

DANIEL S. LEVINE

# Lost in Translation

Eric Topol doesn't just want to understand the genes that drive illness and wellness, he wants to make sure that such knowledge actually changes the way doctors practice medicine.

By Daniel S. Levine

Shortly after arriving in La Jolla, California nearly three years ago, Eric Topol found himself addressing a room full of San Diego's business leaders at the exclusive University Club with its grand views of the city below. The former top cardiologist at Cleveland Clinic had just recently come to town to become director of the Translational Science Institute at the Scripps Research Institute, the world's largest independent non-profit biomedical research facility. Topol, who was speaking about the future of medicine, told the crowd at the end of his talk in March 2007, "You folks are known for wireless and you are known for tourism. But in the future you are going to be known for the future of medicine, for genomics, and individualized medicine."

If Topol succeeds in his efforts to lead broad genomics studies at Scripps—that talk won't be the last time that San Diego's business elite hear about individualized medicine. The term refers to whole medical approach that incorporates the knowledge of a particular individual's genetics to deliver appropriate care. "It's about being able to understand what makes a person either susceptible, or protected, or responsive, or unresponsive to various treatments, devices, drugs, or whatever," says Topol, who at 55 has the fit appearance you'd expect in a cardiologist (at least one you'd trust). Topol, however, bristles at the mention of "personalized medicine," the more commonly used term for this new field, saying it confuses patients. "It sounds like a concierge, the person who takes you around

the hospital and makes sure you have coffee and know where the restrooms are," he says. Individualized medicine is "not about treating someone as a VIP."

It wasn't surprising that weeks after landing in San Diego, Topol would declare that the city's future lies in individualized medicine. After all, he was leading an effort in translating an understanding of human genetics into better medicine. But it was not an idle boast. Since he first settled in at the Scripps Institute in January 2007, Topol has been doing everything in his power to make it so. As a high-profile researcher and clinician, his goal is not just to find genes that can make medicine more predictive, preventive, and individualized. He wants also to make sure these findings get tested in the clinic and put into practice.

The future of medicine is going to be integrating genomic science into the clinical treatment of individuals and there are not very many physicians who are equipped today to perform that or to bring genomics into the clinic. In that sense, Eric is already a global leader.

—David Gollaher, President and CEO, California Healthcare Institute

"The future of medicine is going to be integrating genomic science into the clinical treatment of individuals

and there are not very many physicians who are equipped today to perform that or to bring genomics into the clinic," says David Gollaher, president and CEO of the California Healthcare Institute, a La Jolla, California-based biopharmaceutical industry advocacy group. "In that sense, Eric is already a global leader. There's no question about it. That's the mission he's taken up. He's the prophet of genomics and genomic science."

Eric Topol, director of the Scripps Translational Science Institute, is branching out beyond genomics to include wireless healthcare technology in his work in the hopes of translating findings about genes into improved care for patients





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This is something that's very near and dear to him. Can we leverage genetics and genomics? That's one question—can we design drugs or trials that target people with certain genetic profiles. The other one is to maybe leverage wireless technologies.

—Nicholas Schork, Director of Research, Scripps Genomic Medicine Program

Gollaher notes there is always a big lag between basic scientific discoveries and their application in the clinic. He points to the 19th-century discoveries of Robert Koch and Louis Pasteur and the germ theory of disease, which took more than a generation to be incorporated into clinical medicine in the form of antiseptics. “There will be a lag,” he says, “and it will be people like Eric who compress that and make it available earlier rather than later.”

Though Topol's office sits along the fabled Torrey Pines Golf Course, he says he doesn't get to play often enough to be any good. It's no wonder. Since arriving in La Jolla, he's been quite busy. Among the accomplishments he can already check off on his list: He's brought together basic science researchers and clinicians from the disparate arms of Scripps to launch the Scripps Translational Science Institute. He led the institute's successful effort to land a \$20-million grant from the National Institutes of Health under its Clinical and Translational Science Awards program—the only non-university to date to win such an award. He's also attracted \$45 million in funding from the Gary and Mary

West Foundation to launch the West Wireless Health Institute. The organization is set to conduct clinical research on the use of wireless sensors to prevent, monitor, and manage disease in patients. And, he's mapped out plans for a medical school at Scripps with a focus on translational medicine. But that project for now is stalled over resolving the issue of a \$100-million naming grant.

Were all that not enough, he's been earning style points, too. In 2008, he was one of 10 medical researchers named a “Rock Star of Science.” The distinction resulted in Topol being featured in a *GQ* magazine photo spread wearing designer garb alongside Sheryl Crow, Seal, Will.i.am, Joe Perry, and Josh Groban. It was part of a campaign by designer Geoffrey Beene called “Geoffrey Beene Gives Back” to call attention to the contributions of medical researchers and the need to accelerate the translation of discoveries into cures. “I never have enough to do,” says Topol. “I require a lot of stimulation or I get bored.”

Boredom shouldn't be a problem for Topol at the Scripps Translational Science Institute.

Topol examines a map of the United States that tracks patients in the Welldearly Study. His daughter Sarah Topol (right), a registered nurse, heads up recruitment of participants for the groundbreaking look at the genes of healthy people older than 80 who have never suffered from chronic diseases.

Already, the genomics projects are stacking up. Among the most compelling is the “Welllderly Study,” an examination of the DNA of people 80 and older who have had no history of chronic disease. The goal is to unlock the genetic secrets to longevity. Topol says to date, medical research has largely centered on finding genetic markers for disease. This focus on sickness has neglected the genetics of health.

Already, 750 people have enrolled in the study. Though the results are preliminary, the findings so far are surprising. The welllderly appear to have the same bad genes—those that have been linked to such illnesses as Alzheimer’s, heart disease, and cancer—as everyone else. However, there is an early indication that they may also have modifier genes that are unique to them. These genes appear to mediate the expression of the disease-linked genes.

Another major study underway is an effort to find out the behavioral impact of personal genetic testing on people who want to learn their potential risk for developing certain diseases. About 5,000 participants have enrolled in the Scripps Genomic Health Initiative as it’s called. The study is a joint effort between Scripps, software giant Microsoft, consumer genetics company Navigenics, and genetic analysis tools maker Affymetrix. The study will follow participants for as many as 20 years to see what the near-term and long-term changes they make in their behavior, lifestyle, and the medical care they seek.

Though just begun, the study is already having an effect, Topol says. One participant, a relative of Topol’s who had resisted getting a colonoscopy, decided to have the diagnostic procedure after she learned she had a three-times greater than normal risk for developing colon cancer. In another instance, one colleague learned he had a six-fold elevated risk for psoriasis, a chronic condition characterized by red, scaly patches of skin. In fact, the testing helped him discover he had already been walking around with the condition on his leg for 10 years.

Other studies at the institute examine genetics to better tailor drug therapies to patients. One such study involves using a simple saliva genotyping on patients before prescribing the blood-thinner Plavix. The drug is commonly used to prevent heart attack and stroke in patients at risk for developing blood clots. Plavix relies on the metabolic action of the body to convert the drug into its active form, but patients with a common genetic variant are unable to do so. In fact, 50 percent of Asians and 40 percent of

African Americans cannot properly metabolize the drug. The study is being run in conjunction with all of the Scripps medical facilities, giving researchers access to data from a broad patient cross-section. “They’re taking a drug for \$4 a day for the rest of their lives or whatever, and it doesn’t work,” says Topol, who notes there are other therapies available for such patients. “It’s an exciting project because using this test could become the norm some day.”

Topol’s interest in genetics started long before his medical career. Born in Queens, New York and raised in the Long Island suburb of Ocean-side, Topol was bored with high school, having skipped two grades. At just 15, he entered the University of Virginia in Charlottesville. As a college student in 1975 he wrote his thesis on “The Prospects for Genetic Therapy in Man.”

He supported himself in college by working the night shift at the UVA hospital. He had planned to become a biomedical engineer, but that changed when he saw patients in the intensive care unit. Patients who looked as if they were going to die eventually transformed and became well again. “I said, ‘This medical stuff is pretty impressive,’” he recalls. “Of course I was seeing the rare bird—the person that was actually helped—because most people in the intensive care unit don’t necessarily do so well. But it colored my thinking about how medicine could take people who were critically ill and get them in a much better state.”

Topol went on to study medicine at the University of Rochester. There, in his third year, he met his wife Susan, a nurse at the time. His housemates told him to invite some nurses to a party they were throwing. He was in the midst of an obstetrics rotation. He wanted to invite Susan, but he didn’t know how to overcome his shyness. His solution was to invite all of the nurses in the department, most of whom were over 50. The ruse worked. Within two weeks, he and Susan were engaged. After 31 years, they’re still married and have two grown children.

Growing up, Topol had a close view of the toll of chronic disease. His father had developed type 1 diabetes as a teenager and suffered many of the ill-effects from it later in life, including losing his sight. Though Topol thought he might eventually focus on endocrinology, he became interested in cardiology while doing an externship. He started in the intensive care unit at the University of California, San Francisco in 1979. There, he became influenced by the cardiologist Kanu Chatterjee, whom he calls one of his mentors. It was an unusual time in cardiology as

there were new breakthroughs in the treatment of heart patients. Among them was the injection of streptokinase into the coronary arteries of heart attack patients to dissolve clots. There was also the use of new technologies, such as balloon angioplasty.

“That timing, and having a great mentor at UCSF, really captivated me,” says Topol. “It was Chatterjee and that era. It was just so exciting. You could hardly not feel the palpable excitement of the field at that time.”

Shortly before moving on to a fellowship at Johns Hopkins University, he read a study

Genomics only tells about biology. In any given person all I can say is they have a predisposition to atrial fibrillation or sleep disorders, or this or that. With physiology—the elegant phenotyping we’ve never been able to do before—we can have an entire ICU in someone’s home monitoring all of their vital signs. It gives us a different look at a patient. It gives us their continuous physiology.

—Eric Topol, Director,  
Scripps Translational Science Institute

about a new treatment being developed to dissolve clots called tissue plasminogen activator or tPA. The journal article examined the use of tPA to dissolve vein clots in dogs. He discussed tPA with a colleague, who pointed him to a young biotech company with a handful of employees at the time called Genentech. The company was thinking of developing tPA to treat phlebitis, a condition associated with deep vein blood clots. When Topol contacted Genentech, he told them it would be great to try using it to treat heart attack patients. He met with Bob Swift, the director of research at the time, who suggested he join the company to lead the clinical effort on tPA. Topol explained he couldn’t because he was about to begin a fellowship at Johns Hopkins. So Swift suggested Topol be the first to give tPA to heart attack patients.

Once at Hopkins in Baltimore, Topol immediately went to the chief of cardiology and told him about the unique opportunity. The hospital could be the first to put this new clot-busting biotechnology product in patients. “At first

he thought, ‘this guy is freakin’ crazy,’” recalls Topol. “‘What did I do accepting him in our fellowship program?’” But after a few days—and the realization that the study of the treatment could attract grant money—the chief grew interested, he says. Topol began by studying tPA in rabbits with atherosclerotic clots. Eventually, in 1984, he did deliver the first dose to a patient. He remembers the moment in great detail.

“People were cheering and jumping up and down and crying that we had actually opened up the artery,” he says. “It was one of the most striking moments of my life. February 11, 1984 at around 2:30 in the afternoon. It still plays back as one of those monumental moments. It definitely had a big impact on me and my subsequent career.” In retrospect, Topol says the dose was too low to work. But he believes that the process of repeatedly injecting dye into the patient with a catheter for imaging probably broke apart the clot. Nevertheless, the event drew national headlines.

Topol continued working on tPA at the University of Michigan. There, he became a professor and met his goal of being tenured by the age of 35. He spent six and a half years there, eventually serving as both a professor of internal medicine and director of the catheter lab and director of intervention. At Michigan, Topol started a series of major, multi-center clinical trials including the TAMI trial and later the GUSTO trial—both major trials of tPA in heart attack patients. At the time, GUSTO was the largest randomized trial of any kind initiated in the United States with 41,000 patients. A third trial—EPIC—looked at the use of the monoclonal antibody ReoPro to prevent clots in patients undergoing angioplasty.

Topol left Michigan for the Cleveland Clinic in 1991, bringing all three trials with him. While there, he raised Cleveland Clinic’s profile in cardiology, building it into the country’s leading cardiology program from its ranking as fourth.

Despite the clinical successes, by the early 1990s Topol had grown troubled that heart attack therapy had “hit the wall.” Patients, when he looked at data from the late 1980s forward, were still dying at the same rate. Despite improvements in treatment, patients weren’t coming into the hospital any earlier—about two and a half hours on average after suffering a heart attack. And by the time a doctor dissolved a clot, much of the damage was already done. “Even though it did save lives, nothing was really taking it to the next level,” says Topol. “I started thinking there is only one way we are



# Practicing What He Preaches

Though he is conducting cutting-edge research in genomics, translational medicine, and wireless healthcare technology, Eric Topol still practices medicine with an approach that's informed by his interest in prevention and wellness.

With a long list of titles and a full spate of research projects, it's easy to forget that Eric Topol continues to practice cardiology. Among the people who haven't forgotten, of course, are his patients like telemarketing tycoon Gary West. West's doctor-patient relationship was a tad unusual in that it helped give shape to the West Wireless Health Institute, a first of its kind research institute to focus on the use of wireless technologies to improve human health. But at the end of the day, Topol has also been his cardiologist, providing West with an up-close and personal view of Topol the doctor.

The connection began in 2007 when West, the founder and chairman of the West Wireless

Institute, among other responsibilities, is also focused on prevention in his clinical practice. "In the past, I went in, had a stress test and an echo—the normal things cardiologist do every couple of years. They'd say 'you're doing great, have a good day,' and didn't mention I was 30 pounds overweight. I'm like anybody else—that was good news to me," says West. "Eric took a different approach."

Even though Topol is younger than West, West says Topol sat him down in a fatherly manner. He told him that while his test results could be fine, sooner or later his bad habits would catch up to him. One day, his stress test results wouldn't be as good as he would like



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Health Institute, had been looking for a cardiologist. A friend suggested he try Topol. The two hit it off and West invited Topol to lunch. Over the course of the meal, West discovered they shared a mutual interest in wireless medicine and the potential it offered to cut healthcare cost and transform the field. The thinking is that by monitoring patients as they go about their everyday lives with wireless devices, doctors can detect problems early before they become expensive to treat.

West says Topol, who now serves as chief medical officer for the West Wireless Health

them to be, West recalls Topol telling him. "He's the only cardiologist who has had success in getting me to do what I'm doing now," says West. He credits Topol with persuading him to lose weight, adhere to an exercise plan, and change his eating habits including giving up red meat.

"Eric is a big wellness and prevention guy," says West. "He just flat out believes the stuff and he's right about it. That's the same thing we have to carry over into our whole medical system."

—D.S.L

# Eric Topol At-A-Glance

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## Current Appointments

- Director, Scripps Translational Science Institute
- Professor of translational genomics, department of molecular and experimental medicine, The Scripps Research Institute
- Chief Academic Officer, Scripps Health
- Chief Medical Officer The West Wireless Health Institute

## Education

- University of Virginia, BA
- University of Rochester, MD
- University of California, San Francisco Internal Medicine Residency
- Johns Hopkins Fellowship in Cardiology
- University of Michigan, Tenured Professor
- Cleveland Clinic, Provost and Chief Academic Officer
- Founder of the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University

## Awards & Activities

- Elected to Institute of Medicine, National Academy of Sciences, 2004
  - Simon Dack Award, American College of Cardiology
  - Andreas Gruntzig Award, European Society of Cardiology
  - Johns Hopkins Society of Scholars
  - American Association of Physicians
  - American Society of Clinical Investigation
  - American Heart Association Top 10 Advance (2000,2004)
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Topol appeared in a spread in *GQ* (opposite) with the musical performer Seal as one of the Rock Stars of Science, a campaign from Geoffrey Beene Gives Back to win support for accelerating the development of medical research from the bench to the bedside. Information on the campaign can be found at [www.rockstarsofscience.org](http://www.rockstarsofscience.org).

going to get this thing better, and it is by preventing the event in the first place.”

It was then that Topol started the very first cardiovascular gene bank at Cleveland Clinic. To study the genetics of heart attack, he won an \$18-million, five-year NIH grant. The effort began in 1995 and was built out within three years to 10,000 patients. Part of the project included collecting DNA from 400 families in which parents and siblings suffered heart attacks. The study concluded with major findings, including one that linked heart attacks to people that had a rare gene deletion and the other involved the discovery of a genetic variant that puts people at elevated risk for heart attack. The study won recognition from the American Heart Association, which honored the work with a Top 10 Advance award in 2000 and 2004.

It was while at Cleveland Clinic as chairman of the cardiovascular medicine department that

Topol wrote what was to become the most oft-cited paper of his career. Published in the *Journal of the American Medical Association*, the paper was the first to document that use of painkiller Vioxx, a drug being used by 20 million people, carried an elevated risk of heart attack and stroke. “It kind of took over my life in 2004,” he says. “It wasn’t pleasant in 2001 when I published the paper because Merck sent all sorts of people to go after me, whether it was in the press or in other ways. But then in 2004, when they withdrew the drug, it got much uglier. It was the most unpleasant time in my career.”

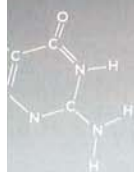
Topol, who remained a vocal critic of Merck, found himself under attack both professionally and personally. Press reports at the time say Merck sent letters to doctors across the country seeking to discredit Topol. He found himself the subject of an article in *Fortune* about conflicts of interest because he served on the medical advisory board of a hedge fund that had shorted Merck’s stock. He and his family received threatening phone calls late at night warning him to stop talking about Vioxx and Merck. Press accounts at the time quoted him as saying that then-Merck CEO Ray Gilmartin took his complaints to Cleveland Clinic chairman of the board of trustees Malachi Mixon, whom he knew personally. Cleveland Clinic never confirmed or denied such conversations took place, but Topol was removed in 2005 as head of the clinic’s medical college. Topol declined to discuss details of what happened at the Cleveland Clinic, saying only that he left voluntarily.

It was not the first time that Topol’s research may have angered the medical establishment. Nicholas Schork, director of research at the Scripps Genomic Medicine Program, recalls Topol ruffling feathers around 1990 when the two met at the University of Michigan. At the time, Schork was a graduate student called upon to help analyze an insurance database. Topol suspected too many bypass procedures were being performed and that surgeons weren’t following guidelines to determine if the procedures were warranted. The study indeed showed that bypass procedures were being done more often than they should be. It looked at regional differences in the use of bypass procedures, differences by type of hospitals, and the dollars involved. Schork says it was a “hot potato.” The study was eventually published, he says, but it took a while because editorial boards were reluctant to run it.

“I thought, here’s a man who wants to push the envelope a little bit,” Schork says. “It wasn’t



09 (L TO R) SEAL, ERIC J. TOPOL, DAVID B. AGUS



eric-j-topol white-satin "cotton-rich" shirt, msrp \$49.50, available at Macy's, Bon-Ton (David B. Agus)  
 "cotton-rich" shirt, msrp \$49.50 available at Macy's, Bon-Ton (All by Geoffrey Beene)



### ERIC J. TOPOL, M.D.

SCRIPPS TRANSLATIONAL SCIENCE INSTITUTION

- Chief Academic Officer/ Chief of Genomics Research
- Pioneer in genomics-based cardiology, critical heart care therapies

### DAVID B. AGUS, M.D.

PROFESSOR, KECK SCHOOL OF MEDICINE, USC

- Director, USC Center Applied Molecular Medicine
- Founder, Oncology.com and co-founder, Navigenics

### SEAL

- Critically acclaimed singer/songwriter and multi-platinum-selling artist, Seal has recently released a chart-topping new album, *Soul*

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like he was doing it for fame. It was more a matter that this is the truth and let's get it out there. I thought that was a great quality to have quite frankly. He was clearly going to piss off his colleagues. I have respect for that."

But, Schork notes, the study also speaks to something else at Topol's core—the desire to put things to the test. Schork says vetting technologies, new drugs, and devices through clinical tests to answer the basic questions like "Does this drug save lives?" has long been Topol's bread and butter. But now, Topol is concerned about how can we make those more efficient so we can get quality drugs out there to save people's lives. "This is something that's very near and dear to him. Can we leverage genetics and genomics? That's one question—can we design drugs or trials that target people with certain genetic profiles," says Schork. "The other one is to maybe leverage wireless technologies. Instead of having people come back every six months to have their blood pressure taken, why not give a little band-aid device that measures blood pressure 24-7. Maybe you don't need 10,000 patients in a study because you'll have so much data."

Marrying wireless technology with genomics is clearly on Topol's radar. Topol, who also serves as the chief medical officer of the newly established West Wireless Health Institute, which is exploring applications of wireless technologies to advance human health, sees an opportunity to tap into the vast network of wireless companies in the region. Initially, he had talks with Don Jones, vice president of health and life sciences for the San Diego wireless giant Qualcomm. The discussions covered what Scripps might be able to do with the technology, but Scripps was constrained by resources. That changed when Topol began treating Gary West, a man who made his fortune in telemarketing. West quickly discovered he and Topol shared a mutual interest in wireless medicine. "He's passionate about changing the way medicine is practiced today," says West. "He thinks it's just wrong."

The belief that the current practice of medicine is dysfunctional is driving The West Wireless Health Institute, which will be housed on the Scripps campus, about 200 yards from Topol's office. Though its home won't be ready for occupancy until October 2009, the institute was spending the summer gearing up for its first clinical trial. The study will seek to reduce heart-failure readmission through the use of technology developed by San Jose, California-based Corventis. Corventis' device, which looks like an oversized band-aid and sticks to the chest, con-

tinuously measures heart rhythm, fluid status, respiratory rate, activity, position, temperature, and heart rate variability.

A recent study found nearly 27 percent of Medicare patients with heart failure, after being discharged from a hospital, are readmitted within 30 days. That revolving door costs the health-care system an estimated \$10 billion annually. The hope is that the device, by providing doctors with an early warning of worsening symptoms, can notify a patient to come in for preemptive treatment before they have another incident. Topol sees similar wireless sensors being developed to do everything from monitoring sleep disorders, to providing people concerned about their weight with real-time reports on their cell phones about their caloric intake and physical activity.

"Genomics only tells about biology," says Topol. "In any given person, all I can say is they have a predisposition to atrial fibrillation or sleep disorders or this or that. With physiology—the elegant phenotyping we've never been able to do before—we can have an entire ICU in someone's home monitoring all of their vital signs. It gives us a different look at a patient. It gives us their continuous physiology."

It is that marriage of genomics and wireless—biology and physiology—that Topol believe sets off Scripps from other research centers. There are plenty of what he calls "gene hunters," centers that do sequencing, identify genes that may be involved in disease, and publish their findings out for others to follow up on. But for Topol, it is the convergence of technologies, the ability to do the translational work, that is so powerful.

"The end strategy is changing medicine, says Topol. "You can't just find a gene and put it out there. That doesn't change medicine at all. You have to actualize that information, like what we're doing with the saliva genotyping with Plavix. You can't just show that the welllderly have these protective genes if you don't go beyond that. That's a nice, fascinating discovery that we hope to have, but you got to drill down to much, much more than that."

Changing medicine is no small goal, but it is a worthy one. And Topol is by no means seeking to do this by himself. He is marshalling the resources not only of Scripps, but also of the surrounding biomedical and technological talent in the greater San Diego area to do so. There will be financial, scientific, and even cultural obstacles along the way, to be sure. But then again, they don't call Topol a rock star for nothing. **TOPOL**