

Photo by Randy Belice

Alfred L. George Jr., MD, the Magerstadt Professor of Pharmacology and director of Northwestern's Center for Pharmacogenomics, works with his laboratory manager Tatiana Abramova (center) and Lyndsey Anderson, a postdoctoral fellow.

# CLOSING IN ON PRECISION MEDICINE

NORTHWESTERN SCIENTISTS ARE HELPING MAKE  
CUSTOMIZED HEALTHCARE A REALITY

## *Call it a pool party of epic proportions.*

Thanks to the Obama administration's recent Precision Medicine Initiative, researchers may soon have access to an unprecedented sampling of the human gene pool. In fact, the resulting dataset may include as many as 25 billion genes.

The president's \$215-million initiative, proposed in January, will combine the genetic details of 1 million volunteers with their medical and biographical records. The effort aims to give researchers additional tools to advance customizable healthcare.

At Northwestern University, research into precision medicine has been growing for more than a decade. It started with the founding of the Center for Genetic Medicine (CGM) in 2000, and continued two years later with the formation of the

NUgene biobank, which has grown to include approximately 12,000 de-identified patient entries. CGM gained wider exposure in 2007 through its inclusion in the nationwide Electronic Medical Records and Genomics Network (eMERGE), a combination of eight sites and hundreds of thousands of electronic health records focused on using that clinical data for complex genomic analysis of disease susceptibility.

“When we began these efforts, we could see opportunity on the horizon,” says CGM founding director **Rex Chisholm**, medicine: cell and molecular biology, who also cochaired a panel that advised President Obama on the use of electronic health records in the federal initiative. “The creation of NUgene, which links DNA samples and health information, means we can provide genomic researchers with data for their specific lines of inquiry.”

## Attacking Tumors

Beyond \$130 million for the genetic database, the president’s budgeted proposal includes \$70 million for the National Cancer Institute. The funding will be used to scale up efforts to identify genomic drivers in cancer and apply that knowledge to developing more effective treatments.

“The idea is to conduct genome sequencing of the tumor cancers have their own genetic makeup and find the Achilles heel within the genetic code,” says **Alfred L. George Jr.**, medicine: pharmacology. “Targeting these genetic vulnerabilities with drugs has already proven to be a very successful approach in some types of cancer, one that we hope to expand upon,” adds George, who also is chair of pharmacology.

The hub for this work will be a new clinical research program at the Robert H. Lurie Comprehensive Cancer of Northwestern University: Onco-SET (Sequence, Evaluate, Treat) personalizes patients’ cancer care by sequencing their tumors’ genetic profiles and evaluating the results to provide treatment options or clinical trials that will benefit them most. “Onco-SET represents the first time cancer treatment in Chicago will be offered in a comprehensive, multidisciplinary program using molecularly defined genomic targets as a basis for determining a patient’s options,” says Robert H. Lurie Comprehensive Cancer Center Director **Leonidas Plataniias**, medicine: hematology/oncology, the Jesse, Sara, Andrew, Abigail, Benjamin and Elizabeth Lurie Professor of Oncology.

## Not Just Cancer

Although cancer researchers have played a large role in precision medicine’s development, that isn’t the only field using this model.

In 2010 researchers revealed that variation in a specific gene prevents some people from activating the drug Plavix. Designed to prevent blood clots from forming in critical arteries, this antiplatelet medication is prescribed to an estimated 40 million people, especially those who have suffered a heart attack or stroke. Physicians who can identify people with the genetic variation can prescribe a different, better-suited therapeutic agent in situations where Plavix is not likely to work as intended.



Rex Chisholm, the Adam and Richard T. Lind Professor of Medical Genetics, associate vice president for research, and vice dean for scientific affairs and graduate education

Photo courtesy of Feinberg School of Medicine

Northwestern researchers identify and study genetic defects that cause muscle disease, including muscular dystrophy. Pictured: A mutation that causes muscle-cell instability is modified by a unique signaling pathway (red). This pathway is being targeted for drug discovery.

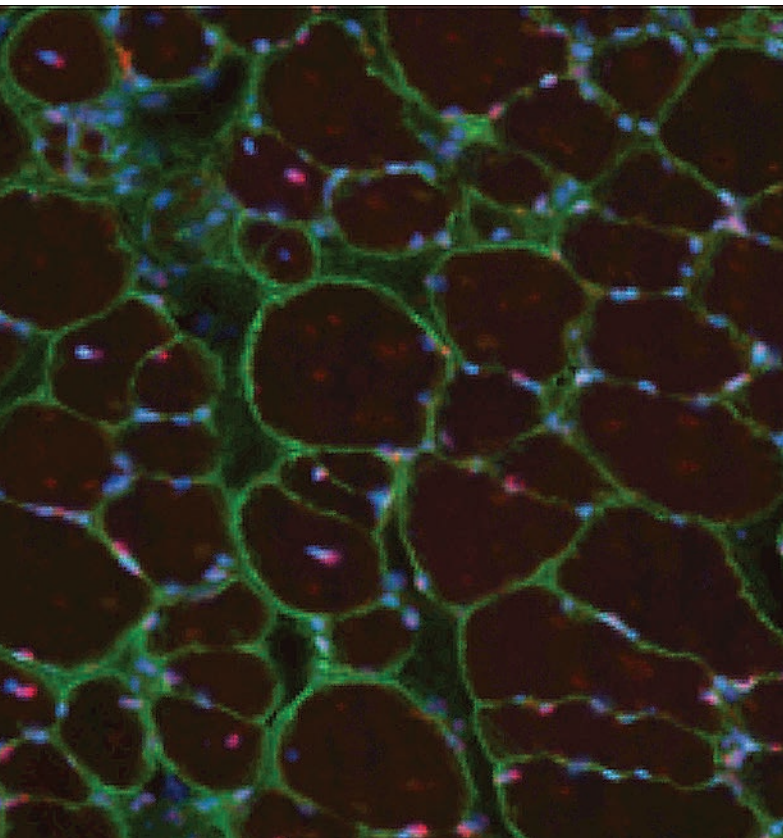


Photo courtesy of Elizabeth McNally

“Precision medicine isn’t just about giving the right drug to the right person at the right time. It’s also about avoiding potentially toxic reactions to drugs,” says George. “We are taking an experimental approach that will result in a new database linking genetic variation with the risk for drug interactions. Such a database would alert physicians about drug combinations that may cause problems in certain genetic backgrounds.” An ongoing eMERGE pharmacogenomics study is examining 86 genes identified as involved in different drug-gene interactions.

Clinical-decision support tools, which provide automatic alerts to physicians at the time of care, can be embedded in electronic health records to enable the implementation of personalized medicine. “We are learning how to better convey genetic information directly to physicians so that it is useful in patient care,” says **Maureen Smith**, NUgene director and co-principal investigator of the eMERGE study. The study also delivers information to patients about their genetic test results.

## Technological Revolution

Fifteen years ago, the first human genome was sequenced at a cost of nearly \$3 billion. Today, sequencing can be completed for less than \$2,000. Cheaper sequencing has brought more answers, though researchers are realizing just how different individuals truly are.

“We can interpret genetic differences and use them to predict risk, diagnose diseases, and better apply our drug therapies. In the future, we will be in the position to fix some of these genetic defects,” says CGM director **Elizabeth M. McNally**, medicine: cardiology and biochemistry and molecular genetics. “Genetic profiling of heart failure is showing us that heart failure is a lot like cancer, in that it is many diseases with different progression rates and risks of abnormal rhythms. We should modulate treatment based on that profile.”

McNally has seen the clinical applications firsthand. When a patient comes to her with a family history of heart disease, she often orders genetic testing.





Photo by Bruce Powell

Elizabeth McNally, MD, the Elizabeth J. Ward Professor of Genetic Medicine (right), talks with Lisa Castillo, a certified genetic counselor, about the Cardiovascular Genetics Clinic, where genetic testing identifies causes of inherited disease.

If a mutation is discovered, McNally and genetic counselors discuss the nature and consequences of the potential disorder with the patient, explaining that an increased disease risk does not guarantee that everyone predisposed to the illness will develop it.

To illustrate her point, McNally cites a genetic mutation in a 30-year-old patient who has experienced a host of symptoms associated with cardiomyopathy, a disease putting him at increased risk of heart failure. Three of his aunts, however, have the same mutation and have been living normal lives for more than 70 years.

“I always say that it’s really important not to be a genetic determinist,” says McNally. “We still don’t know all of the answers why some people develop disease and some don’t. What we do know is that people who carry the genetic variants are at some increased risk. That means we can change our medical practice to increase their quality of life and better react to the disease.”

### Screening at Birth?

As sequencing costs continue to fall, some worry that genomic sequencing will proliferate, perhaps

with undesirable consequences. A person may be living with 100 genetic risks, but too few genetic counselors are available to decode and explain what each risk factor means.

Diminishing costs also raise the possibility that one day all babies could have their genome sequenced at birth. The results would give parents knowledge of the specific risks their children face but also create ethical questions about the responsibility to tell the child of those risks. “I don’t think we’re ready to screen every child just yet,” says Smith. “We still have a lot of work to do regarding when and how to tell people their results.”

As researchers and society further define precision medicine’s role, one goal is to solve these ethical and policy challenges along the way.

“Ultimately, we have an ability in many instances to move beyond treating a disease and, instead, to treat a specific person’s disease, taking into account that person’s unique characteristics,” says Chisholm. “Precision medicine is still in its early days, but it’s an exciting time to be a scientist working in this field.”

— Roger Anderson