Personalized Medicine

Probing the Human Genome to Advance Patient Care
Personalized Medicine
Probing the Human Genome to Advance Patient Care

By Kate O'Neill

Portraits by John Emerson

Photo Illustrations by Barbara Walsh
The Human Genome: The Sum of 25,000 Parts

In the mid-1880s, Georges Seurat introduced Pointillism in revolutionary paintings that depicted the whole as the sum of its parts. In *Sunday Afternoon on the Island of La Grande Jatte*, for example, the artist depicts the setting and every form within it through thousands of small dots of color, carefully arranged on the canvas to present a unified, recognizable image to the viewer’s eye.

A century later, the indiscernible, unifying parts of the whole would again come under analysis. And again, the results would be revolutionary. The Human Genome Project (HGP), a vast, international effort launched in 1990, took ten years — two less than planned — to complete 99 percent of its primary task: to map and sequence a human genome, the unique combination of genes and DNA that distinguishes *Homo sapiens* from all other species. By 2003, the project was complete, having reached or exceeded many of its goals.

The HGP discovered that a human genome is made up of as many as 25,000 individual genes, 10,000 fewer than scientists originally estimated. In any two people, researchers found, the genetic sequence is more than 99.9 percent identical. (To illustrate the importance of seemingly small percentages in genetics: a human genome is 99 percent identical to a chimpanzee’s; it is 90 percent identical to that of a house fly.)

At the start of the project, its leaders established an important precedent that accelerated its accomplishments: within 24 hours of a discovery on genome sequencing, the findings had to be posted for public access. This ensured immediate, maximum benefit to researchers and the public worldwide.

The 0.1 Percent Solution: Translating Genetic Variations into Novel Treatments

Researchers had mapped a human genome and human DNA had been sequenced. Subsequently, they would map the 3.7 million single nucleotide polymorphisms (SNPs) — DNA sequence variations caused by the alteration of a single nucleotide — that not only create recognizable differences between individuals, but also can have enormous health consequences. A single misplaced chromosome can cause serious, even fatal disease. Similarly, people with uncommon or common SNPs can suffer deadly results from a one-size-fits-all prescription.

The HGP did not study these genomic variations; it focused on the basic blueprint, the 99.9 percent of the human genome that is universally shared. But the project unlocked the door to personalized medicine, a revolutionary new field that studies the other 0.1 percent — that fraction of the genome profile that makes each person unique.

Well before the HGP was complete, its findings suggested a new paradigm for medical research and treatment: a world where, years before symptoms emerge, illness will be prevented based on knowledge of the patient’s personal genome. Equally important, pharmagonomics, applying the same knowledge, will prevent adverse drug reactions or identify responders associated with the genetic variability.

The goals of personalized medicine drive research projects in nearly every department at UMDNJ-Robert Wood Johnson Medical School. At two RWJMS institutes, The Cancer Institute of New Jersey (CINJ) and the Environmental and Occupational Health Sciences Institute (EOHSI), concentrations of scientists are advancing the understanding of genomic variability and helping to translate their findings into clinical settings. At the Center for Advanced Biotechnology and Medicine, scientists are immersed in a broad range of individual and multi-institutional bench research defined, at least in part, by the goals of personalized medicine.

Research in personalized medicine explores the health-related consequences of genetic variation, seeking answers to questions about complex human diseases including cancer, type 2 diabetes, Alzheimer’s disease, autism, and cardiovascular disease, as well as normal processes such as the aging of cells. What explains
the disparities between men and women in surviving cancer? Which SNPs put people at risk for which diseases? How do environmental factors interact with certain genotypes to create or heighten disease risk?

The answers to these and other related questions will have vast potential for translation into clinical applications, ranging from prevention to treatment — for example, early screening for people whose personal genomic profile suggests they are at higher risk to develop a disease, or therapies that treat the patient by targeting disease-associated DNA mutations. In some instances, research already has led to the use of drugs tailored to therapeutic targets in individual patients.

By the spring of 2008, the cost of sequencing an individual genome cost had decreased to $350,000, nearly two-thirds less than the $1 million it cost in 2007 to map the genome of James D. Watson, MD, co-discoverer of the structure of DNA. With national grant support and streamlining of the process, the cost may reach an affordable level within the coming decade. Consequently, a personal genome could be scanned and saved onto a memory stick the size of a ballpoint pen and read on a physician’s office computer.

Individual biomarkers in a person’s genome would indicate a susceptibility to developing a certain disease — cardiovascular disease or colorectal cancer, for example — and the patient and physician would begin developing a preventive health plan. Biomarkers would also predict the patient’s match or mismatch with certain drugs, indicating the likelihood of resistance or adverse reaction. For example, the chemotherapy drug 5-Fluorouracil is differentially metabolized by each patient. If a patient has a decreased level of the metabolizing enzyme dihydropyrimidine dehydrogenase, then Fluorouracil, instead of being metabolized, will accumulate in the cells, reaching a toxic, possibly fatal, level.

Customizing Cancer Treatment and Prevention, Patient by Patient

“Personalized medicine? It’s what we’ve always tried to do. Now it’s taken on new meaning.”

— Joseph R. Bertino, MD, university professor of medicine and pharmacology and interim director, the Stem Cell Institute of New Jersey

Personalized medicine encompasses two distinct but related areas, says Robert S. DiPaola, MD, professor of medicine and director, CINJ. Scientists in one area focus on ways in which a personal genomic profile can inform both patient and physician about disease risk and customize preventive efforts. In the second, cancer treatment teams examine the genetic profile of a patient or a tumor to match the host to the treatment.

Dr. DiPaola is one of many physician-scientists at CINJ working on clinical trials that aim to treat cancer by targeting the apoptosis and the metabolism of cancer cells. One study for patients with prostate cancer stems from the knowledge that tumors have increased mechanisms of resistance, such as the overexpression of the resistance protein Beclin (bcl)-2. In multiple Phase I and Phase II trials. Dr. DiPaola and his colleagues have found that they can determine the expression of bcl-2 in a tumor and treat the cancer with agents that target bcl-2. They are hopeful that their analysis will determine the patient’s prognosis and course of treatment.

In a second study, Dr. DiPaola is looking at the role of Beclin-1 as a biomarker for prostate cancer. Normally Beclin-1 regulates autophagy, a process that keeps cells clear of extraneous material. In human prostate cancers, however, its function may be impaired. Because Beclin-1, a tumor suppressor protein, is stainable, it “lights up” in a microarray. This allows its expression to be monitored and may eventually help the oncologist determine the best treatment. The study has moved to the clinical trial stage, with patients receiving 2-deoxymyoglucone to depress excess glycolytic activity, which causes cells to grow and reproduce too quickly. Dr. DiPaola reports that he
Tissue microarray analysis of cancerous tissue can determine the distribution and precise cellular and sub-cellular location where biomarkers are expressed in a tumor, helping to determine the exact stage of disease progression and improving prognostic accuracy. This technology means that "an oncologist will no longer need to proceed from treatment A to B to C to find the one that works best for a given patient," says David J. Foran, PhD, professor of pathology and laboratory medicine and radiology and director, Center for Biomedical Imaging and Informatics, CINJ.

is encouraged by the initial results of laboratory and clinical studies targeting apoptosis and metabolism. But, he adds, further studies will be needed to fully understand these approaches.

Personalized medicine is well suited to treating patients with breast cancer. Long viewed as a single disease, cancer is now known as having many forms and causes, requiring that each patient receive person-alized treatment tailored to his or her disease and genetic variables. The complexity of treatment is demonstrated by the fact that, as a result of genotype variations, the same drug, in an identical dosage, can put one patient into remission while meeting resistance or even causing toxicity in another. Kim M. Hirshfield, MD '99, PhD, assistant professor of medicine and medical oncologist, CINJ, explains that a complete genomic profile is not necessary to determine the best treatment: "In several forms of cancer, including breast and lung, five or six genes may predict the tumor's response. If you find that a breast tumor has progesterone or estrogen receptors — predictive biomarkers for breast cancer — you know it will respond to hormone suppression treatment."

Dr. Hirshfield started her work on predictive biomarkers while completing her post-doctoral training at RWJMS, mentored by Arnold J. Levine, PhD, professor of pediatrics and biochemistry and resident member, CINJ. The collaboration continues with their
research into SNPs as biomarkers that not only predict the occurrence and recurrence of breast cancer but also can suggest optimum treatment modalities. For instance, Dr. Hirshfield explains, radiation and chemotherapy are forms of stress that activate the signaling pathway of p53, a tumor suppressor gene. Knowledge of whether p53 is unstable or disrupted can tell the physician whether to try a different form of treatment — newer medications or a drug in clinical trials. “The Human Genome Project is already helping us to ‘first, do no harm,’” she adds.

Interconnecting The Silos: Using Informatics to Improve Cancer Care

Patients with cancer are already benefiting from one of the legacies of the Human Genome Project: the advancement of high-performance computer technology. The science of informatics, high-throughput computing — often using the power of shared computer grids — has been married to biology through high-speed microarray tissue analysis, producing bioinformatics. The result is a dramatic improvement in the accuracy and speed with which cancer is characterized and classified. Together, these specialties provide the breadth and depth of analysis required to recognize similarities and variations in the human genome and develop personalized medicine as a strategy for disease prevention and treatment.

Tissue microarray analysis of cancerous tissue can determine the distribution and precise cellular and sub-cellular location where biomarkers are expressed in a tumor, helping to determine the exact stage of disease progression and improving prognostic accuracy. High-throughput computers compare these findings against expression signatures in thousands of other patients, giving physicians a comparative basis for determining treatment and predicting the outcome of the disease. This technology means that “an oncologist will no longer need to proceed from treatment A to B to C to find the one that works best for a given patient,” says David J. Foran, PhD, professor of pathology and laboratory medicine and radiology and director, Center for Biomedical Imaging and Informatics, CINJ.

The RWJMS Cancer Informatics Core (CIC) is located at CINJ, where the mission in translational research creates an ideal environment for advancing personalized medicine. “In isolation, basic scientists tend to work with model systems, which don’t always succeed in the real world,” says Gunarettnam Rajagopal, PhD, executive director of bioinformatics, CINJ. “Here at CINJ, basic scientists hear about the real questions every day and fit their research to the questions people really need answers to.

“New Jersey has a phenomenal level of intellectual capability,” he adds. “With the pharmaceutical industry and the universities here, New Jersey is the Silicon Valley of scientific expertise.” The problem, he says, is

This illustration depicts a model used in the design of novel anti-cancer therapeutics based on the inhibition of the enzyme topoisomerase I (orange and purple ribbons). The red, blue, gold, and green ribbon structure is the substrate DNA. The novel therapeutic that blocks the enzyme leading to death of the cancer cell is colored cyan. This research project is an ongoing collaboration between scientists at The Cancer Institute of New Jersey, the RWJMS Department of Pharmacology, and the School of Pharmacy at Rutgers, The State University of New Jersey.
that the experts work in “silos,” more focused on individual projects than on shared endpoints. Dr. Rajagopal is positioning the CIC to serve as a true core, where bridges between silos will interconnect and state-of-the-art information technology will strengthen public and private enterprises. To mine, sort, and find patterns in the volumes of genomic material to be analyzed, the CIC offers the complementary strengths of multi-disciplinary teams of specialists and access to the latest and most powerful information technology.

Together, New Jersey and the Northeast make a perfect test tube for research in personalized medicine, says John Kerrigan, PhD, adjunct associate professor of pharmacology and associate director of bioinformatics, CINJ. He explains that the diverse populations of the region present an ideal opportunity for studying complex common diseases and analyzing the geographic, racial, economic, and ethnic bases for disparities in disease. The volumes of data available on patients treated at hospitals throughout the region will provide the extensive information needed to understand disparities in disease. And NJEDge, the state’s regional optical fiber network, has both the capacity to provide instant sharing of data and images and the potential for speed-of-light electronic collaboration between New Jersey’s governmental, industrial, research, and educational communities.

To facilitate collaborations, translational research, and the identification of disease biomarkers, the CIC has launched a pilot project, PopWeb, to build a statewide data warehouse and bio-specimen repository that will integrate genomic and clinical data to predict specific treatment options for cancer patients. NJEDge will link institutions in the New Jersey cancer research network. PopWeb will also be integrated into the National Cancer Institute’s biomedical informatics grid (caBIG).

In Help Defeat Cancer, a project led by Dr. Foran, researchers from CINJ, IBM, and several U.S. universities developed grid-enabled informatics tools that make use of tissue microarrays, pattern recognition algorithms, and grid-based supercomputing. The focus of the project is the creation of a “retrospective” reference library of staining and protein expression profiles for breast, head and neck, and colorectal cancers. To conduct the proof of concept required to get funding for the project, 100,000 patient tissues with known diagnoses were analyzed using CINJ’s specialized microarray software. Programmers from IBM adapted the software for grid analysis and ran the results on an IBM virtual supercomputer called the World Community Grid (WCG). The project would have taken a single desktop computer 2,900 years to complete, but it took the WCG less than six months, says Robin Willner, IBM’s vice president for global community initiatives.

The project is now supported by a new $2.5 million R01 grant from the National Institutes of Health (NIH), which was awarded to Dr. Foran in October 2007. “The costs of investment in high-performance computing technology are significant; however, the benefits to all disciplines and disease areas far outweigh the expense,” says Dr. Kerrigan.

EOHSI: Connecting the Dots

Because personalized medicine studies complex diseases, the field is well suited to the mission of EOHSI. At this joint institute of RWJMS and Rutgers, The State University of New Jersey, scientists and clinicians address the health issues caused by exposure to environmental agents. Some of the studies focus on common sources of toxic exposure — workplace chemicals, tobacco, solar radiation, airway irritants, pesticides, insecticides, and fertilizers.

Depending on one’s personal genome, the biological response to these and thousands of other environmental agents ranges from null, to slowly emergent disease, to sudden death. Furthermore, the DNA a person is born with changes during a lifetime. Factors ranging from environmental factors to lifestyle and illness alter
gene expression, rearranging the genome by degrees. This explains why identical twins, whose genome is the same at birth, ultimately develop different genomic profiles. Toxic environmental agents can significantly alter DNA, creating a susceptibility to disease that was not previously part of an individual’s genotype.

EOHSI has taken a leadership role in investigating environmental health issues on an international scale. In the past decade, the institute’s researchers have studied the health of veterans of the first Gulf War as well as exposure-related illnesses of the thousands of workers who helped clean up Ground Zero after the 2001 World Trade Center attacks. In collaboration with the UMDNJ-School of Public Health, several scientists at EOHSI also have been studying the health outcomes of China’s efforts to lower levels of air pollution in Beijing during the 2008 Olympic Games.

“People have long been looking at polygenic factors as a cause of disease,” says Howard M. Kipen, MD, MPH, professor of environmental and occupational medicine and acting deputy director, EOHSI. Dr. Kipen, an environmental physician and epidemiologist, investigates how the interaction of genes and the environment makes disease more likely to occur. He says environmental factors are responsible for an estimated 80 percent of all cancers. “Now we are looking at how the two — genes and the environment — working together, may have a greater impact than either one of them would alone,” he adds.

Andrew I. Brooks, PhD, associate professor of environmental and occupational medicine and director, Bionomics Research and Technology Center, EOHSI, investigates the mechanisms by which a polluted environment changes gene expression; he is seeking new evidence of how pollution can lead to disease and death. Dr. Brooks uses genome-based analysis to look at the body’s cell-level defenses against stress-related over-oxidation. He hopes to learn whether these changes occur in response to pollution, and whether they are more common in people of a certain genotype.

Dr. Kipen is collaborating in a multi-institutional, multi-disciplinary study of the biological mechanisms that occur in response to air pollution. He and his colleagues are looking to see whether healthy subjects who are exposed to diesel exhaust fumes exhibit some

“People have long been looking at polygenic factors as a cause of disease,” says Howard M. Kipen, MD, MPH, professor of environmental and occupational medicine and acting deputy director, the Environmental and Occupational Health Sciences Institute (EOHSI) (seated, right), with Andrew I. Brooks, PhD, associate professor of environmental and occupational medicine and director, Bionomics Research and Technology Center, EOHSI.

of the biological changes that can accompany a heart attack. These include inflammation of the endothelial lining of blood vessels, blood vessel dilation, and heart rate variability.

Normally, the body produces low concentrations of nitric oxide (NO) to mitigate these changes. But up to 10 percent of the world population has an SNP in the enzyme known as endothelial nitric oxide synthase (eNOS) that may increase their susceptibility to particle-induced heart attacks, says Dr. Kipen. A sequenced personal genome with the eNOS polymorphism would suggest preventive strategies for those at the highest risk for cardiovascular disease. At a minimum, says Dr. Kipen, those individuals could lower their risk by adjusting their lifestyle to minimize exposure to air pollution, or they could take an aspirin to prevent the onset of a heart attack.

Preventive strategies might also include reducing outdoor activities when particularly potent types of pollution are present. Or, as Dr. Kipen found, it might be relevant to consider avoiding the New Jersey Turnpike’s truck lanes at the peak of the morning commute. At that time, particle mass doubles, with the number of ultrafine particles rising to a maximum eightfold increase over the baseline measurement taken at EOHSI’s labs in Piscataway.

Understanding these biological mechanisms of response may also suggest the use of specific medications and/or dietary intake of particular nutrients that can be targeted to interfere with the exact pathophysiological mechanisms of a certain type of air pollution. This may be particularly effective for those at highest risk by virtue of inheritance or preexisting disease, or for those who live in the world’s most polluted areas.
Personalized medicine holds great promise for practical clinical applications, especially in disease prevention and drug safety. But it also raises new issues that will have to be resolved before it finds a place in the physician's black bag.

“In one form or another, family physicians have always seen genotype expression as we care for families over generations, in routine visits and in treatment,” says Alfred F. Tallia, MD ’78, MPH, professor and chair, Department of Family Medicine. “But for us, personalized medicine puts a new spin on the understanding of the role of heredity and genetics in disease prevention and therapeutic intervention.”

Using personal genome information in the clinic is still in its infancy, but specialists in the field believe that it will become routine once best practices are determined and additional scientific discoveries are made in associating genetic variations with disease. Fast-advancing computer technology and the economics of scale will enable individuals to have electronic medical records that not only capture their health history but also predict future risk of diseases and potential adverse drug reactions.

“We are seeing the payoff from the Human Genome Project,” says Michael F. Christman, PhD, president and CEO, Coriell Institute for Medical Research. In 2007, the institute launched the Coriell Personalized Medicine Collaborative, a pioneering research study involving partnerships with Cooper University Hospital, a principal teaching hospital of RWJMS; Fox Chase Cancer Center; and Virtua Health. The study seeks to explore the utility of using genome information in clinical decision making. It also aims to understand why people often respond differently to treatments, and to discover presently unknown genes that elevate a person’s risk of cancer and other complex diseases. The initial goal is to enroll 10,000 volunteers by the end of 2009, with an ultimate goal of 100,000 participants.

In addition to its ambitious scientific goals, the Coriell study addresses educational and ethical concerns surrounding the use of genome information in the clinic. Study participants are advised that they may choose whether or not to be informed about their susceptibility to potentially “medically actionable” conditions — conditions that have a medical or lifestyle intervention to mitigate risk. In addition, they may choose whether to share all, some, or none of the information with their primary care physician, a specialist, family, or friends. Study participants can access their complete or partial profile online, at any time, using a secure Web site. There is no cost to participate in the study, and genetic counselors are available to discuss genetic results.

The sequenced genome raises other individual and societal concerns. Should an individual’s genome information be available to their family members? For the common good, should health insurers or employers be informed about someone’s potential risk of developing a costly or debilitating illness? Is “genetic discrimination” ever legal or ethical?

Physicians will have to learn how to use information from the genome. “Doctors in primary care settings are generally the patient’s first encounter in the health care system,” says Dr. Tallia. “Usually we are their only continuous encounter.” Physicians will need to know what the human genome contains before they can interpret SNPs as predictors of a patient’s susceptibility to disease or recognize biomarkers that would cause an adverse drug reaction.

“Knowledge of a patient’s personal genome could have a profound effect on patient care,” Dr. Tallia adds. “Genetic variations make drug research catch-as-catch-can at the level of clinical research, with the true test coming when the drug hits the market. If we had a practical way to apply this knowledge and predict a patient’s positive or adverse response to a drug, it would be wonderful.”

“In one form or another, family physicians have always seen genotype expression as we care for families over generations, in routine visits and in treatment,” says Alfred F. Tallia, MD ’78, MPH, professor and chair, Department of Family Medicine. “But for us, personalized medicine puts a new spin on the understanding of the role of heredity and genetics in disease prevention and therapeutic intervention.”