used firefly enzymes to read DNA with light.

The idea evolved into 454 Life Sciences, a Curagen subsidiary Rothberg created to commercialize the new machine. He clung to 454, even after he left Curagen, announcing with dramatic flair in 2005 that he would use the machine to decipher the genome of DNA codiscoverer James Watson for only $1 million, far lower than anything before. The project finished on budget in 2007. By that time Rothberg had lost control of 454. Curagen sold it to Roche for $140 million in 2007 to raise cash; Rothberg's creation is still on the market but has been crushed by machines from rival Illumina.

Rothberg himself is indestructible. It's a little hard to tell whether the 8-foot-high slabs, made of 700 tons of Norwegian granite, he recently installed in his back yard is a monument to Stonehenge--or to his own obstinacy. His neighbors in Guilford hate "The Circle of Life," as the sculpture is known. "I don't do anything out of spite," says Rothberg.

A conversation with his son Noah in 2007 led to the founding of Ion Torrent. Acting the precocious 8-year-old he was, Noah asked his dad to invent a machine to read minds. Rothberg, addressing the boy as he would a peer, told him the best way to do that would be to create a tiny chemical sensor that could read electrical signals passing between brain cells. It slowly dawned on Rothberg that a sensor like that could be used for DNA sequencing.

Most existing DNA sequencers (including the 454 machine) do their reading by attaching light-producing molecules to DNA, taking pictures and analyzing the resulting image. This optical technology requires all sorts of complicated cameras and robotics, along with huge data files to handle the images.

Rothberg's elegant contribution was to come up with a sensor that directly reads telltale electrical signals produced as DNA copies itself. This vastly simplifies the process and allows engineers to make machines for far less. He founded Ion Torrent with an undisclosed amount of his own money in 2007 and later took in $23 million in venture capital. Still smarting from the loss of 454, he made sure this time to retain a supervoting share majority so he couldn't be forced out.

At the heart of the personal genome machine is a silicon chip with 21 million transistors on it--the equivalent of a desktop computer circa 1995. On top of the chip is a tiny channel the width of two human hairs into which DNA is fed. Each DNA molecule in the body contains two long strands of chemical letters, or bases--A,T, C and G--that come together like a twisted ladder (a.k.a. the double helix). The machine takes a single DNA strand and uses an enzyme to attach bases to it. Every time the enzyme connects two bases--an A to a T or a C to a G--an electrically charged ion is released and detected by sensors on the machine. By exposing the DNA sample to only one letter at the time, the machine can reconstruct the entire sequence.

"It is an absolutely beautiful machine," says Randy Scott, chairman of the cancer-gene tester Genomic Health. He adds that his company may switch to the Ion Torrent machines if they live up to their potential. "Jonathan has done a great job at staying ahead of the curve."

That curve is arcing toward guiding cancer treatment. Illumina's Flatley has had his own genome sequenced and learned that he has a gene for a condition that causes people to get a rash when they are cold. His company is seeing "a stream of infants and cancer patients" who want their genomes sequenced. Life Technologies has signed up a network of cancer centers to probe tumors with its current mainframe system. If a DNA scan of a tumor can predict which treatment will work best, insurers will likely pay up, even though treating cancer patients can be hugely expensive.

But existing machines from Illumina and Life Technologies can take up to eight days to return any data--an eternity for cancer patients who need treatment right away. Moreover, the current technology forces cancer pathologists to wait that entire time, even if they just want to analyze a few genes. It's almost like the difference between waiting for a letter and a text message.

Right now all DNA sequencers are only approved for research use, but scientists are trying to move them into clinical practice anyway. Gordon Mills, chairman of the department of molecular therapeutics at MD Anderson Cancer Center in Houston, says such use is "imminent." He is starting a project to sequence 1,000 genes that might serve as targets for cancer drugs in 10,000 patients. He hopes to figure out if this improves the odds for sick patients, as well as to find ways to get and store tumor samples, save data afterward--and leap over barriers set up by Medicare and the Food & Drug Administration.

Rothberg sees potential health care applications for the PGM. Doctors already use genetic mutations in HIV to predict which drugs a patient's virus will be able to fight off. They are always looking for better ways to do this, and the PGM could help, he says.

He says his next machine, due within six months, will data mine 200 or more genes at a time, and that's what oncologists need right now to make diagnoses and pick drugs. That's just what Massachusetts General Hospital pathologist John

Iafrate, who received a free sequencer as part of a contest Ion Torrent held to drum up interest in the technology, is hoping to prove.

There are plenty of uses beyond cancer treatment. Because Rothberg and his wife are both Ashkenazi Jews, they were advised to get 15 genetic tests (for such things as Tay-Sachs disease) before they had children. This, too, he says, represents a perfect niche for the PGM. As new disease genes are discovered by sequencing hundreds of thousands of people, a swelling population will undergo specific panels of tests of 15 genes or more.

Another free-machine recipient, Mitchell Sogin of the Marine Biology Laboratory in Woods Hole, has developed a way to use DNA sequencing to track down sources of fecal contamination in drinking water in developing countries and elsewhere. He is currently using 454 machines for the project but hopes the PGM will be fast enough to pinpoint the source of microbes in real time. Ion Torrent has competition here. In December Pacific Biosciences used its DNA reader to identify the lethal cholera germ in Haiti. The data proved that the microbes did not travel across the ocean, as some feared, and were instead carried by human hosts who might have been caught by better screening.

Ironically, perhaps, the first iteration of Rothberg's genome machine is poorly suited to the one market closest to his heart: rare inherited diseases. These are "at the core of everything I do," he says. There are roughly 6,000 such diseases, including Charcot-Marie-Tooth, a neurological disorder, and Miller Syndrome, characterized by severe facial and limb deformities. Their causes are being identified using DNA scanning. And a few kids had their treatment changed as well. Some diseases may not be so rare. Autism could turn out to be a collection of unusual genetic defects that produce similar symptoms.

Rothberg won't openly discuss his daughter, who was diagnosed with tuberous sclerosis complex (TSC) in 1997 when she was an infant. And yet, during conversations, he constantly steers the subject back to the disease, even though it makes him emotional.

In 2001 Rothberg and his wife, Bonnie, a medical epidemiologist, started the Rothberg Institute for Childhood Diseases in Guilford, near his 11-acre home, to speed the hunt for rare disease cures. Two genes that cause most cases of TSC are already known. Rothberg's Institute is sponsoring a search for a third. In 2003 a small clinical trial sponsored by the Institute showed that the generic transplant drug rapamycin targeted the two bad genes and helped tuberous sclerosis symptoms, making some skin lesions go away. In the wake of the results Novartis decided to test its similar medicine, Afinitor, in kids with the condition. It worked and is now approved for preventing brain tumors in kids with the disease.

Rothberg says a few years ago he would have snapped at anyone who told him that TSC might be curable. "I would have said you're naive, the kidney's damaged, the skin's damaged," he says. Now he is much more optimistic.

There are still respected scientists who think genomic sequencing is doomed to stay forever in the labs, absorbing funds in absurd proportion to the benefits they provide. Cynics are advised to recall what Kenneth Olsen, founder of minicomputer maker Digital Equipment Corp., once told the World Future Society: "There is no reason for any individual to have a computer in his home."