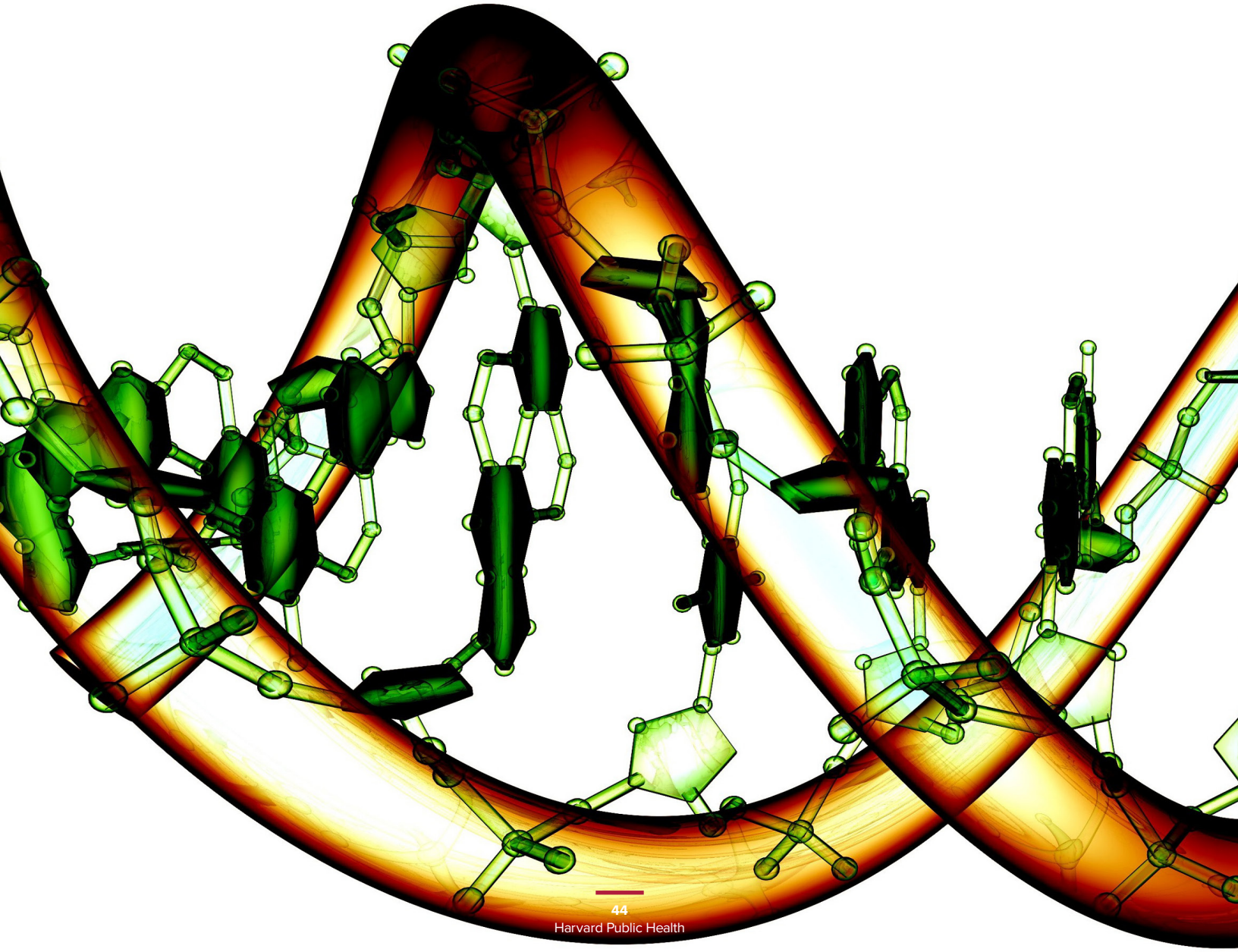
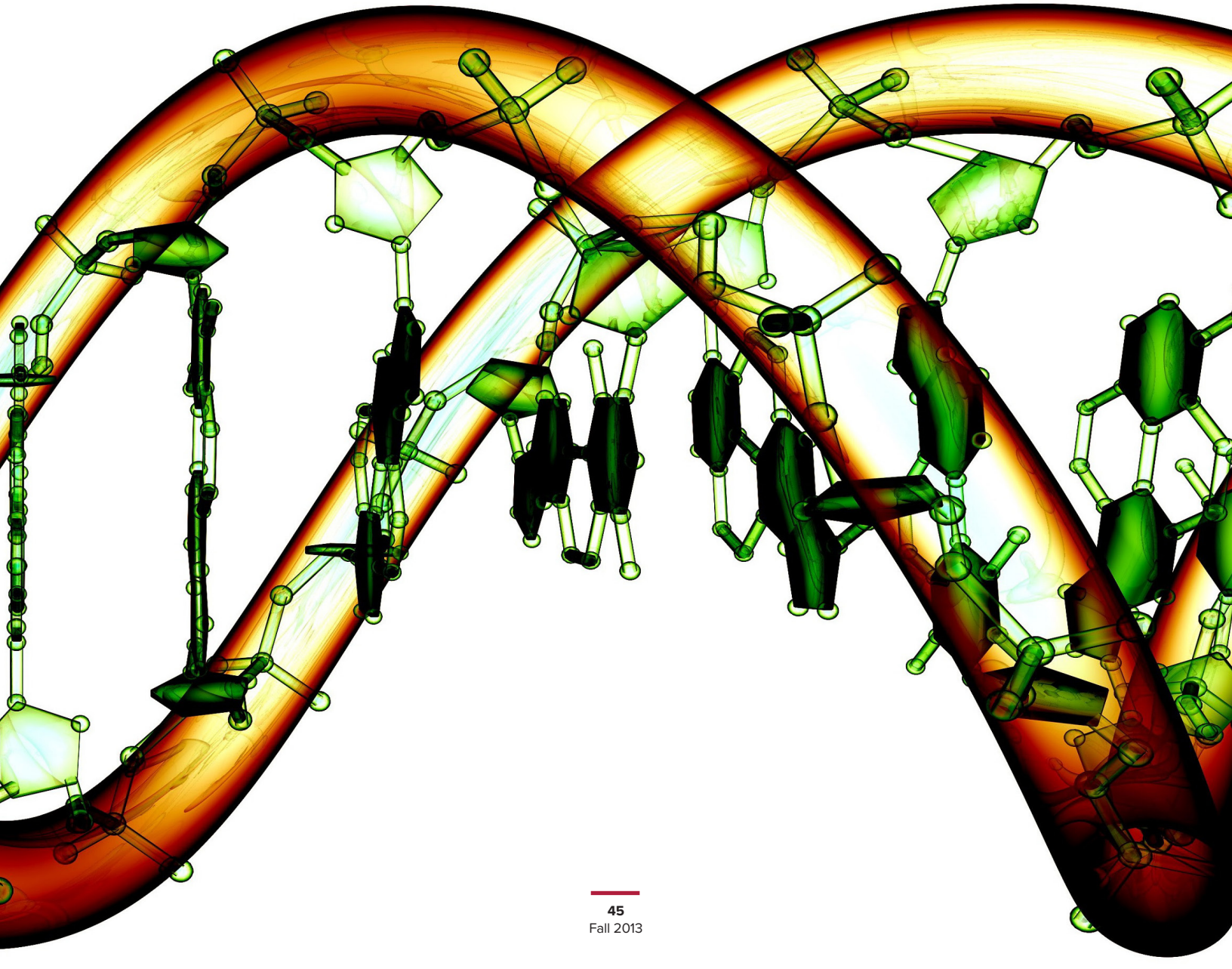
While at first nothing may seem more removed from the broad, humanistic canvas of public health than research on genetics, studies of the molecular mechanisms of disease occupy a central place at Harvard School of Public Health. By revealing the biological underpinnings of disease, genetics research is leading to new and improved methods to diagnosis, treatment, and prevention. Ultimately, this work could help corroborate and refine—or even rewrite—many of today's standard public health recommendations.



THE DNA OF PUBLIC HEALTH



Genes to the Globe

If smoking is the most common cause of lung cancer, why do only 10 to 20 percent of heavy smokers develop the disease? Can a genetic map of the malaria parasite lead to treatments that won't trigger drug resistance? Why are rates of breast cancer higher in the United States than in other parts of the world—though, even in the U.S., most women do not develop the disease? Can genetic studies of obese mice inspire new diabetes drugs?

HSPH is well positioned to answer these questions, because of the School's twin strengths in classic bench science and cutting-edge genetics research. "We're one of the few schools of public health that has wet labs, which use live biological material—and these labs have enabled us to study everything from poliovirus and environmental toxins to malaria and HIV/AIDS. We were also one of the first schools of public health to establish an independent capacity to genotype and do gene sequencing, in order to tie specific genetic variations to specific diseases," said David Hunter, Dean of Academic Affairs and the Vincent L. Gregory Professor in Cancer Prevention. "That has given us the capacity to go from the genes to the globe."

A CENTURY-LONG HISTORY

At HSPH, genetics research is as old as the School—though the title of the first such course in the 1913 catalog—Genetics and Eugenics—is a disturbing reminder of then-prevailing attitudes.

Forty years later, a technological revolution catalyzed the field of public health genetics. It began in 1953, with the discovery of the helical structure of DNA, which led to recombinant methods that are now the backbone of basic research.

Spurred by this breakthrough, HSPH has nurtured two vital strands of genetics research. During the 1960s through the 1990s, School faculty applied molecular techniques to a wide range of nonhuman organisms, from bacteria and viruses to yeasts and mice, to understand the biological machinery in human cancer, heart disease, diabetes, and other afflictions.

This work is currently centered in the School's Department of Genetics and Complex Diseases, established in 2004 and chaired by Gökhan Hotamisligil,

the James Stevens Simmons Professor of Genetics and Metabolism. "When we understand, at a mechanistic level, the basic biology of disease—how things work, how things are integrated—it will absolutely, positively transform what we know as public health," he said.

DECIPHERING THE HUMAN GENOME

In the realm of human genetics, the key scientific breakthrough was the Human Genome Project—the 13-year effort completed in 2003 to identify all of the approximately 20,000–25,000 genes in human DNA. Mapping the first genome took billions of dollars and thousands of scientists. Today, sequencing a genome takes half a day and thousands of dollars—a price that is sure to plummet. "If we look back in another 20 or 30 years, we'll divide time into before and after whole-genome sequencing became routine," said Hunter. "After it becomes routine and costs just a couple hundred dollars for each person, there will be information that we would all be well advised to know."

Initially, that individual and actionable genetic data will likely relate to potential adverse reactions to drugs. But whole-genome sequencing may also open the door to sharper disease prediction. According to Hunter, "People and their health professional advisers will want to know about an individual's profile of common gene variants. Each of these variants may confer only slightly higher risk of disease—but they add up in people who drew a bad hand and have many of these genes, or who have high-risk variants."

The dance between genes and environment is also a burgeoning field of research at the School. Scientists are interested not just in inherited genetic mutations, but also in what turns genes on and off. And they are expanding

continued on page 49

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GÖKHAN HOTAMISLIGIL
Chair, Department of Genetics and Complex Diseases

A Selection of Genetic Discoveries at HSPH

- The late Armen Tashjian Jr., chair of the then-named Department of Molecular and Cellular Toxicology, made pioneering discoveries about how toxic environmental chemicals and therapeutic agents induce molecular changes; he also played a key role in the development of two drugs for treating and preventing osteoporosis.

- John Little, the James Stevens Simmons Professor of Radiobiology, *emeritus*, demonstrated that ionizing radiation induces malignancies in animals.

- Max Essex, chair of the HSPH AIDS Initiative and the Mary Woodard Lasker Professor of Health Sciences, investigated the genetics of cancer-causing retroviruses—a pursuit that ushered in his groundbreaking studies of HIV/AIDS.

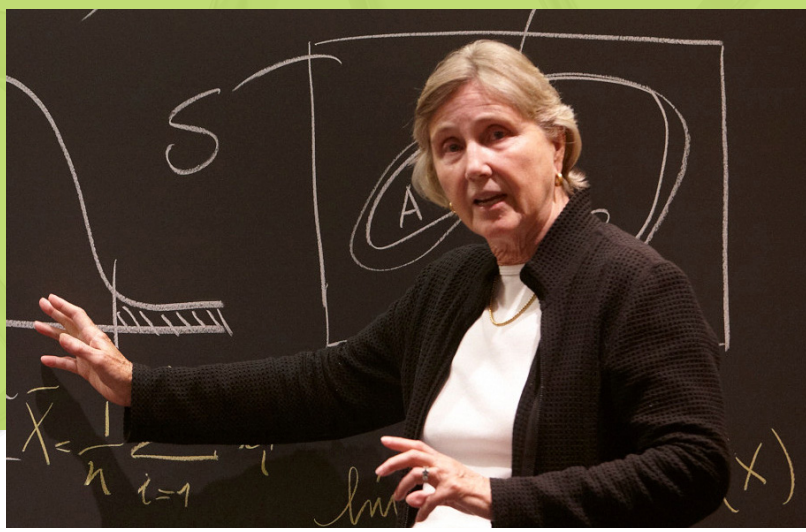
- David Hunter, dean of academic affairs and the Vincent L. Gregory Professor in Cancer Prevention, and colleagues discovered *FGFR2*, the most common gene variant associated with breast cancer.

- Nan Laird, the Harvey V. Fineberg Professor of Public Health and professor of biostatistics, and Christoph Lange, professor of biostatistics, developed methods for discerning familial patterns of Alzheimer's disease, asthma, and other diseases.

- William Hanage, associate professor of epidemiology, used whole-genome sequencing to help trace the path of an *E. coli* outbreak that sickened thousands and killed more than 50 people in Germany and France.

- Dyann Wirth, chair of the Department of Immunology and Infectious Diseases and the Richard Pearson Strong Professor of Infectious Diseases, and Sarah Volkman, principal research scientist in the department, pinpointed sections of the genome of the malaria parasite that may play a role in drug resistance.

- Peter Kraft, professor of epidemiology, participated in an international effort that uncovered 74 new genetic markers linked to three common hormonal cancers—breast, prostate, and ovarian—setting the stage for novel treatments and targeted screening.



Nan Laird, Harvey V. Fineberg Professor of Public Health

Textile factory in Guangdong, China, 2008

the conventional definitions of "environment," such as air pollution or radiation exposure, to include diet, exercise, drugs, bacteria, UV sunlight, and workplace hazards, to name a few. "We're in a great position to explore these areas, because our data sets are drawn from studies that have been collecting detailed information about exposures for 30 years," said Peter Kraft, professor of epidemiology.

GENETICS VS. OLD-FASHIONED PUBLIC HEALTH?

Will these fast-paced advances in gene research herald the decline of traditional public health? Not at all.

In fact, modern genomics may bolster the public health axiom of prevention, noted David Christiani, Elkan Blout Professor of Environmental Genetics in the Departments of Environmental Health and of Epidemiology. Christiani found a common gene variant that made Shanghai cotton textile workers more vulnerable to lung disease. The practical implication of that discovery, Christiani argued, is not to screen out workers who harbor the gene, but to impose stricter environmental standards overall. As he put it, "Protecting the most vulnerable among the population protects everyone better."

"Lung cancer and diabetes are two good examples of retaining current recommendations," added Kraft. "You shouldn't smoke and you should maintain a healthy weight. Regardless of your genes, that's great advice." As the era of public health genetics unfolds, we may find even stronger backing for today's common wisdom—and new ways to protect the health of populations. ❖