special report

THE ‘ME’ IN MEDICINE
PERSONALIZING TREATMENTS

The genome unleashed
Now what?

Genetic medicine 101
An ethical conundrum in the classroom

A dream come true?
Testing a new targeted treatment for breast cancer

Look who’s boss
Genes are just part of the story

Health?
There’s an app for that
A conversation with Thomas Goetz, editor of Wired
2010 is one for the School of Medicine’s record books, with the opening of the most new building space in a single year in the school’s history. Dedication ceremonies took place in late September for the 120,000-square-foot Li Ka Shing Center for Learning and Knowledge, followed one month later by the opening of the Lorry I. Lokey Stem Cell Research Building, at 200,000 square feet. By comparison, when the school first moved from San Francisco to Palo Alto in 1959, the buildings in use that first year (Alway, Lane and Edwards) totaled 268,000 square feet, according to the school’s facilities office.

Together, the new buildings embody the school’s goals of transforming both education and stem cell research, and making discoveries and innovations that will improve the future of health care.

The Center for Learning and Knowledge is the school’s new “front door” and home to its classrooms and training facilities. The five-story structure has a diverse array of technologies that represent the latest in medical education. It is designed for interactive, experiential and team-based approaches to learning for people at all levels, from incoming medical students to experienced clinicians who want to polish their skills.

David Gaba, MD, associate dean for immersive and simulation-based learning, says the building’s simulation center is one of the largest and most comprehensive facilities of its kind.

“We will never entirely replace the apprenticeship model, where you learn based on the idea, ‘See one, do one, teach one,’” Gaba says. “But there is a lot we can do in simulation that fills the gap in the traditional system of learning,” where trainees treat only those patients who come through the door and may not be exposed to the full range of medical problems.

The nearby Lokey building will be the nation’s largest stem cell research facility, with 33 research labs comprising 528 research benches. Scientists in the four-story building — which features a dramatic glass sculpture by artist Dale Chihuly — will be involved in the full spectrum of stem cell programs, including research in embryonic and adult stem cells, cancer stem cells and the development of disease-specific stem cell lines. They represent disciplines that include neurology, cancer, transplantation, immunology, cardiology, developmental biology and bioengineering.

“What is important is that it will give people the opportunity to apply stem cell thinking to different problems, including regeneration, aging and cancer,” says Irving Weissman, MD, director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine, which is housed in the new building.

The new facilities were financed with a mix of philanthropy and school funds and, in the case of the Lokey building, a grant from the California Institute for Regenerative Medicine. Looking further into the future, the school’s construction plans include the 2012 completion of the Jill and John Freidenrich Center for Translational Research, at 800 Welch Road; new buildings that will house the school’s cardiovascular, neuroscience, cancer and immunity/transplantation/infection institutes; and the eventual demolition of the Alway, Lane, Edwards and Grant buildings to make way for three new research facilities. — SUSAN IPAKCHIAN
Special report

THE ‘ME’ IN MEDICINE: PERSONALIZING TREATMENTS

COVER STORY
The genome is out of the bag 8
Now what?
BY KRISTA CONGER

Wired up 16
Health? There’s an app for that
Q&A WITH THOMAS GOETZ

Will breast cancer meet its match? 18
Seeking tailor-made treatments
BY STEPHANIE PAPPAS

Reading between the genes 24
Look who’s boss
BY BRUCE GOLDMAN

Test questions 28
Consumer genomics enters the classroom
BY RUTHANN RICHTER

PLUS
Cell tower 34
The rise of the cilium
BY ROSANNE SPECTOR

Decision time 38
Is dialysis the answer when kidneys start to fail?
BY TRACIE WHITE

DEPARTMENTS
Letter from the dean 2
Upfront 3
Letters to the editor 45
Backstory: Slow on the uptake 46
A gene test speeds accurate dosing of a dangerous drug — but few use it
BY KRISTA CONGER
You’ve probably heard a lot about “personalized medicine” and may well wonder whether it’s a serious approach to improving patient care or just a lot of hype. Actually, it’s both.

Clearly it is not yet close to being an accepted or routine part of medical care. But in certain areas, oncology in particular, clinicians are increasingly basing treatments on the patient’s genetics. As you’ll read in this issue of Stanford Medicine, treatment tailored to each individual is moving from concept to care.

What does this mean in practical terms? For one thing, medical schools must prepare future physicians to work within this new paradigm. Yet few medical schools systematically teach clinically relevant genetics. In fact, a recent study of U.S. and Canadian medical schools found that only 11 percent offered practical training in the use of medical genetics (Thurston et al., Academic Medicine, 2007). And not surprisingly, practicing physicians’ genetics knowledge is underwhelming. This is especially concerning given the pace of new knowledge and the fact that this will continue to increase rapidly in coming years.

Physicians are already fielding questions from patients who’ve had genotype profiling. And most physicians are unprepared to answer them. In fact, most of the primary care physicians in a national study couldn’t correctly answer questions about even single-gene tests for common diseases (Wideroff et al., Journal of Medical Genetics, 2005).

The good news is that many medical schools, including Stanford, are revamping how we teach medicine. Partly we’re motivated by the centennial anniversary of the Flexner report, which set the stage for the education models that still exist in many programs. But even more, we’re motivated by the needs we see before us.

In the past year here at Stanford we’ve had a vigorous debate about a proposal to incorporate the genotyping of medical students into molecular medicine and genetics classes as a way to make genomic testing more real. An article in this magazine fully describes the many ethical questions stirred up by this issue. After months of deliberation, we approved a course that was led by one of our medical students this past summer. To my knowledge it is the first medical school class anywhere to include genotype testing.

Meanwhile, research continues to fill in details about our molecular makeup, painting an exquisitely complex picture. While an individual’s genome sequence will surely become a powerful tool for personalizing medicine, it will be only part of the story. Even greater success at tailoring treatments will come with new knowledge about the genes’ regulators — the proteins and other chemicals that switch them on and off. As you’ll read in this magazine, research into gene regulators is burgeoning.

So I encourage enthusiasm concerning personalized medicine but also caution because of the still nascent state of our knowledge. Though it remains a work in progress, and will evolve in ways that can only barely be predicted, it is already having an impact. But we need to be cautious that hype doesn’t create false expectations and that we stay grounded in science as we seek to incorporate the emerging concept of personalized medicine.

Sincerely,
Philip A. Pizzo, MD
Dean
Stanford University School of Medicine
Carl and Elizabeth Naumann Professor, Pediatrics, Microbiology and Immunology
Bug food

WE ARE WHAT WE EAT, but who are “we”? New, high-powered genomic analytical techniques have established that as many as 1,000 different single-celled species co-exist in relative harmony in every healthy human gut.

“What you eat is proving to be one of the major determinants of the components of your ‘inner self’ — that community of bacteria living in your intestine,” says Justin Sonnenburg, PhD, assistant professor of microbiology and immunology.

Each individual’s microbial ecosystem is different in its relative composition, with potential implications for our health. Disorders such as inflammatory bowel disease, colorectal cancer and even obesity have been linked to skewed intestinal microbe distributions.

Scientists hope that someday they will be able to manipulate microbial populations in the gut as a way to remedy disease and enhance health. One step toward this goal would be taking “genomic censuses” to categorize and count the components of each individual’s bacterial community and how they respond to interventions, such as changes in diet. That’s no small task, because the aggregate gene count of all the micro-organisms dwelling in a typical human gut outnumbers our own by a hundredfold.

In an animal study published June 25 in Cell, Sonnenburg and his colleagues showed that zeroing in on just a small set of bacterial genes allowed them to predict how bugs would respond to a diet change.

Their results set the stage for scaling up germ-free mice, who become living laboratories into which scientists can introduce, one by one, steadily increasing numbers of bacteria found in the human intestine, eventually enabling an understanding of
the complex microbial super-organism that dwells inside each of us.

The team introduced two distinct species of bacteria, both known to abound in the human digestive tract, into mice that had been raised in a sterile environment. Then they fed the mice a diet rich in a particular complex carbohydrate that one bacterial species seemed genetically better equipped to digest. As predicted, that bacterial species became predominant in the mice’s intestines.

The results highlight the potential of the burgeoning new field of prebiotics, which (in contrast to probiotics — the eating of healthful bacterial organisms) involves adding substances to the diet that nourish the healthful micro-organisms.

The researchers caution that it will be a while before the results in this simple experimental system — two competing bacterial species — can be extrapolated to the real, human gut-dwelling microbial community. Since a more complex experimental system would be closer to the reality inside human intestines, they are introducing a greater diversity of human-associated bacteria.

— BRUCE GOLDMAN

The study was funded in part by the National Institutes of Health.

**IVF test**

WOMEN WHO FAIL to become pregnant after undergoing in vitro fertilization treatment often grapple with deciding whether to try IVF again. The procedure carries hefty financial, physical and emotional costs, and there are no guarantees it will work.

Now a team of School of Medicine researchers has developed a model to predict the outcomes of a subsequent round of IVF for those women who have already gone through a cycle. The researchers found that their test, which uses clinical data from prior, failed treatments to provide more personalized predictions, is 1,000 times more accurate than the age-based guidelines currently used to counsel patients.

“Our findings show that the first IVF cycle can provide quantitative, customized prediction of the live birth probability in a subsequent cycle,” the researchers wrote in their paper. “This concept is radically different from the current paradigm, in which age is a major predictor.”

The study, published online July 19 in the Proceedings of the National Academy of Sciences, was led by Mylene Yao, MD, assistant professor of obstetrics and gynecology.

Each year, close to 100,000 IVF cycles are performed using a woman’s fresh eggs, and around 29 percent of the treatments result in live births. Physicians typically use age-based data, with adjustments based on other clinical factors, to counsel patients.
“In an injured human brain or spinal cord, the degenerating myelin just sits there for the rest of the person’s lifetime. But after injury to, say, the sciatic nerve, the degenerating myelin is cleared within a week or less.”

The study was funded by the National Institutes of Health and the Coulter Foundation Translational Research Program at Stanford University. Yao and co-author Wing Wong, PhD, professor of statistics and of health research and policy, have founded a company, univfy, to develop and market prognostic tests to support clinical decision making in infertility. Stanford holds the patent on the test referenced in this study.

Antibody surprise

ANTIBODIES — WARRIOR PROTEINS THE IMMUNE SYSTEM makes to defend the body against invading pathogens such as viruses and bacteria — have a gentler side nobody knew about until now. They function not only as soldiers but also as nurses.

And researchers at the School of Medicine now think antibodies’ absence in the central nervous system (the brain and spinal cord) might be a key reason nerve damage there doesn’t get naturally repaired in humans.

In a study conducted in mice, published online June 14 in Proceedings of the National Academy of Sciences, the Stanford scientists showed for the first time that antibodies are critical in repairing damage to the peripheral nervous system — nervous tissue that extends outside the brain and spinal cord, such as the sciatic nerve, where circulating antibodies have access.

The study also shows that some, but not all, antibodies get the job done. Harnessing the unanticipated nurturing qualities of these proteins might lead to new ways of repairing damage from stroke or spinal-cord injury.

“Nobody has known why, but nerve cells in the central nervous system fail to regenerate after injury whereas those in the peripheral nervous system regenerate robustly,” says senior study author Ben Barres, MD, PhD, professor and chair of neurobiology.

His group was intrigued by one major difference between the two nervous systems: Antibodies have limited access to the brain and spinal cord (these organs are surrounded by an interface called the blood-brain barrier or, in the spinal cord, the blood-spinal cord barrier), while they have ready access to the peripheral nervous system.

Nerve cells convey electro-chemical impulses over long distances by means of long, tubular projections called axons. These axons are typically wrapped in an insulating layer of a fatty substance called myelin.

“After nerve injury, the degenerating myelin downstream from the injury is rapidly cleared in the peripheral, but not the central, nervous system,” says Barres.

In an injured human brain or spinal cord, the degenerating myelin just sits there for the rest of the person’s lifetime. But after injury to, say, the sciatic nerve, the degenerating myelin is cleared within a week or less.”

The researchers wondered whether antibodies might play a role in that clearance. They obtained mutant laboratory mice that can’t make antibodies, and demonstrated that repair of injury to the sciatic nerve is substantially impeded, as is the removal of degenerating myelin downstream from the injury site.

Simply injecting the injured mutant mice with antibodies from healthy, uninjured ones restored both myelin removal...
“We find that AIDS has produced close to a million elderly people in sub-Saharan Africa who are living without the support of their sons, daughters or other younger adults.”

The work was funded by the National Eye Institute, the Adelson Medical Research Foundation, the National Institutes of Health and the National Multiple Sclerosis Society.

Orphaned elders

THE INCREASE IN AIDS DEATHS IN SUB-SAHARIAN AFRICA has led to a burgeoning new category of neglected individuals — nearly a million orphaned elderly, or older adults living alone without the benefit of any caregivers, School of Medicine researchers have found.

The researchers used existing data to develop the first estimates of the number of elders left without any adult support as a result of the AIDS epidemic, says Grant Miller, PhD, MPP, assistant professor of medicine.

“We find that AIDS has produced close to a million elderly people in sub-Saharan Africa who are living without the support of their sons, daughters or other younger adults. Many of them also live with young children under 10 years of age, creating households with a missing generation of adults,” says Miller, senior author of the study, which was published online June 16 in the British Medical Journal.

Miller says he and his colleagues were stunned to learn that no one had taken a systematic look at this group of needy individuals.

“It just blew me away,” he says. “We all know we have this problem with orphaned children. I wondered, do we have a similar problem with orphaned elderly? I searched a variety of publications and didn’t find a clear answer.”

The researchers used data from the Demographic and Health Survey, a USAID-funded database that provides standardized information on maternal/child health, HIV and other health indicators in low- and middle-income countries. The survey covered 123,000 individuals over age 60 living in 22 African countries between 1991 and 2006.

The scientists found a strong correlation between the rise in AIDS deaths in these countries and an increase in elderly individuals living alone. For every one-point increase in AIDS mortality, they found a 1.5 percent increase in elderly people left to manage on their own.

In the 22 countries, the estimates translated into 582,200 to 917,000 elderly people left unattended. About a third of them — or as many as 323,000 — were also caring for young children. These individuals were more likely to be women, uneducated, living in rural areas and poorer than their attended counterparts. The results suggest HIV/AIDS has had a disproportionate impact on elderly people of lower socioeconomic status.

Yet few African countries have public pension programs or formal systems for caring for elders; most rely on traditional family structures, now undercut by the strain of AIDS, to provide this service. The researchers say the study points to the importance of taking these needy elders into consideration when providing resources and planning programs.

“This is another component of the social consequences of HIV. So people in agencies who make resource allocation decisions need to consider this cost of HIV, and it’s a pretty important one,” Miller says. — RUTHANN RICHTER

The study was funded by the National Institutes of Health.

Smoke signals

POINT-OF-SALE TOBACCO ADVERTISING works impressively well on teens — so well that federal regulators should consider barring such marketing efforts from convenience stores, gas stations and small groceries, says a School of Medicine researcher.

A study published in the August issue of Pediatrics led by Lisa Henriksen, PhD, senior research scientist at the Stanford Prevention Research Center, reports that teens’ exposure to cigarette advertising at retail outlets substantially increases the odds they will start smoking. According to the findings, students who visited these stores on a regular basis were at least twice as likely to try smoking as those who visited infrequently.

“The tobacco industry argues the purpose of advertising is to encourage smokers to switch brands, but this shows that advertising encourages teenagers to pick up a deadly habit,” says Henriksen, who has studied tobacco marketing for more than a decade.

Point-of-sale is the major
form of marketing used for tobacco — representing 90 percent of the industry’s $12.5 billion marketing budget in 2006 — and the study suggests that further limits on such activity could affect long-term smoking habits.

Henriksen based the study on repeat surveys of 11- to 14-year-olds at three middle schools in Tracy, Calif., and assessments of cigarette advertisements at stores near the schools. The survey questioned students about smoking experience as well as how often they visited the types of stores with lots of cigarette ads — convenience stores, gas stations and small groceries — and was repeated, first at one year and then at 30 months.

Of the 2,110 students surveyed in 2003 when the study began, 1,681 reported never smoking. A survey of these non-smoking students a year later revealed 18 percent of these students had smoked over the year, at least one puff, and that smoking initiation was much more prevalent among those who had reported frequent visits to stores with the most cigarette ads.

Among the non-smokers who had reported visiting these stores at least twice a week, 29 percent took at least one puff in the study’s first year. Among those who rarely visited — less than twice a month — only 9 percent started smoking that year.

A survey 30 months after the study began found that by then 34 percent of those who had visited stores at least twice a week had tried smoking, and only 21 percent of those who had rarely visited had taken a puff.

When researchers adjusted for all the variables that affect tobacco use, they found a strong relationship between store visits and smoking initiation. A year after the survey, frequent shoppers (two or more visits a week) were more than twice as likely to have taken at least one puff than infrequent shoppers. Thirty months after the initial survey, the apparent influence of the store visits remained: Those who had reported frequent visits were 42 percent more likely than infrequent visitors to have tried smoking.

— ROSANNE SPECTOR

The research was funded by the National Cancer Institute.
On Feb. 15, 2008, Richard Quake’s 17-year-old daughter met him in the driveway of their Pennsylvania home as he returned from work.

“Dad, you have to get upstairs. It’s Richie. I think he’s dead.”

Quake had wondered why his son’s car was still in the driveway. Nineteen-year-old Richie — a sophomore at Drexel University studying architectural engineering — should have been at work at nearby Sesame Place, where he played Big Bird at the popular theme park. Instead, he was dead in his upstairs bedroom. The next few hours were a blur as police and paramedics sought to determine why the healthy teen, with a black belt in karate and D.A.R.E. posters on the walls of his room, had died so unexpectedly. Days passed with no clear answer.

“We were desperate to find out what happened to my son,” says Quake, “but by this point my wife and I had begun to fear for the rest of the family, for our two daughters.
The Heart: Personalizing Treatments
“We wondered if he had a disease, maybe a virus or an infection. We had no idea.”

Although the coroner eventually ruled the death was most likely due to a previously undiagnosed heart problem, Quake was not satisfied. He insisted the coroner collect both blood and tissue samples from his son’s body. “I told him, ‘I need you to save everything you possibly can for future testing.’” says Quake. “At the time, I really had no idea why I said that.”

Richard Quake’s request, and his determination to find an answer to the mystery of Richie’s death in the DNA gathered from his tissue, launched him onto the shaky leading edge of personalized medicine, and into some of its most thorny ethical thickets.

Who owns a person’s genetic information? What can be done with it? What should be done with it? Quake’s journey during the subsequent two years traces the evolution of scientific fields of genotyping, whole-genome sequencing and the interpretation of more genomic data than most clinicians and scientists have ever dreamed of, or can even realistically handle. He would eventually gain an ally in the form of a cousin on the other side of the country — Stanford bioengineering professor Stephen Quake, DPhil, who was himself preparing to break scientific and ethical barriers by sequencing his own complete genome with a new sequencing machine he helped invent.

It’s a conundrum in so many ways. The sequence of your genome — all 6 billion nucleotide letters — is the most personal of personal information, encoding the very building blocks of what makes you you. The sheer power and wonder of what arises when that string of letters is steeped in a cell’s biological stew is staggering. And yet your genome is also inextricably bound with that of your mother and your father, your siblings and your children and even that of more distant relatives. How much right, if any, do we have to expose what others may not want known? And are any of us prepared for our technology to find an answer to the mystery of Richie’s death in the DNA gathered from his tissue, launched him onto the shaky leading edge of personalized medicine, and into some of its most thorny ethical thickets.

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On the other hand, genetic information — in whole or in part, of you or, perhaps, of the cells of your cancer — is the key to much of the promise of personalized medicine. With it we can identify which drugs will work best and how much of them to use. We can slice and dice, poke and prod, and parse those letters into messages about longevity or ancestry, a child’s future height or ability to taste the bitter flavors in some vegetables, breast cancer risk and cholesterol levels. In fact, we can learn so much about a person and his or her medical predictions that it would be foolhardy not to pursue what recent technological advances in sequencing and soft-
cess was more complicated than it would be today. But things were changing quickly.

At the end of 2007 and in early 2008, three companies began offering what’s now known as direct-to-consumer genotyping. Interested people could send in a sample of saliva to Bay Area-based companies 23andMe or Navigenics, or to deCODE Genetics in Iceland. For prices ranging from $985 to $2,500 the companies would scan a customer’s DNA, determine the exact sequence of nucleotide letters in hundreds of thousands of locations throughout the genome, and assess the risks or likelihood of about 12 to 20 diseases or physical traits. (Prices have dropped since that time.)

The ability of the companies to draw conclusions between nucleotide differences known as SNPs (single nucleotide polymorphisms) and disease risk is due to a field of research called genome-wide association studies. These studies sprang from technologies devised during the 10-year push to sequence the entire human genome. Their focus has been on identifying genetic differences among individuals that were associated with either increased risk of or protection from a particular disease. Finding a disease-associated SNP (pronounced “snip”), however, doesn’t necessarily mean that a particular nucleotide change causes the disease, although this can be the case. It’s more like a molecular bar code that indicates that other, surrounding sequences might be involved.

But although some SNPs are quite telling, others are only suggestive. Nonetheless, thousands of people have undergone the tests in the past years despite the fact that most physicians have no clear idea of how to counsel their patients about the results.

“There’s so much we still don’t know,” says bioethicist and associate professor of pediatrics Mildred Cho, PhD. “What does it mean to say you have a 10 percent higher risk of something? Are you going to do anything about it, or just worry?”

Cho is the associate director of Stanford’s Center for Integration of Research on Genetics and Ethics, one of six centers around the country created by the National Human Genome Research Institute to explore the ethical, legal and social implications of genetic research. The centers are one aspect of the Ethical, Legal and Social Implications Research Program established by the institute in 1990.

“When the program first started, we were thinking mostly about things in terms of single-gene disorders,” says Jean McEwen, JD, PhD, director of the ELSI program. “We were looking at one gene at a time. But now with the enormous decrease in the cost of sequencing we can begin to look across the entire genome and try to identify risk factors for complex disorders like cancer and heart disease. But we have to decide how to interpret this data and put it all together. This is where things become very difficult.”

In comparison, the question for Richard Quake was fairly simple: What killed his son? “I was jumping online every night, getting up on all this heart stuff,” he says. “I talked to a specialist at Mayo, and a guy at Penn.” Eventually, after talking to several experts, he asked the coroner to send samples of Richie’s tissue to a specialist in New England to test for a cardiac condition called long QT syndrome that can cause sudden death. Mutations in any of several genes can cause long QT. Two other possible options were Marfan syndrome (like many with Marfan, Richie was very tall and thin, with long arms, legs and fingers) or Brugada syndrome — a heart condition that can cause death unexpectedly during sleep. Mutations in one gene, SCN5A, account for about 20 to 25 percent of Brugada cases.

“It was expensive,” says Quake, “but I said, ‘We do what we have to do.’” Months went by before he received the results of the genetic tests: Richie was negative for any of the mutations known to be involved with the diseases. “Of course they gave me the qualifier, ‘This is new science, we don’t know all the genes that play into this,’” says Quake.

The uncertainty factor has increased exponentially since then with the identification of hundreds of additional disease-associated SNPs and the growing knowledge that most diseases represent the cumulative effect of tens or hundreds
of genes and their interaction with a person’s environment. This is one reason some experts are calling for a halt on direct-to-consumer genetic testing. The field of companies offering such tests has swelled to about 30 and, in July of this year, the U.S. House of Representatives Committee on Energy and Commerce presented the results of an undercover investigation by the Government Accountability Office that it said showed a shocking lack of regulation and consumer protection in the field.

“GAO’s fictitious consumers received test results that are misleading and of little or no practical use,” the report concluded, after pointing out that the same DNA sample sent to four companies returned vastly different predictions for the risk of prostate cancer and hypertension and that in at least one case an individual with a heart condition was told he was at decreased risk for the disorder. When the undercover investigators spoke over the phone with representatives from 15 test providers, they were given information and advice that ranged from simply inaccurate to fraudulent and perhaps illegal.

Supporters of the industry contended, however, that the GAO study was flawed in execution and presentation (the companies investigated were not identified so could not offer any defense or clarification, and they did not receive a copy of the findings until after the hearing). Risk predictions are not in themselves diagnostic, they argue, and a few unscrupulous companies shouldn’t be allowed to tarnish the entire field. What’s more, many of the companies have said directly that they would welcome more regulatory oversight and some have actively sought such guidance since their inception.

The Food and Drug Administration has also taken issue with some of the claims touted by direct-to-consumer genetic companies. Between May and July, the FDA sent letters to 20 of the companies warning them that tests meant to diagnose or prevent diseases qualify as medical devices, subject to regulation by the administration.

Setting aside legal and ethical concerns about the behavior of some of the companies, some experts argue that direct-to-consumer testing is inherently flawed. The general public is not qualified to interpret and respond appropriately to test results that may indicate an increased risk of, say, breast cancer, or perhaps a decreased risk of colon cancer. What if an individual decides to forgo routine screening on the basis of a test result that indicates decreased risk?

Arthur Beaudet, MD, chair of molecular and human genetics at Baylor College in Texas, is concerned enough about the repercussions of unfiltered genomic information to say that the sale of the tests to the general public should be prohibited. People who want the information should go through their physician, he argues in an opinion piece in *Nature* in August, who could help them interpret and act upon the results.

Not so, says Gail Javitt, JD, MPH, a research scholar at the Berman Institute of Bioethics at Johns Hopkins University, who points out in the same issue of the journal that many of the tests have been well-validated, including those for sickle cell anemia and cystic fibrosis. Regulate the tests according to the level of information and risk they provide, she argues.
Similar to pregnancy tests, some could likely be purchased over the counter and used without any professional interpretation. Others would require gatekeepers in the form of genetic counselors or physicians.

Quake’s relentless research eventually led him to have his own cardiac health assessed, but the results offered no clues to the cause of Richie’s death. It was about that time he heard that a professor at the Stanford School of Medicine had sequenced his entire genome for less than $50,000 and with a team of just three people. The name of the faculty member? Stephen Quake.

In August 2009, Stephen Quake, a Howard Hughes Medical Institute investigator, published the sequence of about 90 percent of his DNA using technology called single molecule sequencing he helped develop. He was pondering the results in his office when colleague Euan Ashley, MD, a cardiologist specializing in cardiomyopathy, walked in. “Hey Euan,” said Quake. “What do you know about this gene here?”

Ashley, who directs Stanford’s Center for Inherited Cardiovascular Disease, knew it well. It was myosin-binding protein C — a gene known to be associated with sudden cardiac death.

Unlike genotyping, whole-genome sequencing returns the entire sequence of a person’s DNA. But it presents unique technical challenges. Although the first human genome sequence took 10 years, several billion dollars and hundreds of researchers, Quake’s sequencing of his own genome took one month, three people and about $50,000. Since then researchers have sequenced a family group of four, and even DNA from a Neanderthal. In September, researchers from Duke University published whole-genome sequence data from 20 people — half with hemophilia and half without. Their findings indicated that it’s possible to identify disease-associated genes by comparing groups of unaffected and affected people.

Clearly, whole-genome sequencing is becoming both relatively easy, and popular. In fact, many experts predict that we’re about to reach what’s known as the “$1,000 genome” — a tipping point at which nearly anyone could afford to have his or her entire genome sequenced. But the real challenge may still be ahead: How are we going to manage and interpret all that data? Each sequence, which includes copies of genes from both parents, has about 6 billion base pairs. That in itself is not that difficult to store on a hard drive. But the assembly of the strings of nucleotides into contiguous sequences, coupled with the resulting analysis and comparison with a reference genome, can easily consume up to two terabytes of memory for each person. “It’s very difficult to parse all this down into a format that can be discussed between a physician and a patient,” says Ashley.

Even if the storage issues can be overcome, as they probably will be, there’s a very real concern as to whether researchers and physicians possess enough technical know-how to deal with the information. “The No. 1 concern I hear when I talk to people about whole-genome sequencing,” says the national genome institute’s Green, “is the ability to handle the computational aspects of this type of research. Few people in medical fields have computational backgrounds, and we need new types of software to analyze the data that pour off of and gush out of these sequencing machines.” Hank Greely, JD, professor and director of Stanford’s Center for Law and the Biosciences, agrees. “Patients, doctors and geneticists are about to be hit by a tsunami of genome sequence data. The experience with Steve Quake’s genome shows we need to start thinking — hard and soon — about how we can deal with that information,” says Greely.

Ashley and Quake and a team of other researchers proved it could be done, though not without considerable effort and resources. Together with several dozen Stanford colleagues they devised a way to take Stephen Quake’s genome and make some predictions about his clinical risk for many diseases. On May 1, they published the first-ever medical interpretation of a complete human genome in the journal Lancet.

“Many of us had already been thinking about how you would take someone’s genomic profile and translate what’s in the billions of base pairs in that DNA to something that’s clinically useful,” says Ashley, who headed the group of geneticists, physicians, bioinformaticians and ethicists involved in the study. “Then we realized, ‘Hey, we already have someone’s genome.’”

What’s more, Atul Butte, MD, PhD, assistant professor of bioinformatics, and his lab members had already done a lot of the necessary legwork: They’d spent the previous 18 months meticulously cataloging publications that associated SNPs with specific diseases. It was the first time anyone had compiled all the information in one database, which now contains more than 20,000 SNPs linked to over 1,000 diseases.

“We have read nearly 4,000 publications so far,” says Butte, “and we made a list of every single spot in the genome where we know that, for example, the letter A raises the risk of a particular disease, or the letter T confers protection. And then came Steve with his genome, and we were ready.” Together the researchers designed an algorithm to overlay the genetic data upon what was already known about Quake’s inherent risk — based on his age and gender — for 55 conditions, ranging from obesity and diabetes to schizophrenia and gum disease. For example, as a 40-year-old white male,
Quake entered the study with a 16 percent chance of developing prostate cancer in his lifetime. But as the computer, based on Quake’s genomic sequence, began to incorporate the data of study after study, his risk scooched first lower, then higher. (The researchers weighted the contribution of each variant according to the number, and sample size, of published studies confirming the association.)

The publication of the resulting clinical recommendations for Stephen Quake added to what had become a vigorous debate as to whether physicians were prepared to incorporate this type of data into the clinic. Although Butte and the others had made their software as user-friendly as possible, it was still not clear whether such an analysis is cost-effective or even useful.

“A lot of people now are talking about the $1,000 genome,” says bioethicist Cho. “But one of the things we’re looking at is the other things that have to happen to make such information clinically relevant. If you assume it took 40 highly trained faculty members to figure out what Steve’s genome meant and to communicate it back to him, you begin to realize that the cost of sequencing may not be what we should be focusing on. We need to think about the infrastructure you would need to do this on a large scale — training physicians in informatics, figuring out how to communicate ideas of risk to patients and even whether this would be cost-effective for the average person.”

Training physicians is no small task. This summer, Stanford offered an elective course to medical and graduate students in which they decided whether to analyze genotyping results of tests performed on their own DNA or on a reference sequence. Although popular, the course sparked a firestorm of debate among faculty members that delayed its start date by more than a year as they grappled with the ethical issues of appearing to encourage students to analyze their own DNA. [See the story, page 28.]

“There is no question in my mind that medical educators need to be far more aggressive about incorporating genomic information into their curricula for medical students,” says Green. “But we also need to get much more involved in educating current physicians, who are already under a substantial amount of pressure by patients.”

How many patients might be approaching their physicians with genotyping information? The companies themselves are coy, but Caroline Wright, PhD, the head of science for the international Foundation for Genomics and Population Health, estimates the number of people who purchased and used genotyping kits in 2009 was about 20,000 to 30,000. Not inconsequential, but certainly a minority in a country with a population of more than 300 million. A recent study by the Scripps Research Institute found that more than 80 percent of people undergoing direct-to-consumer genetics testing wanted to know about their risk even for incurable or non-preventable diseases, but that 50 percent also had concerns about the tests.

“We’re funding several grants looking specifically at the direct-to-consumer testing going on,” says the national genomics institute’s McEwen. “We’d like to know people’s motivations for wanting to do it, what they are doing with the information and how they are reacting in terms of changing their health behaviors.”

As Stephen Quake looked at his predicted cardiac risk factors, he thought of Richie. He had spoken to his cousin Richard about his experience with sequencing his genome and even sent him a report detailing some of his own predicted risk factors. Now he introduced him to Euan Ashley.

“I shared my research with Dr. Ashley and told him how I couldn’t sleep at night because I was worried about my daughters,” says Richard Quake. “He said, ‘Let’s take a look at your data and maybe run some tests — this is what the center does — maybe we can put your mind at ease.’”

Most of the tests Ashley had in mind were standard cardiac workups of Richard Quake and his wife and daughters. But he set his sights considerably higher for one: whole-genome sequencing of the DNA in Richie’s tissue sample. It’s believed to be the first time the technology has been used in an attempt to determine the cause of death of an individual. A tantalizing scholarly goal, to be sure. But that’s not why Ashley and his team took on the task.

“I’m desperate to find an answer for him,” says Ashley, who himself has two young children. “You can really feel his pain. If we can find a convincing cause of death for his son, maybe we can test his daughters and either rule them out or make them safe.”

Just feet away from Ashley’s office, computers have been churning away to find possible candidate mutations in Richie’s DNA. Because none of the obvious suspect genes seem abnormal, the team resorted to screening all the genes involved in ion transport in the heart muscle. (Ion transport is an important step in stimulating the synchronized contraction of heart muscle cells.)

“There’s no list anywhere of the cardiac ion transport genes,” says Ashley, who has had to turn to finding genes whose sequence resembles that of known ion transport genes. “That’s part of why this is exciting. This kind of ‘molecular autopsy’ we’re doing will generate a lot of new information for future use. We are literally searching for what could be just a one-base-pair difference in millions of nucleotides. But even though for us it’s an exciting research project, we haven’t forgotten that it’s also an absolute tragedy for Richie’s family.”
A batch of personalized-genomics companies have sprung up in the past few years, offering large-scale determinations of the genetic differences that set you apart from every other human being (identical twins excepted). While their analytical techniques vary a bit, the routine for the consumer is fairly uniform: Place your order online, wait until you get the kit in the mail, follow instructions — in a nutshell, spit into the enclosed vial and close the cap — ship it back and receive a report on your results along with a variable amount of interpretation depending on the company. (In some states, it is necessary to get a doctor’s sign off at some point in this process.) Some companies offer follow-up genetic counseling.

Between the time you mail in your spit kit and the time you get the report, a whirl of activity, made possible by advances in molecular biology and engineering, takes place. Here’s the science behind that activity.

A human cell contains a genome consisting of 46 chromosomes, 23 from each parent. Every chromosome contains a molecule of DNA, a long, linear chain composed of a sequence of four different chemical “links.” Along these sequences lie the genes, which are essentially instructions for protein manufacture. Over eons of evolutionary time, mutations — most often, the substitution of one type of link for another type in a particular spot on the chain — creep into genes, causing people’s genomes to diverge as each generation becomes more removed from our common ancestors. Tiny, single-link differences in the genomic chain are called SNPs (pronounced “snips”).

Checking out every single one of the several billion chemical building blocks in your genome remains too expensive for a mass-market test, though prices are dropping. So the personalized-genomics outfits look at fewer, directing attention to the “mere” hundreds of thousands of hot spots on your DNA where SNPs have been observed to pop up with some frequency and where, furthermore, one SNP variant or another has been at least tentatively associated with increased odds of contracting, say, type-2 diabetes, lung cancer or some other disease. These same kinds of tests can assess your probable sensitivity to various drugs. — BRUCE GOLDMAN

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* Estimated range; the company sells its test to physicians who charge as they see fit
** Cancer or cardio scan, $500; both, $800; both plus neurological and several other conditions, $2,000

Currently the researchers are focusing their attention on 230 genetic variants in Richie’s genome — many that have never before been associated with disease. “The power of what we’re doing takes my breath away compared with what’s previously been offered as the state of the art,” says Ashley. But with power comes questions. What does it mean to vary from the norm? Who is the norm, anyway? Butte, the bioinformatics expert, has begun to apply the findings of his SNP database to a reference human genome used by most researchers.

“A lot of people and clinicians think of their genomes in terms of how they compare with the reference genome, which is a composite of 30-some unidentified individuals,” says Butte.

CONTINUES ON PAGE 43
He says, “A lot of the ways we think about technology in terms of medicine are very cost-intensive — MRIs, CT scans, stents, surgeries.” Yet he feels relatively low-cost gadgets such as iPhone apps that help track calories do the most to help individuals take control of their health.

Oh, and about health care’s escalating costs, Goetz says, you can blame it on the Beatles. The Beatles? You see, in 1961 British company EMI signed the then-unknown Fab Four to a music contract. As a result, the company made millions (and by now probably billions), which it invested in developing new electronic devices, including the CT scanner, invented by an EMI engineer in 1967. In the decades since, use of this miraculous device has burgeoned into overuse, becoming a major contributor to the out-of-control costs of today. Surely the band was EMI’s ticket to ride in health-care technology.

Stanford Medicine’s executive editor Paul Costello spoke with Goetz about how the non-geeks among us can merge technology and medicine to improve our health.

Costello: At the beginning of the book you talk about three projects you see as pivotal for the future of health care. Two are famous medical studies, the Framingham Heart Study and Great Britain’s Whitehall study. The third is about a group of technology early adopters in San Francisco. Can you connect the dots for me?

Goetz: The Framingham study has been going for 60 years, following the health of three generations. For me it’s an example of how we can gather data and learn from our daily experiences.
The Whitehall study recruited 18,000 men from all different classes within the British civil service, from the ministers at the very top to the janitors at the very bottom, and they studied them to see who was most at risk for heart disease. What they found was pretty much a direct correlation between your social rank and your risk of heart disease. So people at the bottom had a profoundly increased risk of heart disease. The core insight — that when we are given control of our health, we tend to have better health — was to me an essential part of laying the groundwork for this new conception of health care.

So that’s where this third group comes in, the Quantified Self group, which is a local meet-up. This is a group of technology geeks who want to start experimenting. In this case, what they’re experimenting with is not computer code, but their own code. They’re tracking their genomes. They’re tracking how much coffee they drink. They’re tracking how much exercise they get. They’re tracking how much sleep they’re getting. They wear all sorts of different sensors and body monitors and use their iPhones to track various things about themselves. The idea is that this sense of control, as we saw with the Whitehall study, starts to kick in and we start to see our way toward better health.

Costello: Data is really king, is what you’re saying?
Goetz: Right. There is great public health research that shows when you give people feedback, when you give them a sense of where they stand in their health, and a goal, and then get them to keep track of how they’re doing — think about weight loss — that kind of feedback loop really is effective at behavior change. The trick is it’s laborious. So what’s changing is that the tools are getting simpler, and it’s getting much easier for more people to start changing those behaviors.

Costello: You wrote that staying healthy is as much a decision-making problem as a health-care problem. What do you mean by that?
Goetz: We know the basic rules of good health: We’re supposed to be exercising more and eating a little less, and eating more healthy foods. The problem that we have as a society is putting those rules into action. That’s really the place of decision making.

That’s when we need to get information delivered to us, at the very point that we’re deciding between having a piece of carrot or the piece of carrot cake.

Costello: Tell me more about how technology can help.
Goetz: What is really cool about what’s happening here is that information technology, like iPhone apps, are a really good way of turning data, that very logical and rational and quantitative approach, into something that we can understand and integrate into our lives. And you don’t have to be a geek.

That’s where iPhone apps are so powerful. Like the Lose It! app for weight loss — there are 10 million people using this app every day. Or there are very good blood glucose monitors that are useful for diabetics or pre-diabetics. If you want to quit smoking, there are quit-smoking apps that help people track their cigarettes.

There’s one great little tool that I might mention. It’s called the Fitbit. It’s a little accelerometer that you clip on to your belt, and it tracks your calories. It tracks how many steps you’re taking. It tracks your cadence. It’s a really great way to make sure that you’re getting enough exercise every day just walking around as much as you can.

In addition to giving you the numbers, it has this great little icon. It’s a flower that grows, so the more you exercise every day, the taller your flower gets. It’s a great example of how it’s not just data that helps people. Making that flower grow is something that pretty much anybody can understand. Once you get this device, you want to make your flower grow every day.

SM

This interview was condensed and edited by Rosanne Spector.
Louisa Gloger was already having a rough day. Her daughters, a 3-year-old and a 14-month-old, fussed all morning. She was frazzled. She needed a shower. So she corralled her daughters into the bathroom and stood under the spray with her youngest in her arms.

“In immediately, it was like alarm bells went off in my head,” the 31-year-old Mill Valley woman says. “It didn’t feel right.”

In some ways, Gloger had built her life around the possibility that this might happen. Her mother was diagnosed with breast cancer at 35, when Gloger herself was just a year old. Gloger’s aunt had the disease in her 30s as well. Both women developed cancer again 20 years later. Gloger’s aunt survived her second bout. Her mother didn’t.

Gloger knew she was at risk, so she did the things that are supposed to keep breast cancer at bay. She exercised, ate organic, avoided the birth control pill, had both babies before 30, breastfed. Yet she got cancer anyway. And when the final diagnosis came, it was still a surprise.

“I was just totally blindsided,” Gloger says.

She was all the more blindsided when her doctor at the California Pacific Medical Center in San Francisco told her she had triple-negative cancer. Gloger had never heard the term before, but her doctor explained it’s a particularly aggressive form that doesn’t respond well to traditional chemotherapy.

“That’s when he said, ‘You need to go down to Stanford and see Dr. Melinda Telli,’” Gloger says. “He told me, ‘It’s your best hope for a cure.’

BY STEPHANIE PAPPAS

ILLUSTRATION BY MATT BANDSUCH
Hope is something that triple-negative breast cancer patients have been short on. In this form of cancer, which makes up 15 percent of all breast cancer, the tumor cells lack abundant receptors for estrogen, progesterone and a growth factor called HER2. Since current breast cancer treatments work by targeting these proteins, there’s little doctors can do for triple-negative patients.

“Even though they represent a small proportion of breast cancers overall, this is the group that’s responsible for a large proportion of cancer deaths,” says Melinda Telli, MD, an assistant professor of oncology at Stanford and the leader of a clinical trial testing a new therapy for triple-negative cancer. According to a 2007 study of all stages of breast cancer, women with triple-negative strains have a 77 percent chance of surviving five years, compared with a 93 percent chance for other cancer types. Triple-negative cancers hit early and disproportionately affect women of African and Hispanic descent. As a young woman with an African-American parent, Gloger fit the profile.

For years, researchers have failed to find a way to target triple-negative cancers. But now, research conducted at Stanford has revealed a new possibility: drugs called PARP inhibitors. Pharmaceutical companies had been testing PARP inhibitors as a chemotherapy adjunct for years, but in the last five years, research on the drug class has exploded. If PARP inhibitors help stem triple-negative cancer, they’ll represent one of the biggest steps forward in breast cancer treatment in years.

They’ll also be in the vanguard of personalized medicine, the attempt by doctors and researchers to match drug treatments to patients most likely to be helped. Breast cancer is fertile ground for personalized medicine, with drugs specifically made to target tumors’ receptors already on the market. Tamoxifen, for example, fights estrogen-positive cancers. Herceptin, a drug approved in 2005 for use on early-stage tumors positive in the HER2 protein, was celebrated as “revolutionary” in the New England Journal of Medicine. As technology has improved, ferreting out more individualized treatments has become a major goal of cancer researchers.

“The idea of personalized or targeted treatments is to tailor treatments to an individual’s cancer based on its genetic makeup,” says James Ford, MD, professor of oncology and of genetics. “The technical feasibility and the cost for sequencing DNA have really gotten into the range where this is now feasible in the individual.”

When Gloger first called Telli in mid-October 2009, she didn’t know what to expect. Her primary physician had told her Telli was running a clinical trial on PARP inhibitors. The idea discomforted Gloger. She didn’t want to be a guinea pig.

But Telli is the kind of doctor described by her patients, unbidden, as warm and compassionate, the kind of doctor who will stay on the phone with you for two hours on a Saturday to discuss an experimental treatment’s pros and cons.

That’s what Telli did when Gloger called. The PARP inhibitor would be combined with DNA-damaging che-
motherapy drugs that also target triple-negative breast tumors, she explained. PARP inhibitors target one of the tumor’s strongest lines of defense, a DNA-repair enzyme called poly (ADP-ribose) polymerase, or PARP.

If the drug, BSI-201 (now called Iniparib), worked as planned, it would be a one-two punch: The chemotherapy would do the dirty work of breaking up the tumor’s DNA, while the PARP inhibitors would block DNA repair. Though PARP inhibitors had been tested in women with advanced breast cancer with encouraging findings, Gloger would be one of the first potentially curable, early-stage patients to receive the drug. For women with localized breast cancers the stakes are high, Telli says. The risk of spread with this aggressive form of breast cancer is substantial, yet long-term side effects of therapy are also a possibility.

Gloger weighed her options and decided to participate. She and her husband began planning a trip to Europe for the next summer to give her something to look forward to. She e-mailed her friends and family telling them she’d be standing on a mountaintop in the Alps in just a few short months. But before that, she had to make it through 12 weeks of the investigational treatment.

To understand how researchers fingered PARP inhibitors as a potential triple-negative cancer treatment, you have to rewind to 1994. That’s when the first breast cancer gene, dubbed BRCA1, was found. A year later, researchers found BRCA2. An inherited mutation in these genes raises the lifetime risk of breast cancer by 65 percent and 45 percent, respectively.

The discoveries told doctors little about why these broken genes cause breast cancer. What it gave them was the chance to test women for the mutations that raised their risk. Myriad Genetics, a firm based in Utah, swiftly patented both genes, making it the only company legally allowed to run the test. For a few thousand dollars, a woman with a family history could have her blood drawn and learn within a few weeks whether she was at increased risk to develop cancer.

A woman who discovers she has a BRCA mutation faces hard choices, from extra screening all the way up to prophylactic mastectomy and oophorectomy (removal of the ovaries). If she has a BRCA1 mutation and develops breast cancer, odds are 80 percent it will be triple-negative, and thus tough to treat. The BRCA discoveries had improved doctors’ ability to predict cancer and take steps to prevent it, but not to cure it.

Then, in 2005, a pair of in vitro laboratory studies on PARP inhibitors published in Nature changed the game.

The first study, carried out by scientists at Cancer Research UK, found that PARP inhibitors weaken BRCA1- and BRCA2-related tumor cells drastically, causing them to stop dividing and die.

The second study’s results were even more promising: When researchers at the University of Sheffield in England treated BRCA2 tumor tissue with PARP inhibitors in the lab, the tumors died. Cells without the BRCA2 mutation survived, suggesting that PARP inhibitors could target tumors without destroying healthy tissue.

The Nature studies marked the first time PARP inhibitors had been tested in BRCA-mutant cancers. Their effectiveness made sense. The BRCA1 and BRCA2 genes make proteins involved in DNA repair. When a tumor is deficient in either BRCA protein (as is the case with the BRCA mutations), it relies more heavily on alternate DNA repair pathways — like PARP — to patch up genetic breaks and keep growing.

In other words, PARP is like a tumor’s plan B. Knock it out, and the cancer runs out of options. Finally, it seemed that the BRCA discoveries of a decade earlier had paid off.

With the publication of the two Nature papers, the oncology field burst into a flurry of research on PARP inhibitors. Around the country, clinical trials were launched in patients carrying BRCA mutations. Meanwhile, in his lab on the Stanford campus, Jim Ford noticed something about the mutations that suggested a route to treating triple-negative breast cancer.

Ford had been studying the BRCA1 mutation for years, trying to determine what goes wrong with a BRCA1-deficient cell’s DNA repair mechanisms. The overlap between BRCA1 and triple-negative cancers intrigued him, and he wondered if there might be some underlying similarity in their defects.

As it turned out, there was. Using cancer cell lines in the lab, Ford showed triple-negative cancers almost completely
share the DNA-repair defects of BRCA-related cancers.

“It was kind of an ‘aha’ moment,” Ford says. If BRCA cancers and triple-negative cancers are both driven by the same DNA repair deficiencies, he reasoned, they should respond to the same treatment. He tested triple-negative tumor tissue in the lab with PARP inhibitors and found that, just like BRCA tumors, triple-negative tumors responded.

Ford shared his results with Telli. She was immediately intrigued, and agreed to lead a clinical study to test the idea in breast cancer patients. The two contacted BiPar Sciences (now owned by Sanofi-Aventis), a South San Francisco drug development firm that makes the PARP inhibitor BSI-201, and arranged a collaboration. By this time, BiPar had launched a clinical trial testing its drug in women with the advanced form of this disease. Ford and Telli obtained additional funding through the Breast Cancer Research Foundation to start a clinical trial in newly diagnosed patients. Last year, the trial began. The plan was to recruit 36 patients in the early stages of triple-negative breast cancer.

The study would provide an opportunity to target a group that stood to benefit the most from treatment. It would also allow Telli and Ford to look for links between individual cancers’ biological features and the cancers’ response to the treatment.

“The early-stage patients are the ones where there is real curative potential,” Telli says.

As one of these patients, Gloger began her treatments at the Stanford Cancer Center in early November 2009. She hated the needles and felt worn out after sessions, but she didn’t become the balding, emaciated cancer victim she’d imagined. Instead, she kept her hair, kept exercising, kept up with her kids.

Even better, she got to watch the tumor shrink away. By the second treatment, it was noticeably smaller, she says. By the third, she couldn’t feel it anymore. While a shrinking tumor doesn’t always mean cancer has been cured, the PARP inhibitor treatment was declared an initial success for Gloger.

“That was kind of amazing,” Gloger says. “And awesome.”

Originally planned as a 36-person trial, the study is now expanding to 80 patients through the Eastern Cooperative Oncology Group. About 40 patients are enrolled, with the other 40 expected by the end of the year.

The biggest remaining question mark — and one the current study won’t fully address — is whether PARP inhibitors are safe in the long term. Inhibiting DNA repair in a tumor is a good thing, but in normal cells it can cause cancer. Ironically enough, it’s possible that by treating cancer now, PARP inhibitors set patients up for a new cancer later.

Researchers hope this won’t be the case, since healthy cells have other DNA repair mechanisms besides PARP. But BSI-201 has been tested only since 2006, Telli warns, and mostly in patients with incurable cancer who died soon after. Cancer patients who live need to be followed for years to be sure that new drugs are safe.

“That’s where you really need to be cautious, when you move it into lower-risk patients,” Telli says.

Meanwhile, in June 2009, just after Telli launched her study, researchers presented the results of BiPar’s clinical trial on their PARP inhibitor in metastatic triple-negative cancer. One hundred twenty women with advanced triple-negative breast cancer tested two DNA-damaging chemotherapy drugs, gemcitabine and carboplatin, the same Telli and Ford used, and the same that Ford’s laboratory had shown worked particularly well together with PARP inhibitors. Half the women also got BSI-201.

In women who got the PARP inhibitor, tumors shrunk three times as fast as in women who received chemotherapy without it. The median survival time was 5.7 months for women whose treatment did not include the PARP inhibitor. Those who received chemotherapy including the inhibitor had a median survival of 9.2 months, 3.5 months longer.

The oncology community was amazed. Three extra months of life represents one of the biggest treatment gains ever seen in patients with this aggressive form of metastatic breast cancer, says Brian Leyland-Jones, MD, PhD, a cancer researcher at Emory University and expert on cancer genetics.

“These differences in response and median survival are almost unheard of in such a small trial,” he says.

BiPar Sciences recently completed recruiting cancer patients to participate in a large, multi-institution phase-3 trial of the BSI-201/chemo combination in metastatic triple-negative cancer. Phase-3 trials are the final step to FDA approval of a drug. If the trial goes well, Telli says, FDA approval of BSI-201 could come very soon.
In March, a federal judge struck down Myriad’s patents on the BRCA genes, which would open up the testing market and possibly drive down prices. Myriad has appealed the decision, and it remains to be seen how the case will play out.

For her part, Gloger got her moment in the Alps. Her treatments finished, she and her family spent three weeks of the summer soaking in Switzerland and Italy. But she’s not putting her cancer experience entirely behind her. She and another woman, who lost her sister to triple-negative cancer, recently teamed up to start a nonprofit called Triple Step for the Cure. The organization is designed to help women deal with the everyday difficulties of cancer treatment. They’ve already raised $175,000 to pay for things like housekeeping, child care and meal services, and they’re supporting their first cancer patient by flying her family to California while she’s in treatment.

“The day that I was able to talk to her and tell her the way in which we’ll be able to help her, it felt like all of this had happened, not for a reason, but like I’m taking something really awful that happened to me and making it something good,” Gloger says. “We feel like we’re filling a gap.”

Meanwhile, Telli and Ford continue to work on filling the treatment gap for women with triple-negative cancer. Telli will be leading another trial of PARP inhibitors in triple-negative breast cancer, this time in combination with different chemotherapy drugs. Her ultimate goal is to conduct a randomized study that will compare different PARP-inhibitor strategies to standard chemotherapy in women with early-stage disease.

Ford is taking tumor samples from before and after patients’ treatment with the PARP inhibitor to look at the molecular changes in the tissue. He hopes to find clues that will help doctors target the treatment even further.

“Is there some signature or some added molecular data that predicts who did very well or who didn’t do very well with the treatment?” he asks. “Maybe there’s a subgroup for whom this is a particularly good treatment.”

The narrower the target, the more personalized cancer therapies can become, Ford says. After all, when it comes to matching treatments to an individual’s genome, it hardly matters what works on the scale of hundreds or thousands of people.

“What you really want to know,” Ford says, “is in this patient in my examining room, what is going on in her tumor?”

Stephanie Pappas is at medmag@stanford.edu
Genes rule. But they’re not quite the dictators some have claimed and others have feared.

In the past decade or two, researchers have learned that genes themselves are governed by a benign bureaucracy of regulatory loops that curb some genes while stimulating others. Now they have discovered a new class of molecules that may play a major role in that regulation, from determining what cells want to be when they grow up to keeping them on task once they do. This means that tailoring medicine to suit an individual requires looking beyond the genes. Or more precisely, looking between the genes, because that’s where the newest of new players originate. These molecules, long linear strands called lincRNA, are the latest surprise to arise from the vast spaces along chromosomes that separate one gene from another — spaces once considered so bereft of purpose they were disparaged as “junk DNA.” And while some pioneering physicians have begun incorporating patients’ genetic information into their treatment plans, they can’t yet factor in molecules like lincRNAs that regulate those genes. At this early stage of discovery, they wouldn’t know what to test for. But with evidence building that at least a couple of

BY BRUCE GOLDMAN

ILLUSTRATION BY GREG MABLY
lincRNAs have been implicated in cancer, it’s realistic to expect that testing people for these gene-regulating molecules will become part of medical practice. Knowing the genes alone will take us only so far along the road to personalized medicine.

RNA in humbler days

LIKE ROYALTY ON A THRONE, GENES NEVER LEAVE THE NUCLEUS, WHICH LIES JUST ABOUT SMACK-DAB in the cell’s center. Yet the molecules that make up the working class of the cell, the proteins, are stitched together in the cell’s watery outer provinces, or cytoplasm. The genome delivers its edicts to the cytoplasm via messengers made of RNA, a substance seen previously as a passive “wax impression” of DNA, but looking more like an Olympic gymnast every day.

Until recently, RNAs main claim to fame was largely as a bit player in the extravaganza that is gene activation. When the DNA double helix is inactive, its two strands are zipped up and spooled around specialized packaging proteins called histones. “Reading” a gene’s instructions requires unzipping the two strands at the site of the gene.

Somewhere around the beginning of life many billions of years ago, cells evolved bulky molecular machines (each of them an assembly including numerous large proteins) that can do this very well. These transcription machines can unzip and unpeel the DNA temporarily from its associated histone husk. They can part its two strands at key points. They can then hover above a strand near the start of a gene, barrel down the exposed DNA and crank out copies of its protein-coding instructions. The copies are made of RNA, which is chemically similar to DNA — they’re both chains of constituent chemical links called nucleotides — but RNA is more travel-ready and short-lived.

Fresh “messenger RNA” molecules float out of the nucleus into the cell’s far reaches. There in the cytoplasm they are fed into still other gigantic molecular machines, called ribosomes, their strings of nucleotides read as consecutive threenucleotide chunks, and the proteins they specify produced according to a code whereby each three-letter RNA “word” indicates which of some 20 different chemical building blocks should next be spliced onto a growing protein molecule.

But not all genes in all cells get copied all the time. Different kinds of cells, and the same cells at different stages of their lives, are different because they make different proteins. Otherwise, we’d all be blobs of undifferentiated tissue. Just how do these differences in protein production come about?

The hulking transcription machines in the nucleus that zip and unzip DNA are exactly the same from one cell to the next. So are the ribosomes in the cytoplasm that decipher the genetic code to manufacture proteins. So those giant complexes can’t determine all by themselves which genes get read within a given cell at a given time.

Still other huge protein complexes sporting Jurassic Parkish names such as Trithorax and Polycomb affix or remove small chemical tags to the DNA or histones in the vicinity of genes. The tags serve as long-lasting “read” or “skip” signals to the gene-reading machinery. But those lumbering juggernauts, Trithorax and Polycomb, are exactly the same in every cell, too. So who tells them where along the genome to slap those “read” and “skip” tags? Who guides them to the appropriate spots in the first place?

Cue the music. Enter lincRNA molecules, discovered by two researchers who looked where no one else was looking and found what no one else had thought would be there.

Eureka moment

A CELL CAN’T MAKE A PROTEIN WITHOUT MAKING RNA FIRST. THUS, A QUICK-AND-DIRTY WAY to see which genes in a cell or tissue are in active use as protein templates is to use a gene-expression chip: a microarray pioneered by Stanford School of Medicine biochemistry professor Pat Brown, PhD, and biochemistry and genetics professor Ronald Davis, PhD, in the mid-1990s. This device represents the amounts of RNA made from each gene on the chip as a separate pixel displayed on a computer screen — the more RNA made from that gene, the brighter the pixel — making it easy to analyze aggregate patterns of gene expression: that is, which ones are actively getting read, and which just sitting there, at any given time.

In 1999, shortly after the Human Genome Project pulled out its first plum from the genomic pudding — the full sequencing of chromosome 22 — Michael Snyder, PhD, at that time a Yale University genetist, used the newly published sequence data to design a high-resolution gene-expression chip he called a tiling array. It combed the entirety of chromosome 22 for small snippets of RNA emanating not just from its known or likely protein-coding portions (“genes,” that is), but from anywhere along its entire length. Snyder’s custom-built tiling array would, in principle, allow the detection of RNA molecules made not only where you’d expect to find them being made — at, near or overlapping all the places where a protein-coding sequence had already been identified — but from anyplace along chromosome 22, including vast mysterious stretches between one gene and the next.

This was ambitious and, some thought, a waste of time and
money. As the Human Genome Project unfolded, it began to look as though not much more than 1 percent of the genome consisted of recipes for viable proteins. The other 99 percent appeared to have no function, save for small sections near genes that served as landing strips and homing beacons for the molecular machines that read or mark up DNA. One high-profile Harvard biologist referred to the overwhelmingly large non-coding stretches as “junk DNA.” The name stuck.

“Many of us never really believed that,” says Snyder, who last year moved to Stanford to become professor and chair of the medical school’s genetics department.

Snyder told one of his graduate students, John Rinn, to take a close look at chromosome 22. Applying Snyder’s tiling array to the just-sequenced chromosome, Rinn found that RNA was getting made at all kinds of sites along the DNA that bore no resemblance to protein-coding genes. Some of these RNA molecules were very small, consisting of tens of nucleotides. But lots of them were thousands of nucleotides long, as lengthy as those that do code for a protein. These RNA molecules weren’t doing that, as could be determined by their nonsensical sequences — for example, they tended to contain too many three-nucleotide signals that, in effect, stop the protein-making machinery in its tracks. Yet they featured many of the same “gene-like” elements (for instance, regulatory nucleotide sequences that invite gene-reading machinery to have a sit) that protein-coding RNA molecules did.

“There were as many genes making RNA but not proteins as there were protein-coding genes,” Rinn recalls. “It was a Eureka moment.”

Of course, that Eureka moment electrified only the people who thought this was interesting — a small minority. “People felt that something had to be wrong,” says Snyder. Mightn’t all this unexpected non-protein-producing RNA, asked the skeptics, simply be the results of a trigger-happy molecular gene-reading machine?

That didn’t seem likely to Rinn and Snyder. A surprising number of the newly discovered longish RNA molecules were being produced in the middle of nowhere, so to speak: in those vast intervening DNA stretches that separate one gene from the next.

Still other evidence pointed to the potential significance of these long, intergenic non-coding RNA molecules, subsequently dubbed lincRNAs. Over evolutionary time, mutations creep into DNA and pile up, so in any stretch of DNA sequence that’s not absolutely essential, you’ll see evidence of evolutionary drift. Any stretch that is “conserved” — maintained largely unchanged over billions of years of evolution — is presumed to be important: For whatever reason, the organism just couldn’t do without it. Interestingly, something like 5 percent of diverse organisms’ genomic sequences shows strong signs of evolutionary conservation, as opposed to the mere 1 percent accounted for by protein-coding genes.

If most of the conserved stretches of our genome lie in its non-coding regions, then that means they’re somehow important for the survival of the organism. They obviously have some kind of function, Rinn reasoned.

Show me, the skeptics said.

What they’re up to

IN 2004, HOWARD CHANG, MD, PHD, WAS A NEWLY MINTED ASSISTANT PROFESSOR of dermatology at Stanford. Rinn showed up that year to be Chang’s first-ever postdoctoral researcher. He arrived, in his own words, “with a chip on my shoulder” owing to others’ doubts about lincRNAs significance. But together he and Chang discovered that these underappreciated molecules have the power to control what a cell becomes when it grows up.

Chang, now an associate professor, naturally thinks about skin a lot. “If you look at your own skin, you can see it’s not the same everywhere,” he says. “You have long hairs growing from your scalp, but not from your palms or soles. How do skin cells, which are constantly dividing, dying and being replaced by new ones, know where they’re located in the body and act accordingly? There must be some sort of address code that tells them where they are. You can find the same kind of thing happening in any other tissue — heart, lung, brain, fat, bone, blood vessels.”

CONTINUES ON PAGE 44
Steve Harris stared at the unopened file on his computer screen containing his risk for Parkinson’s disease. Did he want to open it? Six weeks earlier, he had spit into a test tube, sealed it up, then shipped it off via FedEx to a genetics-testing lab. Now he had the results before him — his risk for more than 80 major health conditions, the Parkinson’s result in a separate file.

He recalled his father’s torturous seven-year struggle with the disease and felt sadness wash over him. “I sat there for 10 minutes, but I didn’t open it,” said Harris, a sixth-year MD/PhD student, who asked that his real name not be used. When he later returned to the file, he still couldn’t bring himself to learn the result.

Better, he decided, at age 30 not to live with the anxiety of knowing he had a dramatically increased risk of a terrible neurological condition with no known cure.

Harris is a pioneer of sorts, one of 54 students in a School of Medicine class called Genomics and Personalized Medicine. The historic class, the first in the country to offer students the option of commercial genotyping, was approved after highly charged debates that Dean Philip Pizzo, MD, said were “among the most important that our faculty and students have engaged in.”

The eight-week course aims to teach medical and graduate students how the explosion of knowledge about genetics could play out in medical practice. As part of the class, students had the opportunity to get their own genotyping results to help them understand, through personal
experience, the myriad ethical, clinical, social, legal and other challenges that patients across the country will face in the near future.

“This information is coming,” cardiologist Euan Ashley, MD, PhD, said in a July presentation to the students. “We need to learn how to apply it for the benefit of our population.”

The class comes at a time of extremely rapid progress in genetics research. Every week brings to light some new discovery of a gene or snippet of DNA related to a particular disease or trait. Meanwhile, the cost of genomic testing is plummeting. In 2003, it took more than $400 million and a gargantuan effort to sequence the first complete human genome, the molecular blueprint of life. Just six years later, in 2009, Stanford bioengineering professor Stephen Quake, DPhil, managed to sequence his own genome for just $48,000, using a technology he invented. Within the next year or two, any individual will be able to secure his or her own genome for just a few thousand dollars, predicted Michael Snyder, MD, PhD, professor and chair of genetics.

“The day is not far away when, at the time you’re born or when you turn 18, it will be standard to have your genome sequenced,” said Keyan Salari, the sixth-year MD/PhD student who proposed and directed the course.

Already, consumer genomics companies charge less than $1,000 for the type of report Harris received. Instead of providing the full genome sequence, which contains billions of nucleotide subunits, these tests report on hundreds of thousands of SNPs, or single nucleotide polymorphisms — single changes in the DNA sequence that can have a meaningful impact on a person’s disease risk or trait.

Though this information thus far has had little impact on clinical practice, ultimately its effects could be far-reaching. Many predict that it will enable doctors to make the best choice of drugs and drug doses. It will also help determine what diagnostic tests patients should get and what lifestyle changes they could make to minimize their disease risks, said Ashley, who directs the Stanford Center for Inherited Cardiovascular Diseases. For instance, a person found to be at greater risk of diabetes could go for blood sugar screening, obtain drug therapy, and change his or her eating and exercise habits to reduce the impact of the disease, he said.

In addition, whole-genome sequencing will offer much greater power to detect the cause of genetic syndromes in families, said Ashley.

“The technology could revolutionize our approach to family screening in these cases,” he said.

But the availability of genetic information also has the potential to generate enormous anxiety, as people might learn they are at higher risk for some devastating disorders, such as Alzheimer’s disease, over which they have little or no control.

While this avalanche of data is due to arrive shortly, few practitioners are equipped to help patients interpret the massively complex results and cope with what could be disquieting news. Currently, there are only about 3,000 genetic counselors in the United States and 1,100 medical geneticists, far too few to accommodate the enormous demand, said Kelly Ormond, director of the genetic counseling training program at Stanford and associate professor of genetics.

“Everyone, no matter what area you work in, is going to need a higher level of knowledge,” Ormond told students in explaining the need for the course.

While no one disputed the value of the class, some faculty members were troubled by the prospect of offering students personal genotyping. Critics said it could be viewed as coercion on the part of the school, as students would feel pressured to submit to testing to please the course instructors. And some questioned how the school could subject students to a test that might deliver devastating results.

“I was alarmed by this possibility, frankly,” Michael Greicius, MD, a professor of neurology, told the students.

When several faculty leaders first planned in 2009 to offer the genotyping to incoming medical students, as well as some graduate students and internal medicine residents, Pizzo put it on hold until the school could assess the risks and liabilities of the genetic testing.

“I fully recognize that genotyping will be an important part of our future, but also that the current technologies are limited and potentially problematic for those who are less than fully informed,” Pizzo said.

A 27-member task force — including clinicians, basic scientists, ethicists, genetic counselors, lawyers and students — debated the issue for a year, ultimately approving the course proposed by Salari, with some modifications. For instance, the course was offered as an elective in which student
Leslie Williamson

Medical student Keyan Salari, pictured here among genome sequencing machines, led a historic class on genomics in medicine.
genotyping was optional. Students could choose one of two commercially available tests offered by 23andMe or Navigenics, which report on SNPs. Students would pay $99 for the testing — enough to prove their commitment but not enough to break their budgets, the task force decided. Stanford would pay the $300 balance for each student.

In classroom exercises, students could use their own data or publicly available genome data, and instructors would not know which set they had chosen. The school also offered free counseling to students by the companies’ genetic counselors or members of the psychiatry faculty who volunteered their services. Test results were kept confidential, and instructors would never know which students came forward for testing.

Pizzo said the debate over the class reflects a field in its infancy. “There will be lots of opportunities for continued dialogue as the sophistication of the technology improves and the costs fall. It is our obligation to educate and train students to be future leaders. It is gratifying to see students behaving as leaders in the present — which certainly speaks well for the future.”

The disagreements about the course were freely discussed in classroom sessions. On the day before students were to decide whether to be tested, Greicius and biomedical ethicist Hank Greely, JD, presented some powerful arguments for why they thought students should opt out.

Greicius, who studies the genetics of neurological disease, warned the students against getting tested for the ApoE4 gene variant, which puts carriers at much greater risk of early Alzheimer’s and is among the variants tested by some personal genotyping companies.

“If you have a healthy 20-year-old without a clinical problem, I don’t think (testing for the gene) makes sense,” he said. “In fact, it does more harm than good, especially when you have 40 years to worry about it. Every time you get a B+ on a test, you will be thinking, ‘It’s early Alzheimer’s.'”

Greicius also pointed out that while this is among the most informative Alzheimer’s test offered, it is still fraught with uncertainty: ApoE4 carriers can live long lives and never get the disease, while a large proportion of Alzheimer’s disease patients do not have the ApoE4 variant at all.

Greely, director of the Center for the Law and Biosciences, assumed a lawyerly stance and with his booming voice presented his arguments point by point as if he were in a court of law. He said he never objected to the class, just the genotyping of students, who could obsess about the results or be misled by them. For instance, a woman who tests negative for the BRCA1 or BRCA2 gene mutations, which carry a greatly increased risk of breast cancer, might forgo cancer screening in the mistaken belief that she had no risk of the disease.

He said he also worried about the lack of government regulation over these direct-to-consumer tests and the fact that Stanford’s use of the tests could amount to a tacit endorsement of them (though class organizers issued a disclaimer to the contrary).

“I think that is a bad message to send because, from the medical side, I don’t think there’s anything valuable here,” Greely told the class. He also argued that the technology employed by the current genotyping tests soon will be replaced by whole-genome sequencing, making them obsolete by the time students begin their medical practices.

Stuart Kim, PhD, professor of developmental biology and of genetics and the course’s faculty sponsor, was visibly tense during the presentation and said later that he sharply disagreed with those views. Similar debates in the task force had left faculty members at odds. Kim said he believes that while the current tests don’t supply the range of data available in a fully sequenced genome, they are still quite useful.

“You don’t wait until it’s perfect before you learn it,” he said. “You learn what you can. You learn the principles of how human genetics works, so that you can best use new genetic discoveries as soon as they are made.”

Kim argued on the side of knowing — that knowledge can be power. For instance, a woman who tests positive for a mutation in the BRCA1 gene could have more frequent screenings and catch the cancer early, when it can be effectively removed before it spreads to the lymph nodes, he said.

“I think it’s worth it for women to have that information,” said Kim, who had his own genotyping done two years ago. “I would take life over ignorance.”

He said in some instances, there is a clear value in having genotype data in hand, the best example being the case of the frequently prescribed drug warfarin, a blood thinner that helps prevent clots. Without genetic information, the drug can be hard to calibrate. Too much can cause hemorrhaging and death,
explained Russ Altman, MD, PhD, a professor of bioengineering, medicine and genetics, who serves on a national advisory panel that is developing physician guidelines for the drug.

“You can’t tell the dose by looking at a patient because genetics plays a huge part,” said Altman, who disclosed to the students that he serves on the scientific advisory board of 23andMe.

Altman led a class exercise using genotype data to get each student’s dose right.

Students engaged in a number of other in-class exercises, including one in which they used genetic data to calculate their chances of living to age 100. Sam Pearlman, a bioinformatics PhD student, and two others in the class created a software tool for the exercise, based on a study published in the July 2 issue of Science Express. The controversial study by Boston scientists identified 150 SNPs associated with longevity and used those genes to build a model for predicting a person’s “aging signature.”

The class winner of the longevity lottery was Kathy Wei, a PhD student in bioengineering who was found to have a 99.8 percent chance of reaching 100. Wei said she was excited though surprised by the result, as nothing in her family history suggests she has such hardy genes.

Kim, who gave her a prize of chocolates and clam chowder (clams are among the longest-living animals in the world), cautioned the students not to put too much stock in the result, as many questions remain about the validity of the study, which used data from Caucasians only. Nonetheless, this is where genetics is headed, he said.

“Whether it’s aging, diabetes or heart disease, this kind of genetic signature is part of the future,” he said.

Ultimately, 33 students in the class opted for the genotyping test, with varying levels of angst. Alexander Morgan, a PhD student in bioinformatics and pediatrics, said he didn’t hesitate to get tested as he thought he could cope with any results that might ensue. “If I had some horrible news, I think I would not consider it a death sentence,” he said. “People do recover emotionally from bad news.”

Pearlman, on the other hand, said he agonized over the decision because of a family history of Parkinson’s.

“Finding out I have this variant would not change anything — it will just make me worry,” said Pearlman, who is considering a career in genetic counseling. On the other hand, “Being a scientist, I probably would want to know because I feel more information is good information, even though at this point I can’t do much about it.” He is still waiting for his results.

Krystal St. Julien, a PhD student in biochemistry, said she decided not to go for the test because she was afraid she would obsess over the data.

“I tend to freak out about the most random things, and I don’t know what I’d be OK with or not OK with,” she said. However, the class has taught her what genotyping has to offer, so she has become more interested in having it done, she said.

Students say the class provoked them to think about many heady issues affecting themselves, their families and the future of medical practice.

Pearlman said the class just reinforced the pitfalls of making genetic data available, as it is poorly regulated, open to widespread confusion and misinterpretation, and constantly changing.

“Scientists like to view information as pure, but when it comes to health, it gets to be a quagmire of ethics, politics and regulation,” he said. “Will it be helpful or destructive?”

St. Julien noted that the class only scratched the surface of what’s to come, as human genome sequencing will open a Pandora’s box of potential problems.

“When you do sequencing, you can pinpoint exactly where something is going wrong,” she said. “I think it’s going to be very hard for physicians and scientists to explain everything to everybody.”

But the class is still a good beginning, she said.

“I think it’s a good start to figure out the logistics of how people should study personalized medicine and the medical implications. It’s good to build a community of people who can express to patients what it all means.”

As for Harris, the class gave him a whole new perspective on the field and the limitations of genetic testing. “Having undergone the kind of testing and knowing the anxiety it can provoke and the meaning of the results and the limitations — that is an experience that is useful for physicians,” he said. “Now you’ll understand what kinds of stresses patients will have. I think it’s a unique way for physicians to empathize with patients because you went through it firsthand.” His Parkinson’s file meanwhile remains unopened.

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But as has been the case for other biologists, once he knew about it, pieces of biological puzzles began to fall into place. Largely ignored for over a century, the primary cilium has provided a key to the bafflingly diverse symptoms exhibited by certain diseases, most notably polycystic kidney disease — the main reason people go on dialysis. In Nachury’s case, investigations into the primary cilium led him to the cause of a rare but terrible condition, Bardet-Biedl syndrome. With these realizations have come potential new paths for treatments.

The primary cilium is not a recent discovery. Swiss anatomist K.W. Zimmermann described the structure and suggested a sensory role in 1898, but other scientists largely ignored it. In later years it was written off as a quirk of evolution. The outburst of research over the past decade has revealed that the tiny projection is acting as the receiving station for cells’ signaling chains, the communication networks that govern and coordinate cell actions.

For Nachury, knowledge of the primary cilium came out of nowhere. At the time, he was looking for something new and interesting about the cell-division cycle to explore — no easy task because the field was already mature and most of the major questions had been answered.

“It was totally mind-blowing,” says Nachury, who was a Stanford postdoctoral scholar at the time, in 2005, and is now an assistant professor of molecular and cellular physiology. “I had never heard of primary cilia. Not in a single lecture, seminar or meeting. I hadn’t even known they existed, yet they were doing all these things.”

BY ROSANNE SPECTOR

ILLUSTRATION BY BRYAN CHRISTIE
ears for anything exciting that would be worth spending a career studying.”

So when he saw that one of the proteins he had singled out as crucial to normal cell division was also at the root of a rare genetic disease, he perked up. He learned that the disease, Alstrom syndrome, causes a wide, seemingly unrelated range of serious problems, notably obesity starting in childhood, blindness, hearing loss, kidney malformation, heart disease and diabetes.

“I was immediately fascinated by the variety of symptoms. It didn’t make any sense that they could be the result of cell cycle defects.”

Then he read an old article on Alstrom syndrome (Journal of Pediatrics, Michaud et al., 1996) and the plot thickened. There in the last paragraph, he read: “Bardet-Biedl syndrome is a distinct disorder with clinical findings overlapping those of Alstrom syndrome.” He learned that patients with Bardet-Biedl, or BBS, have all the symptoms of Alstrom syndrome as well as postaxial polydactyly — an extra finger near the pinky or an extra toe near the fifth toe.

Nachury continued his digging and eventually found more recent scientific literature suggesting that the culprit proteins in Alstrom and BBS normally helped shape the structure and function of a cell organelle called the primary cilium.

**THE PRIMARY CILIUM ACTS LIKE THE CELL’S ANTENNA. THE SIGNALS IT PICKS UP ARE PROTEINS SUCH AS “HEDGEHOG,” WHICH SETS OFF A CASCADE OF MOLECULAR INTERACTIONS EXTENDING INTO THE CELL’S NUCLEUS.**

BBSOMES FERRY CASCADE PROTEINS INTO THE CILIUM, HELPING KEEP THE CONCENTRATION HIGH.
cilia, and this organelle was important for a variety of developmental and cell signaling pathways. It was like the sky opened up for him.

He had long known about “ordinary” cilia, which are flexible, hairlike outcroppings that usually exist in large groupings, and flagella, those whipping tails that propel single-celled algae across ponds and move sperm up fallopian tubes. But primary cilia?

“I felt like a kid discovering the Internet: A whole world was out there that I had never heard of in four years of undergrad plus five years of grad school plus two years of postdoc. I knew nothing about primary cilia and I wanted to know everything.”

What he gathered paints a portrait of a singularly peculiar cellular structure. A ring of nine filaments forms its internal skeleton, which is surrounded by a thick soup of proteins. A semi-permeable wrapper, the plasma membrane, covers the whole thing. A barrel-shaped base with a mysterious knob on its side sits within the cell; the rest of the cilium shoots out beyond. Molecular motors move the structure’s building blocks up from its base to produce the projection. Then, if the cell it’s attached to divides, these motors dismantle the shaft from the tip down. The complexity of the organelle is such that creationists have argued it’s evidence of an intelligent designer at work.

One of the most unusual aspects of the primary cilium is the manner in which it reproduces. The cilium shaft disassembles so all that’s left is the base. A duplicate base forms — no one knows how — abutting one side at a right angle. Eventually the two separate and form opposite ends of the so-called spindle apparatus that pulls chromosomes apart during cell division. After the single cell has become two, a primary cilium rises up anew in each.

Interest in the primary cilium began building in 2000 when researchers made the first definitive connection between dysfunctional primary cilia and disease — polycystic kidney disease, which affects about 600,000 people in the United States. It escalated when another group of scientists reported in 2003 that in mice, and therefore probably other mammals, one of the cell’s most important means of talking with other cells, the curiously named hedgehog signaling pathway, requires the primary cilium. (The name hedgehog protein comes from the hedgehog-like appearance of fly larvae that have a defect in the protein: They’re more rotund than ordinary maggots and covered with clumps of spiky denticles.)

Researchers studying genetics in fruit flies discovered the pathway decades ago, in the 1970s, leading to a revolution in understanding cell communications.

“Cells all start off the same but they don’t stay that way. So what gets them to change? They get signals telling them what to do,” says professor of developmental biology Matthew Scott, PhD, a longtime researcher of cell signaling, who has recently branched out into primary cilium. “The theory was there would be thousands of signals and it would be impossible to figure out. But it has turned out that it’s a reasonable number of signals, about 20, often in different combinations.”

The hedgehog protein is one of these signals. It starts a molecular game of tag when it lands on the outer covering of a mammalian cell, the plasma membrane, and attaches to another protein there, called “patched.” Patched has been holding the rest of the pathway in check, but once hedgehog binds to it, more molecular interactions ensue. Soon the chemical balance in the region changes, allowing another protein to kick into action, which binds with another molecule, which binds to another, and so on, reaching from the plasma membrane into the cell’s nucleus where molecules bind to particular genes, in some cases switching them on, in others, off.

Finally excited about a project, Nachury convinced his advisor, associate professor of pathology Peter Jackson, PhD, that the primary cilium, with its importance to hedgehog signaling and its connection to Bardet-Biedl syndrome, was a frontier worth exploring. By 2007, he had identified a group of seven proteins that normally work together but lead to BBS if impaired. He also found that the primary cilium needs this complex, which he dubbed the BBSome, to function properly. At the time, he didn’t know what that function was but he suspected it was moving proteins around within the dynamic boundary that surrounds cells — the plasma membrane.

“YOU CAN IMAGINE CRYPTOGRAPHERS ALL SITTING AT A DESK, READY AS SOON AS THE MESSAGE COMES IN.”
By this summer, Nachury had confirmed his hunch. His experiments, reported in the June 25 issue of Cell, showed that the BBSome latches on to proteins within the plasma membrane covering the main body of the cell and pulls them through the cordon around the cilium’s base and into the harbor on the surface of the primary cilium. Essentially, the BBSome helps keep the primary cilium crowded with proteins.

“Until now, we knew of essentially no molecules that served this purpose,” says Nachury.

“Now the primary cilium is starting to look less like a mere antenna, and more like the communication hub of the cell,” he says.

To understand the distinction, it helps to picture the cell’s plasma membrane, where many protein molecules mill and bob amid the phospholipid molecules that provide its structure. In the membrane covering the primary cilium, the proteins are more concentrated, with a cluster of hedgehog signaling proteins at the tip. The result is a highly efficient setting for conveying chemical messages. Before the discoveries about the primary cilium, most researchers assumed no place on the plasma membrane was specialized for accepting signals. Now it looks like the primary cilium is particularly suited for picking up signals and passing them along, in part because of the high protein concentrations and in part because of its shape.

“A signal goes out, drifts through tissue, lands on the cell that receives it. It’s very important that the signal be of the right intensity, and reach the right cell,” says Scott. “Cilia can serve as antennae that might make a cell respond more to something coming from one direction than another.

“You can imagine cryptographers all sitting at a desk, ready as soon as the message comes in. Once the signal is received, it goes from the cilium to the nucleus of the cell to turn on or off a bunch of genes. That’s what changes the cell,” Scott says.

Meanwhile, Nachury’s discovery of the BBSome has given drug researchers a handle for developing a treatment for BBS. Most of the BBS mutations in patients destabilize the molecular tugboat — so finding chemical chaperones that can restore BBSome stability would be a promising avenue for therapeutics.

“There’s a whole field, called ‘proteostasis,’ where people are attempting to achieve this type of goal, and their main target is currently the cystic fibrosis gene,” says Nachury. “If their strategy works, it could very well be applied to the BBSome.”

**NOW NACHURY AND HIS COLLEAGUES ARE SEEING WHAT THE PRIMARY CILIAM CAN TELL THEM ABOUT ONE OF BIOLOGY’S LONGEST-STANDING MYSTERIES — THE BRAIN. IN FACT, IN THE PRIMARY CILIAM’S DARK DAYS, ITS ONLY KNOWN FUNCTION WAS AS THE POINT OF ENTRY FOR SENSORY INFORMATION EN ROUTE TO THE BRAIN. MOLECULES THAT WAFT UP THE NOSTRILS INTERACT WITH PROTEINS IN THE PRIMARY CILIAM OF OLFACTORY SENSORY NEURONS, WHICH HAVE ONE END IN THE NASAL CAVITY AND THE OTHER IN THE BRAIN. SIMILARLY, LIGHT THAT STRIKES THE PRIMARY CILIA ON ROD AND CONE CELLS IN THE RETINA GETS TRANSLATED INTO THE BRAIN AS VISION.**

Nachury thinks there must be more to know about the primary cilium in the brain — as nearly every cell in the brain has one.

“What are they up to?” he asks. “From everything we know so far about them elsewhere, they play a role in cell-cell communication. Quite possibly in the brain they’re helping neurons communicate with one another.”

**It’s no wonder the primary cilium isn’t better understood. Many of the world’s leading cell biologists had been clueless about the organelle until recently. When Nachury first asked his postdoctoral advisor about them, he discovered Jackson knew no more than he did. The leading text for U.S. college biology majors — Biology, by Campbell et al. — mentioned nothing about primary cilium until the current edition, published in 2008. Now it includes five sentences.**

But the primary cilium has become a trendy research subject. Stanford has become a particular hotbed, with nine faculty members exploring everything from how the cilium preserves its unique mix of proteins to how it faithfully reproduces during each cell cycle.

And the scientific literature on primary cilium is growing rapidly. A search through the PubMed health sciences literature database, which contains citations from 1949 to the present, shows the phrase “primary cilium” has appeared in the title or abstract of peer-reviewed biomedical articles only 322 times. But more than half of these articles, 187, were published in the past three years, with 92 in the last year alone.

The cell’s primary cilium doesn’t have the celebrity status of the nucleus and its chromosomes, but it’s gaining — fast. SM

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“We have a difficult decision to make together,” Glenn Chertow, MD, tells his patient. It’s early July. He’s holding Stanley Chang’s hand in the examination room at Stanford Hospital & Clinics. Chang, who asked that his real name not be used, is 79 years old and his kidneys are failing. He’s a slight man, maybe 110, 120 pounds. He’s lost much of his appetite and feels fatigued most days.

“You have options,” his doctor says, his words translated into Mandarin by a live translator who is participating through a web-based videoconference. “Even though you’re 79 and that’s not young, based on your overall good health, I think you may live a good healthy life for many years.” Physically Chang is still strong. He’s independent, lives at home with a supportive wife who sits next to him in the examination room. Both have their legs crossed and their brows furrowed. Both are frightened.

Chang is not a candidate for a kidney transplant. The waiting list is too long, five to seven years, and by then he’d be in his mid-80s.
“If I thought you were going to pass away in three or six months, I might not recommend going through the inconvenience of dialysis to extend your life,” says Chertow, chief of the Stanford nephrology division and professor of medicine.

Dialysis is a life-extending procedure that for most patients with kidney failure involves sitting in a chair three or more times a week connected to an artificial kidney machine. Small amounts of blood are slowly cleansed by exchanging fluid and electrolytes across a membrane during each three-to-four-hour session.

“You don’t need dialysis today or tomorrow or next week,” says Chertow.

“But you don’t want to wait too long to decide,” he says. “I’ll see you back in a month.” For the average person, the decision of whether to go on dialysis for a month. “For the average person, the decision of whether to go on dialysis for a month,” he says. “I’ll see you back in tomorrow or next week,” says Chertow.

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“Y ou don’t need dialysis today or to-morrow or next week,” says Chertow.

“Do we recommend dialysis for kidney failure seems to be a simple one. The common perception is that you have no choice. If your kidneys have failed, without dialysis your body can’t cleanse itself of the by-products of metabolism, and these can be toxic. Now, 50 years after the first maintenance dialysis treatments became available in 1960, a growing body of research is challenging that tenet of care, providing evidence that, particularly for the frail elderly who suffer from multiple severe ailments, the decision to start — or to stop — dialysis is more complicated.

As the fastest-growing age group in the country to start dialysis is now those over the age of 75, many are questioning whether a better understanding of the effects of dialysis on the elderly could result in a more judicious use of the procedure, potentially improving quality of care and lowering health-care costs.

The medical community has begun to debate how this decision should be made. The discussions reflect a new tension rending America: While modern medicine builds on its incredible success at extending life, a growing movement seeks to improve the way Americans die.

Dialysis is a burdensome and expensive process that costs about $75,000 to $100,000 per patient per year. While not a cure, it is an amazing feat of technology that has kept millions of people alive for years, sometimes decades. Without functioning kidneys, the buildup of fluids and waste products in the body can lead to failure of key organs and many adverse symptoms. When dialysis technology first became available, access was limited to those who could afford to pay for it. In 1972 Congress passed legislation that extended benefits under Medicare to all Americans with kidney failure regardless of age or ability to pay. Early on, it was assumed that dialysis would be medically suitable only for patients under the age of 54 who were free of other severe illnesses because of its stress on the body.

Today, the population of patients covered under the program presents a radically different picture. The average patient is much older and much sicker. The median age of the 400,000 American patients whose dialysis is covered by Medicare is now over 64. Among those patients who begin dialyzing in their 80s and 90s, nearly half have congestive heart failure and one-third have diabetes or cardiovascular disease, according to an October 2009 commentary by Yale University nephrologists Peter Aronson, MD, and Felix Knauf, MD, in the Journal of the American Society of Nephrology.

While growing research shows dialysis provides only modest benefit to the oldest, sickest patients, most doctors have been willing to start dialysis at any age, Aronson and Knauf write.

That may be changing.

“We’ve been putting all our seniors with kidney failure on dialysis every single time because we’ve had insufficient information,” says Alvin Moss, MD, professor of medicine at West Virginia University who chaired the committee that wrote the Renal Physicians Association’s guidelines on starting and stopping dialysis: Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis. An updated edition expected in October includes new studies that spell out the benefits and drawbacks of dialysis for the frail elderly with multiple severe diseases.

“But the questions now for each individual patient are, ‘Will it lengthen life? Will the quality of care improve?’ We don’t want to torture our seniors.”

For patients with kidney failure at the Pacific Coast Manor, a nursing home in Capitola, Calif., dialysis determines the structure of their days. At 7 a.m. a van picks them up and takes them to the nearby Satellite Dialysis center.

For three to four hours, these seniors — most of whom are over the age of 80 and have other ailments such as heart disease or high blood pressure — sit back in big, black, padded recliners,

**will it lengthen life?**

**IMPROVE ITS QUALITY? “WE DON’T WANT TO TORTURE OUR SENIORS.”**
their bodies attached by clear tubes to an artificial kidney machine. Some have arthritis, back pain, circulation problems. The tubes turn red as their blood streams out through one, and back in through the other.

On one particular morning at the dialysis center, 10 patients fill up about half of the chairs. Most are seniors resting quietly in reclining chairs, watching TV, sometimes dozing. Several are from nursing homes. A woman in her 80s with short, gray hair is curled up under a crocheted blanket with slippers on her feet, knitting to pass the time.

It’s a scene that gets repeated in centers across the nation with patients returning week after week, year after year. Some patients continue for decades.

The Pacific Coast nursing home residents, some in wheelchairs, return home at 2 p.m. They’ll repeat the process in two days and then two days after that for the rest of their lives or until they choose to stop.

It’s a difficult routine for the older seniors at the nursing home, says Terri Jones, the director of nursing there. “They come back really tired. They lie down and go to bed. I haven’t seen anyone feel better, just weaker.

“Some patients do choose to stop,” Jones says. “Some of our 90- and 100-year-old patients don’t want dialysis at all. They’ll choose end-of-life care with our staff or with hospice. They know their bodies are starting to break down.”

Evidence that the frail elderly with severe ailments might not always benefit from dialysis was supported by a study led by Manjula Kurella Tamura, MD, assistant professor of nephrology, that appeared in the Oct. 15, 2009, issue of the New England Journal of Medicine. Chertow was a co-author. The study, an analysis of seniors on dialysis living in nursing homes across the country, found that patients tend to experience a significant decline in their ability to perform simple daily tasks such as feeding themselves, getting dressed or brushing their teeth after starting dialysis.

Why the decline? In some patients, kidney failure may be a sign of the dying process, and this may explain why functioning continues to decline despite starting dialysis, Kurella Tamura says. If a patient is dying of cancer or heart disease, the kidneys, along with other organs, will naturally fail. Because kidney failure is not what’s killing them, dialysis won’t help.

“In some of these patients dialysis may be prolonging suffering rather than prolonging life,” she adds.

The hope is that, with new research uncovering the actual affects of dialysis on the elderly, doctors and patients can hold more fruitful discussions when deciding whether to start the procedure, she says.

“There should be an individualized approach that takes into account the patient’s goals of care along with prognostic information,” she says. “Some patients may choose a palliative treatment approach, and others may choose dialysis. Regardless of what treatment they choose, this information can help patients prepare for a decrease in their abilities to function and plan for that.”

For Chang, the decision is just beginning. In the coming week he’ll grow agitated and uncomfortable as he realizes dialysis means that he would no longer be able to fly to China to visit his daughter. That his diet would be severely restricted. He’d be spending a significant portion of his remaining life sitting in a chair hooked up to an artificial kidney machine.

“No one wants to start dialysis,” says Chertow, who has held these sensitive discussions with patients many times. “It sustains life, but generally, for most patients it doesn’t restore health. They don’t feel well. The question for doctors is, how do we provide sufficient information to the patient that enables them to make an informed decision while being as optimistic and as realistic as we can about the future. We can’t lie to patients and say everything is going to be hunky-dory.”

But Chertow remains optimistic for Chang. He’s not in a wheelchair and has no difficulty getting around. He lives independently. He has no heart failure, no liver disease.

“He’s not in the best of health, but he’s OK,” Chertow says. “The decision is even harder for someone who has cancer and is getting chemotherapy. Maybe they’ve decided enough is enough. For someone like [Mr. Chang], it’s very reasonable to at least give it a try. His life could potentially be improved.”

The quandary over dialysis for older patients is but one of many concerning the use of life-extending technologies for this group. Tangled up with efforts to improve the quality of lives are matters of money. Many critics maintain that while increasing use of these technologies — extended chemotherapy, breathing tubes — stokes America’s massive health-care spending, the quality of care has not increased. In fact, it has diminished, creating an American way of death that has grown slow, painful and expensive.
“People have concerns besides simply prolonging their lives,” writes Atul Gawande, MD, a Harvard University surgeon and Stanford University alumnus whose writings have influenced the political debate surrounding health-care reform, in the Aug. 2 issue of the *New Yorker*. “Avoiding suffering, being with family, being mentally aware, not becoming a burden. Technological care has not met those needs.”

According to Gawande, 25 percent of Medicare spending is for the 5 percent of patients who are in their final year of life, and most of that money goes for care in their last couple of months, which is of little apparent benefit.

While the cost of kidney dialysis is a fraction of this — Medicare spends more than $20 billion per year on dialysis treatment and medications — the rapid growth in spending represents “in microcosm the escalating costs of the overall health-care system,” write Aronson and Knauf.

“Providing real data on how patients actually do on dialysis is making a difference,” says Aronson in a follow-up interview. “Studies elucidating outcomes that are not very good even if you do start dialysis are encouraging more conversations between doctors and their patients, and encouraging nephrologists to get better training in geriatric care.”

Aronson points to a 2009 study in the *Clinical Journal of the American Society of Nephrology* that found dialysis for elderly kidney failure patients with multiple severe ailments extended life by two years, while similar patients who did not get dialysis but instead received palliative or pain-reducing care survived about a year but with significantly fewer days in the hospital or time spent receiving medical care.

It’s important for patients to realize the benefits and drawbacks of choosing dialysis so they can make a decision that best reflects their personal values.

“Most physicians were trained to extend life unless explicitly requested not to,” says Arnold Milstein, MD, professor of medicine at Stanford and director of the Clinical Excellence Research Center. “As a result, we are rarely skillful in the psychologically nuanced job of helping patients to select the end-of-life treatment option best aligned with their personal values.”

The solution is more discussions between doctors and patients about these choices. “If discussions take place on what patients want,” says Moss, “there is less pain and suffering and less expense. The question is, ‘Are people and families willing to have these conversations?’”

**In mid-July, Chertow moves up his appointment with Chang by two weeks. His recent blood test results are worrisome. Chertow has been discussing dialysis with Chang during several appointments over months now. Dialysis will not be easy for Chang. Chertow has made that clear. But now he wants to make it very clear that it’s time to make a decision.**

“Your lab tests are terrible,” Chertow says. “I’m fearful that your kidneys are failing. As your kidney function got worse, the potassium went up. Some of your body chemistries are very much out of balance because your kidneys are not working.

“Now, Mr. Chang,” he says, placing his hand over Chang’s. He moves his chair close, their knees almost touching. “This dramatic change has made me very concerned that you will get very sick very soon.”

Chang and his wife both nod nervously. “Maybe you’re ready to pass on. If you want a chance to stay alive and healthy for the next several years, you need to start dialysis. If you want to stay off dialysis, that’s your decision. … If your lab tests are worse next week, I need to bring you into the hospital. … I just can’t manufacture time. I’m very worried about you. If dialysis is able to keep you alive and well, embrace dialysis, do not fear it.”

Three days later, Chertow calls Chang at home on a Sunday. His lab tests are worse. He recommends Chang come into the hospital right away. He tells him it’s time to make a decision. Without dialysis his kidneys can’t keep him alive. And that’s when Chang makes up his mind. He goes to the hospital.

It’s several days before Chang is released home. After starting dialysis he does feel better and stronger.

“We can’t just assume we should start dialysis because it’s technically feasible,” Chertow says. “That doesn’t mean we should do it. It’s not right for all patients.”

But for Chang, he’s relieved to say, it seems to be the right decision. He’s doing extremely well.

“For a 79-year-old gentleman with other problems, he feels really good,” Chertow says. SM

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“But we’re beginning to learn that the reference genome itself actually contains significant amounts of disease risk.”

In other words, normal doesn’t equal perfect. And because the people used to compile the reference genome were mostly of European ancestry, it’s not clear how well any findings may apply to people of other ethnicities.

“The issues of race and genetics and even behavior are a big area of study,” says McEwen, director of the national genome institute’s Ethical Legal and Societal Implications Research Program. “There are some very complicated questions where those areas intersect. Allele frequencies do vary, but we have to understand what genetics can and cannot tell us about differences among populations.” As whole-genome sequencing, and even genotyping, becomes more common, researchers and clinicians will face another problem — that of communicating new findings to patients who’ve had their DNA analyzed at some point in the past. Keeping people up to date on new findings involving genetic variants that they carry will be a tricky business. Clinicians of the future will walk a tightrope of informing people who’ve had their genome sequenced of ongoing discoveries while also presenting the information as uncertain and likely to change. In fact, Greely and several colleagues published a companion piece to the *Lancet* article discussing the special challenges of such knowledge.

“The world of medicine is going to change beyond belief,” says Ashley. “We are all going to have to learn how to deal with questions like these.”

Only one question really matters to Richard Quake’s family. “What killed Richie?” Unbelievably, they may be nearing an answer. The round-the-clock research by Ashley and his colleagues has led them to a likely candidate — a mutation in a gene for an ion channel known to be associated with very rare cases of sudden cardiac death. But more testing remains to be done.

“It’s all going to come down to how confident we are that this is the mutation that caused Richie’s death,” says Ashley. “There’s still more work to be done, but this is our top suspect. If we’re convinced, we can test Richard and his wife and daughters for the mutation and discuss options with them like implantable cardiac defibrillators to keep them safe.”

Is this the end of Richard Quake’s quest? Or the beginning of another saga in which his remaining family members struggle with the same set of uncertainties as they come face to face with their own genomes? Without question, it’s bittersweet.

“My wife and I are just shells of the people we were before Richie died,” Quake says. “If we can save one other life or help one other family, it’s certainly worth it. But, in truth, it feels like a consolation prize.”

Regardless, it may not be a prize that will be available to anyone else any time soon. “I think there’s going to be a lot of push back from the clinical community about incorporating genomics into the clinical system,” says bioethicist Cho. “Physicians are so overwhelmed already that there will have to be very high standards to show that it’s worth it. Think of it: A new drug has to be better, cheaper and easier to use than the standard of care. Otherwise the pressure in the clinical setting will be not to use it.”

“We’re not going to really know what it means for a while,” adds McEwen. “Our basic biological tendency is to rush to find a variant associated with disease, to rush to develop a test and to rush to put it into the clinic. But there needs to be a recognition that this is basic research and it will take some time. We need to have optimism, but still be patient.”

Like Icarus flying too close to the sun, are we expecting more of this technology than it can deliver at this point? Just because we *can* get the information doesn’t mean that we should. Are we doing more harm than good by pursuing this information now? Maybe yes, maybe no. It’s likely a question that can only fully be answered in retrospect. But Richard Quake, at least, is grateful for the information gleaned from such studies. And maybe one day personalized medicine can help others like Richie.

“We take for granted that we are living, breathing beings when really, in fact, life is so incredibly fragile,” says Quake. “All because one little letter in a sequence of billions is off. My son…I kissed him goodnight the night before when he gave me a shirt for my birthday. My wife talked to him that morning; she went in to wake him and he said he was a little chilly. He said he was going to stay in bed for a little bit to warm up. She said, ‘OK, I love you,’ and she kissed him goodbye.”

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Reading between the genes

Further investigation using tiling arrays revealed that numerous lincRNAs were being produced in or near these hot spots (not, mind you, from the protein-coding genes themselves) in relative amounts that corresponded to which part of the body the fibroblasts were from. Not only that, but some of these lincRNA molecules seemed to be doing something that shut down banks of genes within the various clusters. One lincRNA in particular was present in detectable amounts only in fibroblasts from the body’s lower half, particularly at extremities such as foot or foreskin. Lower-body fibroblasts in which Chang and Rinn experimentally blocked this lincRNA’s activity started acting like fibroblasts from the body’s upper half, and their “address code” genes took on an “upper-body fibroblast” expression pattern.

The duo dubbed the newly identified lincRNA “HOTAIR,” in an act of humility befitting the smirks they expected to see on their peers’ faces once they went public with this finding. But the smirks, if ever there were any, have faded.

Chang has subsequently implicated HOTAIR in cancer. Biopsied breast-tumor samples in which high levels of HOTAIR are detected are more likely to metastasize, making HOTAIR a potential clinical marker of cancer’s aggressiveness — and possibly a target for drug therapy, as forcing up HOTAIR levels in breast-tumor cells increases the chances of metastasis. A group at Massachusetts General Hospital has independently found inordinate HOTAIR levels in a particular subtype of kidney cancer. This August, Rinn published a study in Cell showing the centrality of another lincRNA to one of the body’s critical, natural anti-tumor defense pathways.

How they work

PROBING HOTAIR’S MODUS OPERANDI, CHANG, RINN AND THEIR COLLEAGUES SHOWED in a 2007 Cell study that HOTAIR binds to Polycomb, the massive gene-suppressor complex. This year, in experiments published in Science, Chang demonstrated that HOTAIR can simultaneously bind to not only Polycomb but also other big gene-regulating protein complexes. It seems that HOTAIR chauffeurs the entire entourage to as many as 800 different genetic locations it thinks they should see. The visited genes are then silenced, presumably due to the bound regulatory complexes’ combined efforts.

In 2008 Rinn, now in his own lab as an assistant professor at Harvard Medical School, got a rough count of all the places in the genome from which long RNA molecules, coding or not, are being produced. After discounting for the ones associated with protein-coding genes, the team found at least 1,500 different lincRNA-production sites. A similar study the next year boosted that estimate to over 3,300, and Rinn says he thinks there may be far more. And, he adds, there’s no reason to assume this army of lincRNA molecules will prove to be any less diverse regarding what they do in living cells than the proteins specified by their cousins, the messenger RNAs.

These RNA chains are not the first molecules found to control genes. For more than four decades researchers have known about proteins called transcription factors that perch on certain stretches of DNA, causing quiet genes to go active, or active genes to become more so or less so. About 1,500 of the 25,000 genes in the human genome encode transcription factors, according to Snyder, who is cataloging them.

In fact, lincRNA isn’t even the first type of RNA to be implicated in the control of gene expression. One recent example is a class of very short RNA strands, called microRNA, that can temporarily shut down or reduce targeted proteins’ production. This finding won a Nobel prize in 2006 for Andrew Fire, PhD, professor of pathology and of genetics at Stanford, and Craig Mello, PhD, professor of molecular medicine at the University of Massachusetts.

HOTAIR exerts long-lasting effects that can lock in a cell’s gene-activity patterns for a lifetime. But maybe other lincRNAs with less-long-lasting effects are generated in reaction to fluctuating conditions in the microenvironment of a cell — such as its nutrition status, the arrival of hormones from the bloodstream, stress signals from adjacent cells, infection or other short-term cues.

Because lincRNAs require one less time-consuming production step than proteins do, they could be ideal for quickly and broadly shifting a cell’s behavior in reaction to variations in its microenvironment. In that case, testing tissues’ levels of various lincRNAs may someday tell clinicians a good deal about the state of a patient’s health and recent physiological history. Many disease-associated genetic variations areturning out to be, in fact, in spots where lincRNAs are made. Sensing lincRNAs’ commercial potential, companies are holding private discussions with both Chang and Rinn.

Nor is it just cancer that is showing links to lincRNA. “In collaboration with many colleagues at Stanford and elsewhere, we have started to discover lincRNAs that are associated with many different diseases,” Chang says. “We’re creating animal models to address whether altering lincRNA function can provide therapeutic benefits. And we’ve started to search for drugs that can do that.”

There’s a message here for medical research and development. Yes, genes rule. But not in a vacuum. SM

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**LETTERS TO THE EDITORS**

**In favor of physicals**

I was absolutely delighted to read Ruthann Richter’s article “The Healing Hand” in the summer edition of Stanford Medicine. It addressed an issue that has concerned me, a retired physician, for several years now: the apparent reluctance of young physicians to do a thorough physical examination. As medical students, my classmates and I were thoroughly trained in the art of the physical examination at the old school at Clay and Webster Streets in San Francisco, and I have always been convinced of its importance.

I have a personal anecdote relating to this current lack of utilization of a physical examination. Not long ago, my adult daughter informed me that she had visited a new internist in the city where she lives. That physician did not touch her body in any way, not even with a stethoscope, but rather ordered a huge battery of laboratory tests in lieu of any physical examination. Needless to say, I advised my daughter to seek the care of a “real” physician!

So I say three cheers to you for your article, with the hope that the renewed emphasis on the physical examination will continue to grow. There is no substitute for the physical examination.

KENNETH DUNN, MD
Stanford medical school class of 1958

Of course the people who own clinical labs and sell CT and MRI scanners are delighted to radiate me instead of examine me. Medicine has gone expensive backward in 50 years.

THOMAS LOWRY, MD
Stanford medical school class of 1957

I very much enjoyed your article “The Healing Hand.” As a practicing diagnostic radiologist, I have seen firsthand the explosion of imaging and understand the concern that the physical examination is being partially supplanted by CT and other diagnostic tools.

However, I’m surprised your article cited the CT examination for abdominal pain/appendicitis as being in the category. No doubt there are plenty of negative and possibly unnecessary CT scans being ordered. However, the increased use of CT scan for suspected appendicitis has resulted in a marked reduction in the negative appendectomy rate (the percentage of time a normal appendix is found at surgery when the physical exam was positive — i.e., the false positive rate has plummeted). That means fewer people are getting unnecessary surgeries, fewer surgical and anesthesia complications, etc.

Before radiology gets too much of a black eye, let’s remember that a lot of good has come from imaging. From time to time, we even hit a home run, as above. I’m sure the middle ground is best — using physical examination to better triage patients for the judicious use of imaging.

HIRESH PATEL, MD
Stanford medical school class of 1997

Letters are edited for clarity and length

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About 2 million people in the United States each year are prescribed warfarin, a blood-thinning drug, to prevent clotting after having a stroke or a heart attack. But to be used safely, the drug dose has to be precisely calibrated: Too much can cause life-threatening bleeding. The standard dosing approach for the drug (commonly marketed as Coumadin) has been to start low and inch up, with frequent blood tests to determine when the proper concentration is reached, a process that takes weeks to months. • Recent advances in genetic testing, however, have made it possible to quickly and (relatively) inexpensively test each patient’s DNA to determine an optimal starting dose, resulting in an adjustment period that’s less lengthy and less hazardous. In January, the Food and Drug Administration added gene-based dosing information to the label, and in March, Medco Health Solutions Inc. — one of the largest managers of drug benefits in this country — began encouraging doctors and patients to use the genetic test, which costs about $200.

It sounds like a no-brainer. Why wouldn’t doctors use the test to keep their patients safer? Turns out, there are a lot of reasons.

“Physicians have not been trained to use genetics when making drug-prescribing decisions,” says Russ Altman, MD, PhD, professor of bioengineering, genetics and medicine at Stanford’s School of Medicine, “so this is a big change in their work flow. We need to educate them and build a health information infrastructure to fully deliver the promise of modern genomic medicine.” Less than 1 percent of physicians who prescribe warfarin use the test to determine their patients’ starting doses, Altman estimates.

Altman and senior researcher Teri Klein, PhD, led a group of collaborators in a 2009 study that correlated variations in two genes with a patient’s optimum warfarin dose. Together they designed a computerized algorithm to predict an appropriate starting dose based on genetic, demographic and clinical information about each patient.

But education and infrastructure aren’t the only issues for physicians: They’re just not all that convinced it’s necessary. “It’s all about cost, efficiency and value,” says Edward Abrahams, PhD, president of the nonprofit education and advocacy-focused Personalized Medicine Coalition. “Until those questions are answered, it’s difficult to institute change in medicine, which is a notoriously conservative field.” It’s not just individual physicians who need convincing. In 2009, the Centers for Medicare and Medicaid Services decided not to cover the genetic test. That is, unless the patients were enrolled in a prospective, randomized clinical trial to determine the effectiveness of such an approach.

Clinical trials are under way, with preliminary results expected at the end of this year. If they show that patients are less likely to be hospitalized or suffer complications, the tide might begin to shift, with some caveats.

“There are two groups of people,” says Caroline Berube, MD, medical director of Stanford’s Oral Anticoagulation Clinic. “Some really believe in and are pushing for the test. Others argue that even though dosing is more predictable with the test, more than half the variation in dose response among patients remains unexplained by genetics. But if the trials show clinical benefit, if the cost of the test comes down and if we can order and have access to the results within 24 hours, I think physicians will start to use it.” — KRISTA CONGER
Sure, dogs are special. You might not be aware, however, that knowledge of their genomes can lead to advances in human health. So next time you gaze soulfully into a dog's eyes, take note of the length of its nose or the size of its body. Although such attributes can vary wildly among different breeds — in fact, the dog is the most physically variable land animal — a team of investigators has discovered that just a few genetic regions determine dogs' shapes.

In humans, such traits as body weight and height are usually influenced by the net impact of hundreds if not thousands of different genes, says co-senior author Carlos Bustamante, PhD, professor of genetics at Stanford and recipient of a 2010 MacArthur "genius grant" fellowship. Some of those genes play a bigger role than others, yet no one knows which. But now that Bustamante and his co-authors have identified the relatively few chromosome regions that control dogs' basic physical attributes, they can look for the genetic counterparts in humans — the genes likely to be key for determining our health and physiques.

The research, published in the Aug. 10 Public Library of Science-Biology, is a product of the CanMap project, a collaborative effort at several institutions to gather genetic information from dogs for research.

The new findings result from the most comprehensive genetic analysis of dogs to date, based on the genotypes of more than 900 individual dogs. The researchers used 57 traits that visually differentiate one breed from another, including body size, snout length and ear type (upright versus floppy). Then they identified what regions of the dog genome contributed to each of these different characteristics — and found that just a few did most of the job. Take height and weight:

"We've found that only six or seven locations in the dog genome are necessary to explain about 80 percent of the differences in height and weight among dog breeds," says Bustamante. His collaborators were at the National Human Genome Research Institute, Cornell University, the University of California-Los Angeles and Stanford.

In the future, the researchers plan to investigate whether dog behavioral traits can be linked to specific genomic regions and, if so, how these genes affect our own behavior. — KRISTA CONGER