

SPECIAL REPORT

UP CLOSE

AND

With advances in genetics, a new type of medicine has emerged: one that's tailored just for you and your DNA.


Could it transform the paradigm of how we treat and prevent diseases?

PERSONAL

They collaborated at research centers and universities in the United States, the United Kingdom, Germany, France, Japan, and China. It took a little over 10 years—a blink of an eye in scientific time—but in 2003, when they were done, the international consortium of geneticists in the Human Genome Project had mapped and sequenced a human genome, deciphering the unique combination of genes and DNA that makes us distinctively human.

This single effort is widely recognized as revolutionary, and has advanced science in ways as life changing as Edison's invention of the light bulb or Salk's development of the polio vaccine. By largely coding the three billion strands of DNA and identifying the nearly 25,000 genes that guide the development and functioning of all human beings, these geneticists had, in a way, archived the language of life. The Human Genome Project (HGP) showed that in any two people the genetic sequence is more than 99.9 percent identical. But the project did much more than just outline our basic genetic blueprint: It launched the era of personalized medicine, a radical new field that studies the 0.1 percent difference—the tiny, but critical fraction that makes each individual truly unique.

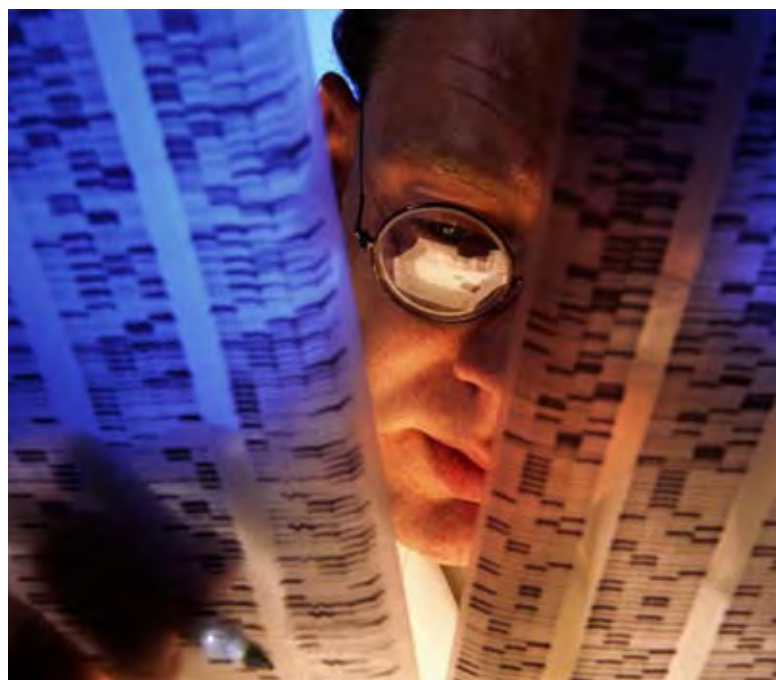
The prospects are simply stunning: Today, scientists have the capability to look for common genetic variations or mutations within specific populations, and design treatments matched exactly for those genetic profiles. Tomorrow, this paradigm may allow doctors to prevent a disease from developing years before symptoms emerge, based solely on the knowledge of a patient's genome. "Five or 10 years from now," says Michael H. Weisman, MD, director of the Division of Rheumatology at Cedars-Sinai, "we could see a patient's complete genetic makeup, their blood test results, their medical background all stored on an information chip, and it might guide what to do to cure them."

 Personalized medicine is not a one-size-fits-all approach to diagnosis and treatment. Instead, it is a comprehensive approach to preventing, diagnosing, treating, and monitoring disease.

Variations in DNA sequence caused by the alteration of a single molecule can have enormous health consequences. These variations are called SNPs (pronounced snips), which stands for single nucleotide polymorphisms. There are an estimated 3.7 million SNPs that can affect how humans develop diseases or respond to certain drugs, bacteria, viruses, vaccines, or therapies. Scientists believe that mapping SNPs the way we have mapped genes will help identify multiple genes associated with complex ailments such as cancer, diabetes, vascular disease, and some forms of mental illness. SNPs do not cause disease, but they can help determine the likelihood

that someone will develop a particular illness, which will allow patients and physicians to customize preventive efforts.

Not only is personalized medicine being applied to the treatment of heart disease, diabetes, and cancer, it is also driving a growing number of research projects in many departments at Cedars-Sinai. Take cardiomyopathy, a serious disease in which the heart muscle becomes enlarged, thick, and rigid, weakening its ability to pump blood through the body. It can lead to heart failure or arrhythmia. Cardiomyopathy can be inherited, but in many cases the cause is unknown. Up to 25 percent of those cases can be linked to identifiable genetic mutations. Genetic counselors can screen for variations in these genes and may recommend early medical therapy and lifestyle changes.



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Individuals who carry another gene variant are twice as likely as the general population to have type 2 diabetes. A genetic test that identifies that SNP in young adults may lead to adopting a preventive treatment approach, such as helping them aggressively manage weight and diet in the hopes that they never develop the disease.

The branch of pharmacology known as pharmacogenomics applies the knowledge of a patient's genome to prevent adverse drug reactions or to maximize a patient's response to a specific medicine. For instance, the HIV drug abacavir can cause anaphylactic shock in patients with an immune system gene variant. Accordingly, the FDA recommends that doctors genetically screen patients before prescribing this drug. Another medication receiving special attention is the common blood thinner warfarin (see story page 32).

If you have ever had a relative who developed deafness after being treated with antibiotics, then you may wish to have your mitochondrial genes analyzed. Those are cellular genes that are only transmitted from mother to child. If you carry a mutation in one of those genes then you may be susceptible to going deaf from a class of antibiotics called aminoglycosides, including the common drug gentamicin.



Much of medical practice we know today draws on studies of large groups. Over the past 50 years, this evidence-based approach has been key in shaping healthcare as we know it. However, results

from large population-based studies are not always applicable to the individual: Physicians can also take into account specific characteristics—such as age, gender, height/weight, diet, and environment—when evaluating a patient and recommending a specific treatment. Personalized medicine represents a true value shift from current medical practice (see OpEd page 37). Advances in computer technologies have spurred the development of personalized medicine by facilitating the study of large data such as proteomics (the large-scale study of protein structure and function) or metabolomics (the analysis of metabolites, the small molecules required in the process of metabolism). Biostatistics, the field that supports such analysis, is being applied to a series of diverse cancer research efforts at the Samuel Oschin Comprehensive Cancer Institute (see insert page 22).

By the spring of 2008, the cost of sequencing an individual genome was \$350,000 (down from the \$1 million it cost in 2007 to map the genome of James D. Watson, MD, co-discoverer of the structure of DNA). Genetic testing is also expensive. Tests range from about \$450 to identify

Pretty Fly for a Primate

What enables you to read this copy of *Discoveries* instead of getting swatted by it? A mere 10 percent difference in genetic code.

The human genome (the entirety of our hereditary information) is 99 percent identical to a chimpanzee's; it is 90 percent identical to that of a housefly.

99%




a single gene mutation known to exist in a family to about \$3,000 for a more comprehensive test to seek a mutation among multiple genes. (Insurance or third-party payers generally cover the costs of these tests.) Testing is therefore reserved for individuals that have a specific risk of mutations based on family and personal history. But the potential cost benefits in preventing expensive surgeries or long-term care are clear.

Prevention is at the core of predictive medicine. Predictive medicine entails forecasting disease based on knowledge of the patient's personal genome and instituting preventive measures years before symptoms emerge. The goal is to prevent the disease altogether or diminish its physical and financial impact significantly. Predictive medicine changes the fundamental paradigm of medicine from being reactive to proactive, and has the potential to decrease the incidence and prevalence of both common and rare diseases.

Ora Karp Gordon, MD, MS, is director of the GenRISK Adult Genetics Program at Cedars-Sinai, where she and her genetic counselors emphasize the identification

of genetic risk factors for disease. "If results of a genetic test can help prevent patients from suffering a hemorrhagic stroke, for example, that is an extraordinary accomplishment," she says.

Of course, there is a flip side: Commercial enterprises market DNA testing directly to consumers, generally at a high premium and often with limitations. "These target the 'worried well': people who want to know if they are at risk for a number of conditions," says Dr. Gordon. "But in my opinion, there is little practical value to these costly genomic-based tests for risk, and a potential for significant harm." The reasons are that it is hard to interpret results in isolation of environmental and lifestyle factors, and there is little, if any, medical oversight. "At Cedars-Sinai, we do not perform any broad-based genomic testing for 80 conditions at once," she says. "Testing is tailored, based on family history and individual concerns."

Whether personalized medicine marks a turning point in healthcare is still unknown, but it carries an enticing promise. "What is important for people to know," says Dr. Gordon, "is that personalized medicine is more than a genetic test to determine if you are at risk for a condition. It is more than pre-drug genotyping to see how you might respond to a specific therapy. For all of us in medicine, it is about advancing our understanding of the genetic basis of disease and keeping our eye on the prize: to treat individuals more effectively than ever before." 

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