Waiting for the Revolution

Having the complete human DNA sequence hasn’t yet produced big advances in primary medicine, prompting some to ask what’s delaying the genomic revolution in health care

IN 2009, THE SCHOOL OF MEDICINE AT Johns Hopkins University turned itself inside out for the human genome. Although ranking consistently among the top medical schools in the United States, it scrapped the existing curriculum and installed a shiny new “Genes to Society” agenda over the summer. A committee slotted genetics into every nook and cranny of the school’s 4-year program. Edward Miller, dean and CEO of Johns Hopkins Medicine, who backed the change, said at the time, “It’s the biggest thing to happen in 100 years.”

Among the faculty members, geneticist David Valle took the lead in championing the overhaul. Valle says the impetus came from his late colleague Barton Childs, a geneticist who argued in his writings that doctors have been trained in an overly rigid concept of disease. Students are “taught everything … in terms of the average patient and the classic case,” Valle explains. But there are no such patients. Every case is unique because each person’s genome is unique, Valle says. With its new education strategy, Johns Hopkins set out to show students that they should treat each patient as an individual.

To do this, the school redid its course plan. Breaking with tradition, it added clinical encounters to the first 2 years—normally a time for book-learning—and inserted basic science into the third and fourth years, when doctors in training generally leave such lectures behind for clinical rounds. Johns Hopkins further added a series of short seminars over the 4 years to meld genetics and medicine in focused studies. With $20 million in gifts so far, Johns Hopkins has created a $2 million simulation center and a $52 million new curriculum building—complete with an anatomy lab where every dissecting table has an Internet connection.

This departure is a gamble, but Johns Hopkins isn’t taking it alone. Other medical schools and research centers are investing tens of millions of dollars each to join the genomic medicine bandwagon. Yet despite the excitement, some say this is a huge leap into uncharted clinical territory.

As doctors and scientists look back over the decade since the human genome was published, some are asking tough questions. Is the translation of DNA research into medical practice taking longer than expected? Has the genomic medicine revolution faltered? Such questions can elicit a sharp response from leaders in clinical genomics. Eric Topol, a pioneering researcher on DNA-related treatments in cardiovascular disease and cancer at the Scripps Translational Science Institute in San Diego, California, says the medical establishment is slow to change because it’s “sclerotic.” In his view, studies that find insufficient evidence of benefit are often used as an “excuse” for not learning about new science.

Still, Topol and many others in the field agree that proof of clinical usefulness is in short supply. “We need to … demand evidence and not get caught up in a naïve view that just because something sounds good, it’s going to be good,” says James Evans, a medical geneticist at the University of North Carolina, Chapel Hill.

Can you prove it?

No one is more aware of the gap between today’s health care and the promised future of genomic medicine than Greg Feero, an M.D.-Ph.D. who lives in both worlds. Feero studied neuromuscular diseases but now practices as a family doctor in Fairfield, Maine. From 2007 to 2009, he worked at the National Human Genome Research Institute (NHGRI) in Bethesda, Maryland. The
agency employed him (and now retains him from afar) as an adviser. More than ever, he says, he is aware of the “stresses” piling up on primary care. In fact, you could say he is adding to them.

Feero’s job at NHGRI is to integrate genomics into medicine. Specifically, he aims to nudge primary care doctors, along with nurses and physician’s assistants, to join the revolution, building up networks of like-minded medical leaders. They push credential-granting bodies to test for and certify “competencies,” or practical knowledge, of genetics. The approach has bite, because candidates learn whatever is required for board certification.

Organizations that represent nurses and physician’s assistants are quickly embracing genetic competency testing, Feero says. Specialist groups in cancer and cardiovascular disease have been “ramping up” training, too. But primary care physicians “have been very difficult to engage.” One reason, Feero says, is that doctors already have too many obligations. They are trying to adopt digital record-keeping methods, follow more stringent rules in training, and adhere to new working-hour rules for residents. Their “plate is more full than when I left [Maine]” half a decade ago, he says. That often leaves physicians with little time for taking detailed family histories or learning about other genetic tools (see sidebar, p. 528).

Competition for time is an important issue. But the bigger one, many doctors say, is the scarcity of data showing that gene-based methods actually protect or improve patients’ health. “Practitioners are looking for evidence of impact before they make [genomic medicine] a priority,” says Gary Rosenthal, president of the Society of General Internal Medicine and a professor at the University of Iowa Carver College of Medicine in Iowa City. Like many, he argues that doctors will move fast if they see clear benefits—but they don’t see them now and don’t want to jump the gun.

Evans, who is also editor of *Genetics in Medicine*, agrees. “We need to quit trying to push genetics into medicine,” he says. “We hear these grandiose statements that genomic technology is going to revolutionize medicine.” That may be true, but the revolution is going to take “decades,” he thinks. Like Rosenthal, he believes doctors will embrace technologies as they prove valid.

But relatively few genomic approaches have been reviewed for clinical utility. For example, in 2 decades, the government-funded U.S. Preventive Services Task Force (USPSTF) has looked at just two topics in genetics. It approved one: In 2005, it recommended that women whose families have a high risk for *BRCA* cancer gene mutations be evaluated for genetic testing. Genetics “was not very much on [USPSTF’s] radar screen,” says Muin Khoury, director of the Office of Public Health Genomics at the Centers for Disease Control and Prevention (CDC) in Atlanta.

That’s why Khoury, a geneticist, pushed CDC to help evaluate DNA-based technologies for public health. In 2005, CDC created an independent working group called Evaluation of Genomic Applications in Practice and Prevention (EGAPP). Khoury says he hoped its seal of approval would speed new ideas into clinical use.

EGAPP has done six comprehensive reviews in 6 years. Four more are planned this year, says Khoury, adding that the group is trying to become “faster and nimbler” to take on a growing caseload. “In the last 6 to 9 months, we have identified more than 200 new applications, mostly new genomic tests, and mostly in cancer,” says Khoury. But rumors are circulating in the genomics community that CDC may cut funding for this office. Khoury has no comment.

All but one of EGAPP’s reviews have been unfavorable or neutral, generally because the panel didn’t see evidence of a health benefit. For example, in January an EGAPP group recommended against routine testing for factor V Leiden and prothrombin gene variants in people with a history of deep-vein blood clots. Both genes influence such clotting. People who have had such clots should be treated with anticoagulants anyway, regardless of genetic status, the panel concluded. And in a second group—relatives of people who have had clots but who themselves have not—the panel judged that it would be too risky to treat preemptively with anticoagulants (which can cause hemorrhaging) based on genetic status alone.

The exception to EGAPP’s general pattern was a decision in 2009 in favor of a test for mutations linked to an inherited type of colorectal cancer, called Lynch syndrome. The evidence, EGAPP concluded, justifies testing colon tumors of newly diagnosed patients—not to help the patient but to alert relatives of those who test positive that they have a 50% risk of being affected.

Although its EGAPP’s blessing, the Lynch syndrome test has complexities that may put off some clinicians. It looks “simple and straightforward,” says Douglas Campos-Outcalt, a leader in family medicine and associate head of the University of Arizona Cancer Center in Phoenix. But it isn’t. “What if the patient doesn’t want their test results spread around?” Campos-Outcalt asks. And what do you tell the relatives about their own risk? “Basically,” he says, the message is, “refer them to a genetic counselor.”

There’s another practical question: Who should pay? There’s no evidence so far that this test can be used to guide the treatment of the person with the tumor. So doctors must
be creative about billing. At Intermountain Healthcare in Salt Lake City, clinical geneticist Marc Williams has persuaded hospitals in the system that they should pay because the test “returns money to the health plan” in the long run. It “appropriately” enables the system to recruit other individuals who would subsequently pay for their own testing. And it identifies a certain number of people who may be able to avoid cancer, and the accompanying health care costs, by having a polyp removed.

Some genetic tests make sense primarily in a public health context, Khoury says. This is one of them. He speaks of using the Lynch syndrome assay for “cascade testing” of affected families. By screening 150,000 individuals, one can find 4000 to 5000 high-risk individuals.

Making medicine precise
In contrast to those who focus on missing evidence, Topol sees genomic medicine’s glass as half-full—and filling fast. He rattles off a series of recent DNA-based technologies that appear to have important uses in medicine already. Tumor analysis heads his list; Topol points out that major clinical centers—including the Massachusetts General Hospital in Boston, MD Anderson Cancer Center in Houston, and the U.K. National Health Service—are now sequencing DNA from patients’ tumors with an aim to improving therapy. The data are used in research, but Topol expects DNA-guided clinical approaches to emerge soon.

Human Genetics in the Clinic, One Click Away
The number of genes identified as factors in human disease has exploded in the past decade. Although the exact influence of many remains elusive, the potential impact on medicine is huge, as suggested by a global tally on a public Web site called GeneTests (www.genetests.org). It now lists 2267 available genetic tests. The volume and the tentative nature of the information are a problem for medicine, however. “The fact is, it is not possible for most primary care doctors to be highly knowledgeable about all aspects of medical conditions,” wrote Gary Rosenthal, president of the Society of General Internal Medicine and a University of Iowa professor of medicine, in comments last year to a U.S. Health and Human Services panel on genetic education. He told the group that it seemed “unjustified” to ask doctors to keep up with everything in genetics. They don’t have time.

Finding a way to give medical practitioners the right genetic information, but not too much, at the point of care is one of the biggest challenges in the field, says Bruce Korf, chair of human genetics at the University of Alabama, Birmingham. Indeed, Korf ranks this issue as second only to the main one: developing evidence that genomic medicine can make patients healthier (see main text, p. 526).

Computer technology may come to the rescue. At Intermountain Healthcare network in Salt Lake City, geneticist Marc Williams (right) is using digital tools to slip up-to-date education into the daily run of medicine in ways that doctors may find helpful. One trick is to insert “info buttons” into Intermountain’s data files. This health care network uses electronic records throughout the system to track patients’ progress. As doctors fill in the forms, they see an
One indication that genetic testing has value is that business clients are willing to pay for it, says epidemiologist Robert Epstein, president of the Medco Research Institute of Franklin Lakes, New Jersey. Several years ago, his company began to look for customers who would pay for expert advice on the utility of gene tests, particularly those used in prescribing drugs. Since 2008, he says, the company has signed up 300 health plans, insurers, and unions, representing 65 million individuals. In that time, Medco has reviewed “hundreds” of genetic tests and approved 12 as valid and worth paying for—a judgment that is both about clinical efficacy and economics.

Epstein is “bullish” on pharmacogenomic tests. “They give more precision to medicine,” he says, and who could not want that? In his view, EGAPP has been unduly conservative in its approach to vetting new technologies, and he thinks its high rejection rate in the past may not be a good indicator of the quality of products now in the pipeline. His company is now running half a dozen major pharmacogenomic trials.

Speaking last October in Washington, D.C., FDA Commissioner Margaret Hamburg noted that despite $2.7 billion spent to decode the human genome and a decade of analysis, “fewer than 50 therapies actually have genetic tests as part of their labeling” to guide users. Still, FDA expects to see a surge of new gene tests and gene-targeted therapies this decade, and Hamburg is concerned that the agency may not have the data or the scientists it will need to do the necessary evaluations. She made a pitch in her October talk for funds to do more “regulatory science.” And to help keep up with the pace of discovery, FDA and the National Institutes of Health last year agreed to work together to identify, monitor, and evaluate new therapies as they emerge from research labs.

If Johns Hopkins’s gamble is right, it’s not only FDA that will need to adapt. Medical geneticist Bruce Korf of the University of Alabama, Birmingham, has been involved in national efforts to reshape medical school curricula, and he argues that although there’s little published evidence of health benefits from genom-ics, clinical institutions across the board will need to keep up or risk finding themselves “behind the eight ball.” Changes are coming, perhaps slowly at first, but the effect over time will be “pervasive” and “transformational,” he maintains.

The genomic revolution is sometimes described as a tidal wave that’s racing toward the shore, says Feero. He thinks that’s the wrong metaphor. New ideas are flooding in, he says, but they are filtering through the health care system in spurts, as they always have. Most people will perceive the change not as tsunami but as a “slowly rising tide.”

—ELIOT MARSHALL

"i" surrounded by a small blue circle pop up at certain points, explains Williams, director of the Intermountain Healthcare Clinical Genetics Institute in Salt Lake City. These clickable spots offer help when doctors are describing a patient’s complaint, ordering a lab test, or prescribing drugs.

If one entered “Marfan syndrome” as a patient problem, for example, a blue info button would appear with a list of links offering a genetic reference service, gene reviews, or perhaps more readable articles from Internet resources. “You get the content much, much more quickly than going to Google,” he says.

Info buttons of the future may gently direct the course of treatment. For example, cardiac patients can get into serious trouble if, because of the genes they’ve inherited, they metabolize the anticoagulant Plavix (clopidogrel) too slowly. An info button might therefore note a genetic test to evaluate how fast a person metabolizes the drug. But Williams says that Intermountain’s cardiology department has decided that the genetic test isn’t as useful as a platelet reactivity test, which gives a more direct indication of clotting risk. So the info button could say, “Maybe you shouldn’t order the genetic test,” or “Maybe you should consider a different test.”

Intermountain aims to use digital methods to crack another knotty problem in primary care: the failure to gather useful family medical histories. Asking patients about their relatives is a quick way to get into genetic risks. But doctors typically don’t do this thoroughly, many studies have concluded, mainly because they don’t have time. Intermountain is trying a new tack. A few months ago, it added a program to its Web site, Williams says, in which patients are invited to build their own family medical history. It’s too early to say whether the strategy is working, but the idea is that the patient gathers the raw information, the computer analyzes it, and the doctor and patient together discuss the results. It should help identify high-risk cases of genetic diseases.

Intermountain is one of several networks in the United States that are beginning to integrate genetic data into primary health care. A wave of innovation in point-of-service education is likely to spread over the wider health community in time, but this may be limited by the sluggish rate of change in electronic health record-keeping. At the moment, Williams says, not one of the commercial programs he’s seen is capable of converting results from genetic tests into data files. This means that automated tools like those at Intermountain designed to scour medical records and give summary reports to physicians can’t incorporate genetic data. Williams is waiting for two revolutions: one in medicine and another in records management.

—E.M.