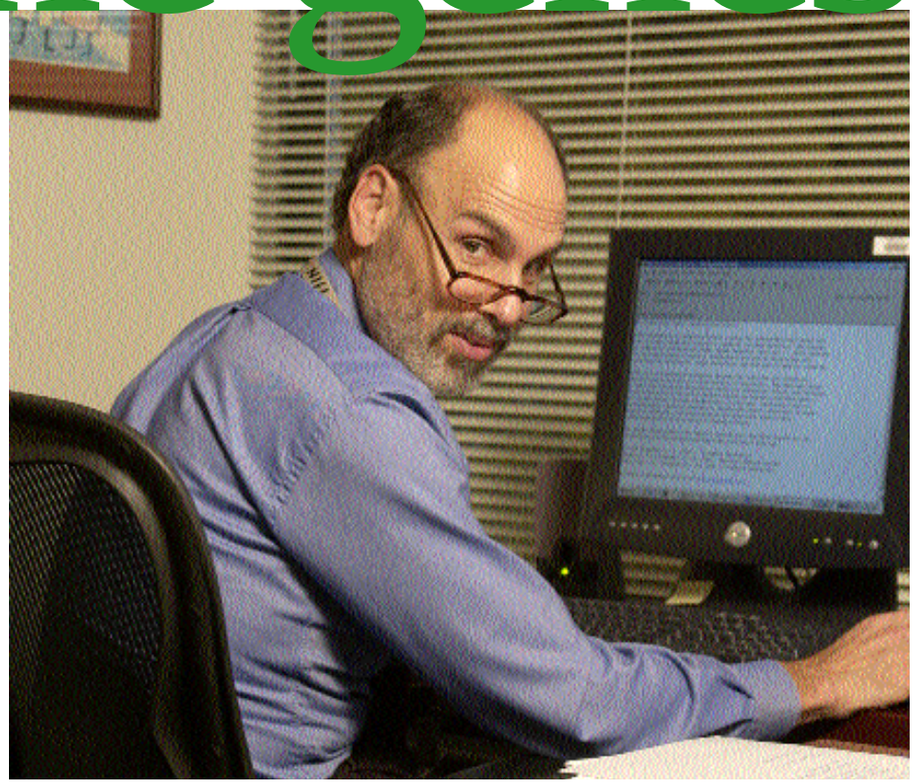
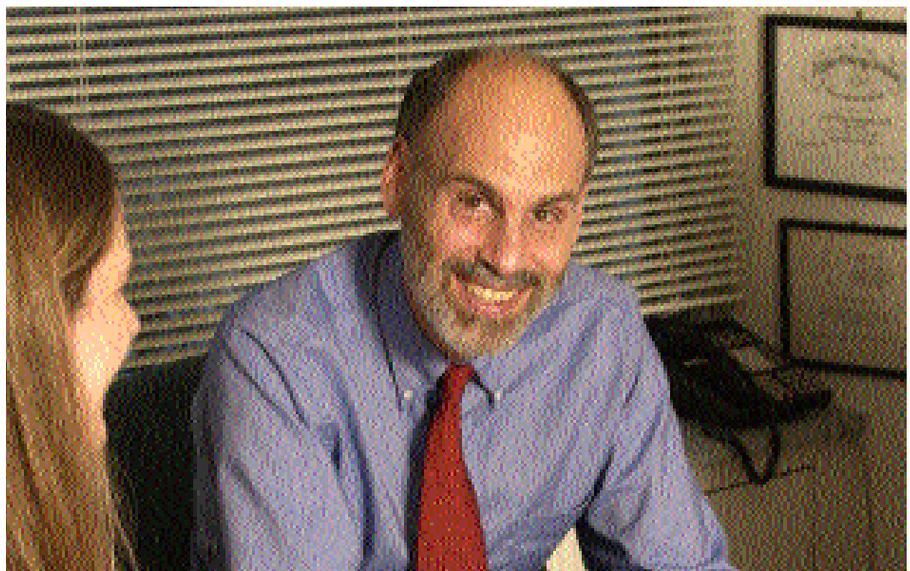
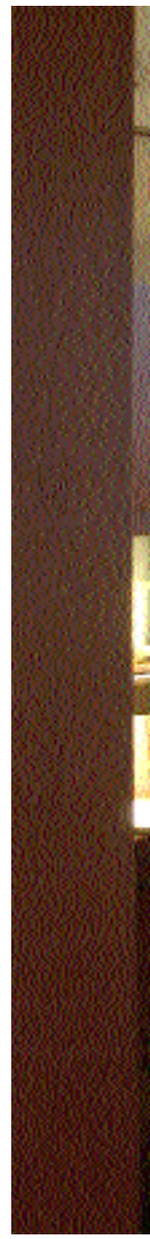
BY KIM RIBBINK

In the genes

AS THE RECENTLY APPOINTED SECOND DEPUTY DIRECTOR OF THE NATIONAL HUMAN GENOME RESEARCH INSTITUTE, THE INSTITUTION RESPONSIBLE FOR LEADING THE HUMAN GENOME PROJECT, **DR. ALAN GUTTMACHER'S** EXTENSIVE CLINICAL GENETICS BACKGROUND WILL BE INVALUABLE AT A TIME WHEN RESEARCHERS ARE BEGINNING TO TRANSLATE THE INFORMATION CONTAINED IN THE NEARLY COMPLETED HUMAN GENOME SEQUENCE INTO MEDICAL ADVANCES.







One might conclude that Dr. Guttmacher's penchant for medicine was genetically predetermined — both of his parents are physicians, as are his siblings, and the uncle for whom he is named. The irony of his eventual career choice is not lost on Dr. Guttmacher, who explored a variety of interwoven paths before becoming a renowned geneticist and physician.

"When I entered college I thought I was going to be a criminologist, I was very interested in social psychology and social relations," he recalls. "I even did an internship at a local correctional facility. For various reasons, however, I decided that was really not what I wanted to do with my life."

After graduating with a degree in social relations, Dr. Guttmacher pursued a number of avenues, including politics, working on a farm, and teaching middle school for a couple of years. Teaching caught his interest, and eventually became one of his life's passions — a pursuit he holds dear to this day. Teaching also helped form the framework for his future expertise in genetics research.

"I decided that I wanted to do something that had a broad impact," he says. "I applied to and was accepted to attend graduate school to pursue a career in public health. However, my older brother talked me into going to medical school first. Having only taken one science course as an undergraduate, I spent a year and a half taking pre-med courses. Then I spent a year before med school working in rural health administration because I thought I might like to practice primary care in a rural health environment. Once in med school I decided to specialize in pediatrics for a couple of reasons."

His interest in pediatrics was piqued by his experiences in teaching middle school, where he developed an interest in learning disorders.

"I became convinced, perhaps in error, that

the folks who really had knowledge of learning disorders were not so much the educators, but the researchers who were publishing scientifically rigorous and valid findings in pediatric literature. I wanted to work more effectively with kids who had learning disorders.

"I also wanted to be involved in an area of medicine that allowed me to interact, on a regular basis, with both with kids and adults," he says. "Pediatrics allowed for both. Intellectually, I find pediatric illnesses interesting. I also enjoyed working with pediatricians — they are a nice bunch of people."

The plan, according to Dr. Guttmacher, was to pursue primary-care pediatrics for a number of years, then hone in on one specialty. Not surprisingly, with a keen interest in human behavior, that specialty became genetics.

As fate would have it, Dr. Guttmacher's long-term goal quickly became a reality.

"I owed time to the National Service Corp. to pay back my med school loan, and I ended up doing a genetics scholarship right away," he says. "I picked genetics because I had an intellectual interest in the way genetic factors work, I also liked dealing with families in clinical genetic settings."

Dr. Guttmacher's diverse background allowed him to pursue a variety of assignments throughout his career.

During his tenure at the University of Vermont College of Medicine — first as an associate professor of pediatrics and later as the founding director of both the Vermont Human Genetics Institute and the university's Familial Cancer Program, Vermont Cancer Center — he juggled his time between clinical genetics, teaching, administrative work, research, seeing patients in genetic clinics, as well as being the founding director of the first pediatric intensive-care unit in Vermont.

Reading the Tea Leaves

For Dr. Guttmacher the area of genetics held the greatest promise, which at the time — back in the early 1980s — was a specialty relatively in its infancy.

"Of all the areas of medicine, it seemed to me that genetics was the one that was going to change the most and be the most exciting during my professional lifetime," he says. "And of all the decisions I have made, this is the one decision I tap myself on the back about. I really read the tea leaves correctly back then."

Dr. Guttmacher believed that genetics would provide him an opportunity to pursue exciting research and make contributions to medicine that would have a broad impact.

"We are just launching into an era when a genomic approach to medicine is not only going to change the way we look at healthcare in general, but enable us to really make a difference in people's lives in terms of their own health," he says. "This is a wonderfully exciting time."

As the new second deputy director of the National Human Genome Research Institute (NHGRI), the institution responsible for leading the Human Genome Project, Dr. Guttmacher is bringing his extensive clinical genetics background to the HGP at a time when researchers are beginning to translate the information contained in the nearly completed human genome sequence into medical advances.

In his new role at the NHGRI, Dr. Guttmacher is helping to integrate genomics into medical practice, assisting the NHGRI with developing new research tools to translate the findings of the human genome project into new diagnostic tests and therapies, and overseeing strategic planning for the institute and its impact on the field of genomics.

"I'm very excited about the new position," Dr. Guttmacher says. "It's an incredible opportunity at this particular place, at this particular point in time, to do a job that can make a difference in the way we answer some important scientific questions. And, to me probably more important, is how we accomplish a new kind of healthcare that will make a real difference in people's lives."

A Century of Change

Genomics, Dr. Guttmacher believes, has the potential to be for healthcare in the 21st


ALAN GUTTMACHER

A double-strand approach

IN AN EXCLUSIVE INTERVIEW WITH PHARMAVOICE, ALAN E. GUTTMACHER, M.D., TALKS ABOUT THE CHALLENGES AND OPPORTUNITIES OF WORKING FOR THE NHGRI, AND WHAT LED HIM TO THE INSTITUTE.

YOU SPENT MANY YEARS WORKING IN ACADEMIA AND HAVE AN EXTENSIVE BACKGROUND AS AN EDUCATOR. HOW ARE YOU FINDING THE TRANSITION FROM ACADEMIA TO GOVERNMENT?

My biggest concern about moving to a governmental role was the amount of bureaucracy I was going to deal with. But I've found that, in general, I deal with much less bureaucracy as a government employee than I did when I was in academia.

I find I'm given the resources I need to do my job instead of having to spend much of my job wondering how I'm going to get resources and how I am going to function if I spend time on a committee, etc.?

Although it is very rewarding, at this particular point in time, an academic career has a great deal of challenges. I love academia and had planned to stay there forever, and may well go back someday, but now that I'm out of it I can see that there were difficulties involved. For those in academic medicine it's not an easy time, because of the challenge of finding the resources to do the job one wants to do.

WHAT DO YOU MISS MOST ABOUT YOUR ROLES IN ACADEMIA AND CLINICAL PRACTICE?

I don't get to teach students very much anymore, and I don't have much

century what knowledge of infectious disease was for the last.

"The most important advances in health status and care, in the U.S. and globally, in the last century stemmed from our understanding of infectious disease and being able to impact mortality and morbidity," he says. "The same idea of applying knowledge of genomics to diagnosis, to therapy, to prevention, just as we did for infectious disease, will have the same lasting impact."

This vision to apply genetics research to practical medicine has won him much support and acclaim.

"It's wonderful for NHGRI to have Dr. Guttmacher as its deputy director," says Francis S. Collins, M.D., Ph.D., director of the NHGRI. "Alan is an exceptional medical geneticist and has been a valuable advisor to the institute. His ability to see how genomic medicine can be applied in the clinical setting and his passion as a physician will be a tremendous asset in taking NHGRI into a new era of applying the fruits of the Human Genome Project to improved human health."

Before joining the National Institutes of Health, Dr. Guttmacher ran a number of genetics-related projects in Vermont, investigating ways to integrate a genomics approach into the state's healthcare.

"When there was an opening in Washington to do the same kind of thinking, involving the same kinds of issues in a more national way with people whom I believed I would really enjoy working with, it was a pretty easy decision to make the move," he says.

Having joined the institute just three years ago, Dr. Guttmacher's rise to second deputy director of the NHGRI has been fairly rapid. His approach to genetics, coming from a clinical healthcare perspective rather than strictly research, is somewhat unusual in the institute, but undoubtedly this was the linchpin for his appointment.

Since his arrival at the institute, Dr. Guttmacher has been focused on finding ways to integrate genomics into the nation's healthcare. In addition, he also has served as acting director of the office of Policy, Planning and Communications. The office was formed to look at policy development and analysis related to the ethical, legal, and social implications of human genome research; administer a communications program aimed at disseminating information about the science and policies of the HGP and the NHGRI's genetics research programs; track and analyze legislation; and oversee program planning and evaluation.

As the institute began to address its future role, Dr. Guttmacher's background made him an ideal candidate to fill the role of deputy director, which was vacated by Dr. Elke Jordan who retired in July after 30 years of service to NIH. Dr. Jordan secured her place in NIH history as an integral leader of the Human Genome Project.

"The institute had been founded primarily to coordinate the Human Genome Project," Dr. Guttmacher says. "While the institute is clearly going to continue to be involved in basic science, in genomics, in sequencing of other organisms, it also is going to be more involved in areas of translational research, and thinking about how to move genomics into patient care. Since I'd been involved with those issues for the past few years, Dr. Collins decided I might be a good person for this role at this point in time."

Thinking Outside the Box

As the NHGRI prepares to move into the next phase of its development, which involves a significant planning process to decide what its contribution to the future of genomics will be, one of Dr. Guttmacher's role is to help coordinate this process and monitor the institute's progress going forward.

"There clearly remain scientific and technical challenges in terms of research questions that need to be answered, but there also is the huge challenge of educating health professionals and the general public about this new knowledge base," he says.

Dr. Guttmacher's penchant for teaching continues to come into play in his role at the NHGRI.

"I give about 50 talks a year, the plurality of which are to various professional groups about integrating genetics into medicine," he says. "That's part of what I really love doing — to go out and teach people about the possibilities.

"This is particularly important, because there are a number of ways in which genomics can be misapplied and misunderstood, which could lead to ethical consequences," he says. "There will be a seductive power in that this

direct patient contact. I love being a doctor, it's a wonderful privilege. Intellectually I know I'm able to do things at the NHGRI that will improve more people's lives more than my individual medical practice. But on a day-to-day basis, I do miss the individual patient contact.

YOU HAVE BEEN THE RECIPIENT OF MANY AWARDS. CAN YOU MENTION ONE OR TWO THAT HAVE PARTICULAR SIGNIFICANCE FOR YOU?

I was elected as a faculty member to Alpha Omega Alpha, which is the medical honorary society. Every year students at the University of Vermont elect one faculty member to this national honorary society. This moved me because it was about the relationship with students, which is important to me.

Another honor was being selected to the Hereditary Hemorrhagic Telangiectasia Foundation International, which is a family support group.

Hereditary hemorrhagic telangiectasia is a specific genetic disorder that has been one of my primary research interests. It was an honor to be selected by my patients and research subjects.

WHO HAVE BEEN YOUR MENTORS?

My mentors have been primarily my family, and some teachers from high school. Both my parents taught me wonderful life lessons and, since they're both physicians, professional lessons as well. But particularly life lessons. They've been my most important mentors.

In medicine there are people who have, and continue to, serve as role models. When I was younger, I thought at some point in life one doesn't have mentors anymore, but I don't know if that ever happens. No matter what age you are, you still have mentors.

AS A MENTOR YOURSELF, WHAT ARE THE MOST IMPORTANT THINGS IN GUIDING OTHERS?

The most important thing is having a genuine interest in their lives and careers. Mentoring is not just teaching people information, but being willing to engage on a personal level. Some aspects of being a role model are conducting your professional life in a way that is good and honorable and effective, but also it's taking a personal interest in students, maintaining those relationships, and being available for those people.

new knowledge base may lead people to think that their genetic makeup completely predicts their future. There is a danger of oversimplifying the role of genomics. Just because we have the human genome sequence in hand, and that within the next few years we will have a better understanding of the genetic factors involved with disease, doesn't suddenly make the non-genetic factors, the environmental factors, less important than they were last year. These are just as important as they ever were.

Dr. Guttmacher's passion for education also has led to the formation of a cohesive Internet program at the institute.

"For example, if somebody is shown to have a genetic predisposition to a certain type of cancer, the most important thing they can do is stop smoking," he says. "Having genetic knowledge won't necessarily result in gene therapy. We may know our genetic make up, but disease management will have a lot to do with how we handle our environment."

Caution aside, Dr. Guttmacher believes that this is the most exciting time in history to be involved in genetic science.

"I marvel at the science and technology involved in the human genome sequence — it's a real technological and scientific *tour de force*, it's beautiful," Dr. Guttmacher says. "But what we're about to launch into now is much more engaging and interesting because it has to do with integrating this knowledge into human life, influencing the way people think about health, changing the way they practice prevention strategies to stay healthy, and designing drugs to meet these needs."

This type of forward thinking requires the institute to anticipate the future, but, Dr. Guttmacher says, this is nothing new for NHGRI since it was just this type of thinking that led to the sequencing of the human genome.

"When the human genome project was started there were many people who thought it wasn't doable from a technical standpoint, and even when it was feasible, they doubted its worth," he says. "But the people involved with the project understood that once the basic framework had been created, it would launch other research initiatives that wouldn't have been undertaken nearly as effectively or efficiently without it."

Already, the institute is forging ahead with some out-of-the-box thinking, such as addressing key issues around diversity in relation to genomics.

"Our institute is keenly interested in diversity issues for a number of reasons," Dr. Guttmacher says. "Part of the interest comes from the ethical, legal, and social implications of genomics. Clearly genomics plays a part in the relationship between biology and constructs of race and ethnicity, for instance.

"We also are keenly aware that individuals from minority populations are significantly

Career sequencing

ALAN E. GUTTMACHER — RESUME

SEPTEMBER 2002. Second deputy director of the National Human Genome Research Institute. The NHGRI is the institution responsible for leading the Human Genome Project for the National Institutes of Health

1999–2002. Senior clinical advisor to the director, NHGRI; acting director of the NHGRI Office of Policy, Planning and Communications

1996-1999. Medical staff, Rutland Regional Medical Center, Rutland, Vt.

1995-1999. Founding Director, Vermont Human Genetics Initiative, University of Vermont College of Medicine

1993-1999. Founding Director, Familial Cancer Program, Vermont Cancer Center, University of Vermont College of Medicine

1993-1996. Associate Professor of Pediatrics with tenure, University of Vermont College of Medicine

1991. Founding Director, Pediatric Intensive Care Unit, Medical Center Hospital of Vermont

1989-1999. Founding Medical Director, Vermont Newborn Screening Program

1987-1993. Assistant Professor of Pediatrics, University of Vermont College of Medicine

1987-1999. Director, Vermont Regional Genetics Center and Pregnancy Risk Information Service, University of Vermont College of Medicine

1987-1999. Referring consulting staff, Champlain Valley Physicians Hospital, Plattsburgh, N.Y.

1987-1999. Attending in pediatrics, Medical Center Hospital of Vermont, Burlington, Vt.

1986-1987. Senior Associate in Pediatrics, Beth Israel Hospital, Boston, MA

1985-1987. Fellow in Medical Genetics, Children's Hospital and Harvard Medical School, Boston

1982-1985. Intern and Resident in Pediatrics, Children's Hospital, Boston

1981-1982. Physician, Developmental Pediatrics Clinics, Children's Hospital, Boston

Board Certification

1987. American Board of Medical Genetics, Diplomate and Certification in Clinical Genetics

1989-1996. American Board of Pediatrics, Diplomate

EDUCATION:

1977-1981. M.D., Harvard University

1975-1976. Pre-medical student, Duke University

1975. Pre-medical student, Johns Hopkins University

1967-1972. A.B. cum laude in Social Relations, Harvard University

AWARDS AND HONORS:

2000. Joseph E. Cannon Award, New England Public Health Association

1999. Honorable Mention, American Medical Women's Association Gender Equity Award, University of Vermont

1996. Volunteer of the Year, Hereditary Hemorrhagic Telangiectasia Foundation International

1990. Alpha Omega Alpha Medical Honorary Society, University of Vermont

1989. Volunteer of the Year, Vermont Chapter, March of Dimes Birth Defects Foundation

1985-1987. National Research Service Award, U.S. Public Health Service

1985-1986. Farley Fellowship, Children's Hospital, Boston

1978-1981. National Health Service Corps Scholarship, U.S. Public Health Service

under represented in the genomics workforce," he says. "If genomics is going to be integrated into society in a useful and meaningful way, we need to have people from all populations involved in the decision-making process as health professionals and in research. There is an overwhelming importance to honor diversity and to explore it scientifically, but also to make sure that we are sensitive to cultural issues involving different populations and issues about genetics. By diversity, I'm including the involvement of under-represented communities, about the scientific and sociocultural relationship between genetics and constructs of race and ethnicity."

For Dr. Guttmacher, this is uncharted territory. And while many questions remain to be answered in terms of how genomic medicine will change healthcare in terms of environmental disparities in the U.S. and in developing countries, he is confident that genetic research will make a difference.

"This will be one of the most important areas of focus for us over the next few years and will become part of the planning process as we move forward," he says.

To that end, the institute recently hired a senior consultant to look specifically at health disparity issues.

Reaching the Masses

Dr. Guttmacher's passion for education also has led to the formation of a cohesive Internet program at the institute. In 1999, Dr. Guttmacher and Dr. Collins founded Genetic Resources On the Web, otherwise known as GROW, which works with organizations sponsoring genetics-related Websites to ensure that they contain high-quality information.

GROW's membership includes some three dozen organizations, including health professional groups, patient-support groups, federal agencies, foundations, non-profit agencies, and for-profit companies.

"GROW started just as a meeting and has become a semi-formal organization of several dozen institutions that have an interest in the Internet as a way to provide genetics information primarily to the general public, in addition to healthcare professionals," Dr. Guttmacher says.

Through education, technology, and research, genomics will help answer some very important scientific questions and make a difference in how healthcare is approached in the U.S. and the rest of the world.

"I feel as though I've been struck by lightening to be able to work at the institute and have the opportunity to do things that make a difference in people's lives," he says. ✦

PharmaVoice welcomes comments about this article. E-mail us at feedback@pharmalinx.com.

Mission accomplished: the NHGRI and the human genome

The National Human Genome Research Institute (NHGRI) originally was established as the National Center for Human Genome Research (NCHGR) in 1989. Its primary mission is to lead the National Institutes of Health's (NIH) contribution to the Human Genome Project — an international research effort to determine the location of all human genes and to read the entire set of genetic instructions encoded in human DNA.

The NHGRI carries out this mission by providing financial support to scientists at universities and other public research laboratories throughout the U.S. In addition to supporting the Human Genome Project, the NHGRI established a Division of Intramural Research in 1993 to develop genome technologies that would accelerate the process of identifying and understanding the molecular basis of human genetic diseases.

HUMAN GENOME PROJECT

The Human Genome Project (HGP) officially began in 1990 and is coordinated in the U.S. by the NHGRI and the U.S. Department of Energy. International HGP partners include the U.K., France, Germany, Japan, and China. Once scientists complete the ultimate task of sequencing all 3 billion base pairs in the human genome, they will have created a virtual blueprint for a human being.

From 1990 to 1994, the activities of the HGP were primarily devoted to developing genetic and physical maps that allow precise localization of genes, and to exploring technologies that enable the sequencing of very large amounts of DNA with high accuracy and low cost. Pilot projects were initiated in 1996 to explore the feasibility of such large-scale sequencing of human DNA. These projects were extremely successful and resulted in creative laboratory innovations that automated and accelerated the sequencing process. By September 1997, the pilot projects had sequenced approximately 2% of human DNA. Now, with current technology, HGP centers can sequence 1,000 base pairs per second at a very low cost.

The HGP's goal of producing a highly accurate "finished" sequence will be met in 2003 — under budget and two years ahead of the original schedule.

Scientific leaders of the HGP also made an important decision in 1996 — to deposit sequence in public databases within 24 hours of its assembly, with no restrictions on its use or redistribution. This defining moment in the HGP made the sequence immediately available to anyone with an Internet connection, ensuring that the sequence would ultimately benefit the public by empowering all the world's best minds.

In June 2000, the International Human Genome Sequencing Consortium announced that a "working draft" sequence of the human genome, nearly 90% complete, had been produced. In February 2001, the consortium published this sequence and an initial analysis of the human genome that reported a number of discoveries. The most surprising of these was that humans have only 30,000 to 35,000 genes, whereas previous predictions had ranged from 80,000 to 150,000 genes.

The HGP's goal of producing a highly accurate "finished" sequence will be met in 2003 — under budget and two years ahead of the original schedule.

As the HGP nears completion, the mission of the NHGRI has expanded to encompass a broad range of studies aimed at understanding the structure and function of the human genome and its role in health and disease.