

NATIONAL ADVISORY COUNCIL FOR HUMAN GENOME RESEARCH
SUMMARY OF MEETING¹
May 19, 2008

The National Advisory Council for Human Genome Research was convened for its fifty-third meeting at 8:31 A.M. on May 19, 2008 at the Fishers Lane Conference Center, Rockville, MD. Francis Collins, Director of the National Human Genome Research Institute, called the meeting to order.

The meeting was open to the public from 8:30 A.M. until 3:40 P.M. on May 19, 2008. In accordance with the provisions of Public Law 92-463, the meeting was closed to the public from 3:40 P.M. on May 19, 2008 until adjournment for the review, discussion, and evaluation of grant applications.

Council members present:

Eric Boerwinkle
Andrew Clark
Jorge Contreras
Vanessa Northington Gamble
Richard Gibbs
Geoffrey Ginsburg
Caryn Lerman
Deirdre Meldrum
Patrice Milos
Pilar Ossorio
David Page
Stephen Prescott (participating by teleconference)
Harold Shapiro
Paul Sternberg (participating by teleconference)
David Valle
Richard Weinshilboum

Ad Hoc Members absent:

Claire Fraser-Liggett

Ex Officio Members absent:

Gerard Schellenberg

Staff from the National Human Genome Research Institute:

¹ For the record, it is noted that to avoid a conflict of interest, Council members absent themselves from the meeting when the Council discusses applications from their respective institutions or in which a conflict of interest may occur. Members are asked to sign a statement to this effect. This does not apply to "en bloc".

Ajay, DER	Teri Manolio, DER
Glory Baldwin, DER	Jean McEwen, DER
Catherine Bennet, DER	Keith McKenney, DER
Victoria Bishton, DER	Lisa McNeil, DER
Vivien Bonazzi, DER	Anika Mirick, DER
Vence Bonham, OD	Ken Nakamura, DER
Joy Boyer, DER	Kenneth Ow, OD
Pamela Bradley, OD	Brad Ozenberger, DER
Lisa Brooks, DER	Thom Person, DER
Comfort Browne, DER	Carmen Perera, OD
Gloria Butler, OD	Jane Peterson, DER
Ernsly Charles, DER	Anne Pierson, DER
Debbie Chen, DER	Ed Ramos, DER
Cheryl Chick, DER	Charles Rotimi, DER
Monika Christman, DER	Rudy Pozzatti, DER
Francis Collins, OD	Eddie Rivera, OD
Karen DeLeon, OD	Jerry Roberts, DER
Irene Dorsey, OD	Cristen Robinson, DER
Gwen Dudley, DER	Jeff Schloss, DER
Elise Feingold, DER	Geoff Spencer, OD
Adam Felsenfeld, DER	Jeff Struewing, DER
Colin Fletcher, DER	Carolyn Taylor, DER
Peter Good, DER	Gary Temple, DER
Alan Guttmacher, OD	Elizabeth Thomson, DER
Mark Guyer, DER	Larry Thompson, OD
Emily Harris, DER	Susan Vasquez, OD
M.K. Holohan, OD	Lu Wang, DER
Chris Juenger, DER	Chris Wellington, DER
Mike Kabatt, DER	Kris Wetterstrand, DER
Carson Loomis, DER	Diane Williams-Bey, DER
Murugu Manickam, OD	

Others present for all or a portion of the meeting:

Diane Baker, Genetic Alliance
Joann Boughman, American Society of Human Genetics
Khaled Bouri, George Washington University
Sharon Olson, International Society of Nurses in Genetics

INTRODUCTION OF NEW MEMBERS AND STAFF, LIAISONS AND GUESTS

Dr. Guyer introduced new NHGRI staff: Victoria Bishton, Grants Specialist; Ed Ramos, Science Policy Analyst; Charles Rotimi, Director of the Center for Research on Genomics and Global Health.

Dr. Guyer welcomed members of the press and liaisons from professional societies: Diane Baker from the Genetic Alliance, Joann Boughman from the American Society of Human Genetics, and Sharon Olson from the International Society of Nurses in Genetics.

APPROVAL OF MINUTES

The minutes from the February 2008 Council meeting were approved as submitted.

FUTURE MEETING DATES

The following dates were proposed for future meetings: September 8-9, 2008, February 9-10, 2009, May 18-19, 2009, September 14-15, 2009, February 8-9, 2010, and May 17-18, 2010.

DIRECTOR'S REPORT

I. GENERAL ANNOUNCEMENTS

Awards:

Charles Lee, an assistant professor of Pathology at Brigham and Women's Hospital and Harvard Medical School, a Broad Institute Associate Member, and an NHGRI grantee, has been awarded the 2008 Ho-Am Prize in Medicine. The award recognizes Lee's fundamental contributions in the study of copy number variants.

Former Council member and member of the Sequencing Advisory Panel, Rick Lifton was awarded the Riley Prize in biomedical sciences.

NHGRI Planning Process

It has been almost seven years since NHGRI began its last planning process. While the result of that process, the "Vision for the Future of Genomic Research," has worn well over time, the tremendous advances in genomics and related fields warrant NHGRI taking a new look at the future of genomic research. To discuss the possibility of a new

planning effort, NHGRI held a “Planning Kick-Off Meeting” on April 3-4, 2008 with NHGRI staff and a few outside experts. The discussion at this meeting focused on content areas that could be included in a planning process and new approaches to obtain input from the community. NHGRI leadership has begun using the information gathered at this meeting to develop a path forward for the planning process. Ideas being developed include white papers, wiki contributions, webinars, in-person workshops, and a large community meeting. More details will be presented at the next Council meeting. Council members should anticipate participating in this process. At present, 2010 is a target date for the completion of this new attempt to describe a vision for the future of genomic research.

The Genetics Society of America’s Thomas Hunt Morgan Medal for lifetime contributions was presented to Michael Ashburner.

II. NEW NHGRI INITIATIVES

The Genes, Environment and Health Initiative (GEI) is strongly supported by both Secretary Levitt and Dr. Zerhouni to investigate both genetic and environmental contributions to common diseases. One notice and several RFAs have been released and a number of grants funded. Forthcoming initiatives will pursue two directions, replication and validation of GWAS findings on the one hand, and functional characterization on the other.

The ENCODE Project has released an RFA entitled “A Data Analysis Center for the Encyclopedia of DNA Elements (ENCODE) Project.”

The Human Microbiome Project released a notice providing applicants with more time to prepare applications in response to the demonstration projects RFA.

III. RECENT SCIENTIFIC ACCOMPLISHMENTS AND ISSUES

NHGRI - EXTRAMURAL PROGRAM

Sequencing Program. At the February, 2008 Council meeting, NHGRI staff proposed a plan to encourage the rapid implementation of new sequencing platforms in the large-scale sequencing centers over the subsequent 12 months. Conceptually, half of the funds in the sequencing grants were to be used "in production" for approved sequencing projects, and monitored under the previously established production metrics, while the other half were to be used for implementation of the new technologies in a production setting. The idea of an implementation period was designed to allow the centers time to gain more experience and a better understanding of the performance of the new sequencing platforms in a variety of applications at high throughput. As part of the implementation effort, NHGRI staff and the centers were to develop appropriate production metrics for the new platforms that could allow effective monitoring of production and the quality of the sequence products, and that could be used as benchmarks to determine when a specific application could transition from

"implementation" to "production." During these 12 months, NHGRI staff was to maintain close communication with the centers to understand progress. The implementation process got underway immediately, and the center P.I.s will discuss their progress toward developing metrics with NHGRI Staff and the Sequencing Advisory Panel at a meeting that will be held in July in New York City. By the end of the 12 months, reliable and useful cost and performance data for the new sequencing technologies should be available. A number of working groups from other projects, notably the Human Microbiome Project, the Tumor Sequencing Project, and the 1000 Genomes Project, have contributed to the discussion of the development of metrics.

Platypus genome sequence. The publication of the sequence of the genome of the duck-billed platypus has been met with great deal of public and scientific interest. As one of only two monotremes, the platypus occupies a special position in mammalian evolution, separated from the rest of the mammalian lineage by approximately 166 million years. Thus, the sequence has been extremely informative for the scientific community. For example, the sequence includes venom genes that are very similar to those in reptiles but come from a different lineage.

Cold Spring Harbor meeting. This year's "The Biology of Genomes" meeting, which was held at the Cold Spring Harbor Laboratory from May 6 – 10, was dominated by the application of new sequencing technology platforms to many research projects, including the resequencing of specific genomic targets, the detection of point mutations and structural variants, the description of gene expression levels and methylation profiles and *de novo* genome sequencing. Another major theme was the association of genetic variation with human phenotypes, both disease studies, including GWA studies for cancers, and others, such as BMI. There were also notable presentations addressing evolutionary forces acting on the genome, such as a sequence motif associated with recombination hotspots in humans, the overall recombinational landscape of the human genome, transcription as a mutagenic process, genetic variation generated by transposable elements and sequence duplications, and the role of neutral variation in genome evolution.

Among the NHGRI-supported projects that received attention were modENCODE, the skin microbiome, 1000 Genomes Project, HapMap 3, and the platypus genome sequencing effort. Once again, significant progress was apparent in many aspects of genomics, such as analytical and computational approaches for comparative genomics, reconstruction of ancestral sequences, short read genome assembly and sequence alignment algorithms.

The ELSI session at the Cold Spring Harbor meeting focused on direct-to-consumer (DTC) genomic test marketing. Presentations were given by representatives of DTC companies, including Kari Stefansson of deCODEme, Dietrich Stephan of Navigenics, and Linda Avey of 23andMe. Presentations were also given by Kathy Hudson of the Genetics and Public Policy Center at Johns Hopkins University and Joseph McInerney of the National Coalition for Health Professional Education in Genetics (NCHPEG). The presentations were followed by a panel discussion and questions from the audience.

The guest speakers on the last night of the conference were Mike Levine of University of California, Berkeley, who described his long history of work in *Drosophila* development and recent work with the sea squirt, *Ciona intestinalis* and Michael Lynch of Indiana University, who presented his work on the evolution of eukaryotic genome complexity as influenced by small effective population size such as that seen in humans.

Sequencing Technology Grantees Meeting. The annual grantee meeting for \$100,000 and \$1,000 genome technologies was held in San Diego in mid-March. As in the past, the meetings facilitated the development of several new collaborations to test new ideas. To share the results of this program with the rest of the world and facilitate information sharing among grantees, all of the presentations have been posted on a web page. The participants also discussed key technical challenges to achieving the program's goals and a manuscript to summarize these challenges is being prepared.

Nanopore sequencing has been a particularly interesting area of discussion. Recent highlights include:

- better ways to control the orientation of DNA relative to sensing electrodes;
 - improved understanding of the control of translocation rate, including feedback control to re-sequence the same molecule;
 - better electronics for ion flow measurements;
 - demonstration of the ability of a modified protein nanopore to clearly distinguish among the 4 monodeoxynucleosides by ion current (so products of exonuclease cleavage could be sequenced);
- and
- development of an alternate protein pore with a short sensing channel (the sensing channel in alpha-hemolysin is several nucleotides long)

1000 Genomes. There have been significant clarifications and revisions to the 1000 Genomes project as a result of recent discussions that will be presented later in the open session.

HapMap. The Baylor sequencing center determined 1.3 Mb in the 955 unrelated samples in the extended set of HapMap samples, from the 4 initial populations, plus additional samples from those populations, and additional samples from 7 other populations. All of the 1301 samples were genotyped by Broad and Sanger for a combined total of 1.6 million SNPs. These data were presented at the CSHL Genome Meeting and at the 1000 Genomes meeting. This additional information gives a fuller view of human haplotype diversity

Cancer Genome sequencing. The collaboration between NCI and NHGRI, TCGA is designed to obtain a comprehensive description of the genetic basis of human cancer (as described at <http://cancergenome.nih.gov>). Seven Cancer Genome Characterization Centers are investigating variations in copy number, gene expression, and methylation of high-quality cancer specimens, while three sequencing centers are re-sequencing the same samples. All data are released rapidly through the TCGA data portal at <http://cancergenome.nih.gov/data/portal>. The sequencing centers began with a target list

of 602 genes culled from the literature. Now, data from the array-based characterizations have been analyzed to generate a second target list of 725 additional genes and regions. An initial TCGA consortium report describing findings from analyses of the first ~200 glioblastoma multiforme cases is in preparation. Investigations of ovarian and lung squamous cell carcinomas are queued. Still, many challenges remain for the project, especially in the area of sample procurement.

The International Cancer Genome Consortium (ICGC) has been set up to bring together international groups from interested countries. Membership is limited to projects with the ability to operate on a large enough scale to independently tackle at least one tumor type. The official launch of this consortium occurred on April 29th, 2008 . Dr. Tom Hudson, director of the Ontario Institute for Cancer Research, has served as the primary organizer. A recent announcement describes the rationale and principles supporting the formation of this consortium, and acts as an invitation for membership. ICGC membership already includes:

- **Australia:** National Health and Research Council
- **Canada:** Genome Canada; Ontario Institute for Cancer Research
- **China:** Chinese Cancer Genome Consortium
- **Europe:** European Commission
- **France:** Institut National du Cancer
- **India:** Department of Biotechnology, Ministry of Science & Technology
- **Japan:** RIKEN, National Cancer Center
- **Singapore:** Genome Institute of Singapore
- **United Kingdom:** The Wellcome Trust; Wellcome Trust Sanger Institute
- **United States:** National Institutes of Health (NIH)

Each ICGC member plans to conduct a comprehensive, high-resolution analysis of the full range of genomic changes in at least one specific type or subtype of cancer, with studies built around common standards of data collection and analysis. Each project is expected to involve specimens from approximately 500 patients and have an estimated cost of \$20 million. All ICGC data will be released rapidly and be freely available to the global research community. For more information, see <http://www.icgc.org> . NHGRI, NCI, and the TCGA research network are expected to provide important leadership functions for the ICGC.

ENCODE/modENCODE. The ENCODE and ModENCODE projects are designed to define functional elements of human and model organism genomes. NHGRI funded an ENCODE Data Analysis Center (DAC) at EBI to work with the ENCODE Analysis Working Group and the ENCODE Data Coordination Center to coordinate, support, and assist in the analysis of data produced by the ENCODE Consortium. Meetings of the ENCODE and ModENCODE consortia are planned for June, which will also provide an opportunity for the external consultants panel to review progress.

KOMP. A meeting of the International Knockout Mouse Consortium was held Tuesday May 13th, which revealed both a number of challenges with the international consortium and also the potential of the international group to accomplish the scientific goals of the

project. Currently there are approximately 5,000 knockouts in hand, with the target for 2011 being 21,000.

MGC. The Mammalian Gene Collection program is preparing for its final External Steering Committee Meeting on September 22nd and an open symposium the following day to present research that has benefited from the work of the MGC. A manuscript is currently in preparation that will summarize the final results and key findings of the program.

HMP. The Human Microbiome Project is proceeding in the Jumpstart phase. The Genome Centers at Baylor College of Medicine, the Broad Institute, the J. Craig Venter Institute and Washington University School of Medicine have received jumpstart funds in October 2007 to generate the genome sequences of 200 microbial strains (representing human-associated oral, nasal, vaginal, gut and skin microbes), to recruit donors and secure microbiome samples, and to perform metagenomic sequencing of the microbiome samples. Strain selection, donor recruitment and metagenomic sampling protocols are nearing completion. Preliminary standards to allow accurate base calling and faithful assembly and annotation from the 454 read-outs have been proposed. An interim Data Analysis and Coordination Center (DACC) has been created to facilitate project tracking as well as protocol and data sharing. RDP and Greengenes are both being investigated as potential rRNA databases. An interim advisory committee of five advisors has been appointed for the Jumpstart phase. Applications responding to an RFA to fund demonstration projects are now not due until June.

Molecular Libraries. Molecular Libraries continues to develop its capacity to put new small molecular research reagents into the hands of individual academic researchers, providing the sort of resources that are normally only available in the industrial domain. The pilot phase, which ends next month, has been successful and there is now a great deal of effort going on to effect the move into the full phase. Solicitation for proposals to participate in the full phase was done by a two-part process, with an initial RFA for X02 pre-proposals to allow focus on the most competitive applications, which were then invited to submit a the full U54 application. Of the ten centers that participated in the pilot phase, eight have been asked to submit full applications. The plans for the full phase involve a mix of comprehensive centers, specialized screening centers, and specialized chemistry centers. The applications have been reviewed and a funding plan is under development. Recently the EPA has expressed interest in the potential to predict human toxicology without doing animal tests by using the infrastructure developed by these centers for high-throughput compound screening.

Statistical Genetics. A workshop to discuss research training needs in statistical genetics and genetic epidemiology is currently being planned. The participants in the NIH Director's 2008 NIH Leadership Forum noted that there is an increasing number of genome-wide association studies being supported, and as the technology moves from genotyping to sequencing the community will be deluged with data that will require interpretation by scientists who can: (1) develop new methods of analyses and (2) perform the analyses. There is concern that there are not enough sufficiently trained

scientists to carry out this aspect of the research. On May 21, NHGRI and NIGMS staff will be convening a small workshop to discuss this issue.

ELSI. The meeting “Translating ELSI” was held in Cleveland from May 1-3, hosted by one of the CEERs. In total, 175 abstracts were submitted and selected for an oral presentation or a poster. Presentations were organized into 3 tracks: research, clinical, and society. The vast majority of science presented was funded by the regular ELSI program (some under RFAs, such as the CEERs, but most as result of investigator-initiated grants). The meeting was preceded by a trainee workshop and a grant writing workshop, both of which were found by the participants to be effective and valuable.

NHGRI – INTRAMURAL PROGRAM

NIH Intramural Center for Genomics and Health Disparities (NICGHD). The NICGHD is a new venue for research into the way that populations are affected by disease, including obesity, diabetes and hypertension. NICGHD will employ a genomics approach, collecting and analyzing genetic, clinical, lifestyle and socio-economic data to study a range of clinical conditions that have puzzled and troubled public health experts for decades. The trans-NIH center will be directed by internationally renowned genetic epidemiologist Charles N. Rotimi, Ph.D., former director of the National Human Genome Center at Howard University who will be making a presentation later in the Open Session.

Type 2 Diabetes genes. An international team that included scientists from the NHGRI has identified six more genetic variants involved in type 2 diabetes, boosting to 16 the total number of genetic factors associated with increased risk of the disease. Intriguingly, the new variant most strongly associated with type 2 diabetes also was recently implicated in a very different condition, prostate cancer. The unprecedented analysis combined genetic data from more than 70,000 people. The work was carried out through the collaborative efforts of more than 90 researchers at more than 40 centers in Europe and North America. The identification of six new genetic variants provides important clues and opportunities for potential treatments or preventions of the widespread condition.

Undiagnosed Diseases Program. A new NIH program, called the Undiagnosed Diseases Program, will be announced today with a telephone briefing for advocacy groups and for the media. This is an important collaboration between the NIH Office of Rare Diseases, the NIH Clinical Center and the NHGRI’s intramural program. The trans-NIH initiative will focus on the most puzzling medical cases referred to the NIH Clinical Center in Bethesda, Md., by physicians across the nation. This program will be an important new initiative in the NIH Clinical Center, specifically reaching out to individuals throughout the United States who suffer from diseases that their doctors have not been able to identify. While intended to be a research program with the hopes of discovering and addressing new disorders, the program will provide hope for many Americans who now struggle with mysterious illnesses.

NHGRI OFFICE OF THE DIRECTOR

dbGaP. Data from one of the first genome-wide association studies (GWAS), which focused on Parkinson's Disease and was funded in part by The Michael J. Fox Foundation for Parkinson's Research, have been deposited in dbGaP and are now being made available to researchers through the NHGRI and the National Center for Biotechnology Information (NCBI).

The NHGRI Catalog of Published Genome-Wide Association Studies. The Office of Population Genomics (OPG) has compiled a summary of the ~150 published genome-wide association studies that included at least 100,000 single nucleotide polymorphisms (SNPs) in the initial stage. The catalog will be available at <http://www.genome.gov/GWAsStudies> and will be updated regularly. Information available for each study includes the PubMed link, the number of initial and replication subjects and SNPs passing quality control, specific SNPs and alleles associated at $p < 10^{-6}$ and their genomic regions, nearby genes, frequencies, p-values and odds ratios. . Efforts are in progress to link the summary to other genomic resources. A related symposium entitled "Analyze This!" will be held by the Genes, Environment, and Health Initiative (GEI) in early August in Bethesda.

DNA Day. National DNA Day commemorates the Watson and Crick's original description of the DNA double helix in April 1953 and the completion, fifty years later, of the Human Genome Project in April 2003 and. It is an opportunity to excite students about the field of genetics and genomics, as well as to inform them of the broad career options the fields of genetics and genomics have to offer. On April 25, teachers and students across the nation joined in the annual celebration of the genome. Through the use of educational materials, online resources, and speakers, students were engaged in learning about the latest advances and technologies in genetics, and how they might get involved in the field.

For the first time, NHGRI provided small contract funding opportunities for groups to create National DNA Day programs in their own communities. Awards were made to the University of Nebraska Medical Center, Oklahoma City Community College, Miami University in Ohio, and the Wisconsin Department of Health. In addition, the Division of Extramural Research funded DNA programs at the University of Washington and Baylor College of Medicine. The Education and Community Involvement Branch (ECIBO) also partnered with the American Society of Human Genetics, the Genetic Alliance, the American College of Medical Genetics, the International Society of Nurses in Genetics, and the National Society of Genetic Counselors to bring attention to the many DNA Day events taking place this year. More than 30 Ambassadors from the NHGRI provided presentations to students at 32 local high schools in Maryland, Virginia and D.C., and to students at 11 high schools in Midwestern states, including Ohio, Michigan, Illinois, Minnesota, Missouri and Iowa. Overall, Ambassadors made DNA Day presentations for more than 3000 students.

As in previous years, NHGRI intramural investigators and trainees and staff from the Office of Director and the Division of Extramural Research answered questions in the DNA Day chatroom. A transcript of the questions and the responses from 2008 and past years are currently available on the NHGRI website. For the second year, the winners of the American Society for Human Genetics essay contest for middle and high school students were announced during the chatroom. Overall, over 1000 questions were answered during the chatroom, an increase of more than 50% compared to 2007.

Family Histroy. In March 2008 a document titled “Family Health History Multi-Stakeholder Workgroup Data Requirements Summary” was finalized following a period of public comment. The document culminates approximately 6 months of work by the Personalized Healthcare workgroup of the American Health Information Community (AHIC) on the topic of family history health information technology standards development. The document provides a summary of requirements for family history information for developers of electronic health record and personal health record software, and has been submitted to the Healthcare Information Technology Standards Panel (HITSP) as part of the Personalized Healthcare Use Case (<http://www.hhs.gov/healthit/usecases/phc.html>). This effort was lead in part by Alan Guttmacher and Greg Feero in the Office of the Director of NHGRI, as well as by members of the office of the U.S. Surgeon General and the Office of the Secretary of DHHS.

Direct-to-Consumer (DTC) Marketing. Within the past year, several private companies have started marketing genetic tests or genomic scans directly to consumers, often making claims that appear to exceed current knowledge. Spurred by these and other developments, Dr. Zerhouni charged several IC directors to organize a group to create an authoritative source of information for the public on the issue of genetic factors in common disease. The “Trans-NIH Communications Group on Genetics and Common Disease,” which has been meeting for the past few months, recently held a brainstorming session with NIH experts to develop a core set of messages around these issues. These core messages, together with fact sheets and other supporting material, will serve as the centerpiece for a new NIH website dedicated to educating consumers and health care professionals about genome scans and their current application to health care. The website will be available this summer.

OPCE. On April 1, 2008 NHGRI announced the search for a Director of the Office of Policy, Communications and Education (OPCE) in the immediate Office of the Director. This position will be a Senior Executive Service (SES) Federal career position. A number of impressive applications were received before the application deadline of May 1. The Search Committee has since met to screen these applications and will forward a number for formal interviews by NHGRI leadership. By next Council meeting, we anticipate being able to introduce a new OPCE Director.

NHGRI – POLICY

It appears that NHGRI, along with NIH in general, should be prepared for a lengthy period of a flat budget. The President's Budget request for FY 2009 for NHGRI is \$487,878,000, an increase of just \$1,099,000 from the FY2008 enacted level of \$486,779,000. However, not surprisingly in an election year, the appropriations process for FY09 is moving very slowly and is not expected to be completed this year. There has been a suggestion of providing supplemental funding to NIH, but its prospect of passing the House and Senate is unknown.

The Genetic Non-Discrimination Act (H.R. 493, S. 358) has been passed by both houses of Congress and is awaiting the President to sign the bill into law, which should occur as early as this week. Regulations to implement the bill will be written over the next year by HHS, DOL, and the EEOC. The insurance protections go into effect 12 months after the bill is signed into law, whereas the employment protections go into effect 18 months after the bill is signed. This topic has been under discussion since 1993.

The Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) recently released a report on the oversight of genetic testing entitled "*U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*". The report called for more oversight of genetic testing, citing "significant gaps" in validating the tests' usefulness, especially those sold directly to consumers. The mechanisms by which the recommendations of this task force will be implemented are still unclear, but the report represents an important step forward towards providing sound oversight of genetic testing.

ANNUAL REPORT ON THE DIVISION OF INTRAMURAL RESEARCH

Dr. Eric Green presented the annual report on the NHGRI Division of Intramural Research (DIR). The mission of DIR is to develop genetic and genomic approaches for understanding genome function, for identifying the molecular basis of human genetic disease, and for developing effective diagnostic and therapeutic interventions. The program was launched in 1993 and continues to be a focal point for genetics and genomics research at NIH.

Forty-six people comprise the research faculty of DIR, including 20 senior investigators, 17 associate investigators, 9 tenure-track investigators, and 4 adjunct investigators. There are a total of 520 people working in DIR, including 25 Ph.D. students (out of the 400 graduate students across the NIH intramural programs). The DIR occupies space in nine buildings in four cities across Maryland. Collaborations with outside researchers, both elsewhere at NIH and outside of NIH constitute an important approach by many DIR investigators. These collaborations are evidenced by the publication track record, which shows that of the more than 1000 papers that have come from NHGRI's DIR, approximately 60% involve collaborations outside the Institute.

The DIR is comprised of seven divisions, each of which has one or more branches. Most ranches are composed of four or five tenured or tenure-track investigators. Each division undergoes a rigorous review under the Board of Scientific Counselors (BSC) every four

years; thus, there are approximately two reviews held each year. The five-year review of the NHGRI Scientific Director was held this year, with participation by two Council members. One unique feature of the DIR that was recognized by this review is the strong functional connection among the Deputy Director, the Executive Officer, the DER Director, and the DIR director. Like much of NIH, the DIR has been experiencing flat budgets recently. Given the flat budget, it is difficult to maintain a tenure system, but it has been a major asset to the program. Despite the difficulty of recruiting in the areas of statistical and computational genomics, the leadership recognizes that these are critical areas and is seeking ways to expand this portion of the portfolio.

The NHGRI DIR represents approximately 3.7% of the total NIH intramural budget, and 20% of the total NHGRI budget. Approximately one-third of the funds go to infrastructure, such as the Clinical Center, one-third to personnel, and one-third to operating funds.

Highlights of the program include the creation of a new intramural center for genomics and health disparities, and the Undiagnosed Diseases Program (UDP), both of which were mentioned earlier in the Director's Report. Another initiative is the development of a more formal mission statement for the DIR aimed at helping to define the forces that make the intramural program uniquely valuable.

THE NIH INTRAMURAL CENTER FOR GENOMICS AND HEALTH DISPARITIES

Dr. Charles Rotimi presented the NIH Intramural Center for Genomics and Health Disparities. The mission of this new center is to advance research into the roles played by culture, lifestyle, genetics, and genomics in health disparities. The researchers involved will develop genetic epidemiology models to explore patterns of complex diseases in minority US populations, especially those of African descent. Ultimately, the goal is to develop resources that can facilitate the study of these factors in health disparities globally, thereby contributing to the knowledge and understanding of genetic and genomic factors in health disparities in a way that can translate into policies and interventions to reduce those disparities. A powerful tool in this goal is to develop a training program that focuses on minorities that are under-represented in the field, an area of focus for this project.

This program aims to fully document and describe human genetic variation and its link to disease risks in different populations. One of the motivations for the program is the belief that failure to bring a global perspective to the genomic revolution will lead to the possibility that tomorrow's medicine and technologies may not apply to US minorities or to global populations. Therefore, study of diversity is necessary to fully understand disease distribution and variable drug response within the historic and cultural experiences of human populations. Research activities falling under this umbrella include GWAS in African-Americans to search for genes associated with obesity, hypertension, diabetes, and metabolic syndromes. The Black Women's Health Study is

developing a project to conduct GWAS in 4000 African-American women, half with Type II diabetes and half without. Field work is also ongoing to investigate the genetics of Type II diabetes in West Africa. A number of other studies are proceeding to investigate hypertension, non-filarial elephantiasis, and numerous other conditions.

This program deals with many sensitive areas and has come under charge of being reductionist by focusing on with genetic variation. However, there is consensus that genetics is an important factor in many diseases and that a better understanding of how genetic variation alters susceptibility or outcomes will allow the development of more intelligent interventions. Another important understanding that will come out of the program's efforts will be the recognition that there is a tremendous amount of significant diversity within the very broad population categories most commonly used, such as African-American.

CONCEPT CLEARANCES

Genome-wide Association Studies of Treatment Response in Randomized Clinical Trials

At present, a significant number of genetic variants have been connected to drug responses. However, despite the large number of well-designed cohort studies that are performed when testing drugs, there have been very few GWA studies in this area. The randomization assigned in clinical trials, coupled with the extensive phenotypic information collected, makes them a potentially extremely valuable resource. This RFA would expand population genomics into a new area closely tied to clinical interventions. Staff proposed funding three to five investigative teams to work together in a pilot program to conduct these studies. Each research arm would need to consist of at least 2,000 individuals to ensure reasonable power. The funds would be approximately 21 million dollars over three years with roughly 10 million for genotyping costs. Council raised a concern about the potential for bias if re-consent were not to provide an even sampling of the trial population. A significant challenge of this approach will be to convince researchers to unmask the trials, even only in part, before the conclusion of the study. Council unanimously supported the proposed RFA.

Developing Statistical Methods for Applying Genomic Technologies to Population Research: Opportunities and Challenges

The presentation started with a background discussion of the NHGRI's portfolio in statistical genetics, which consists of research projects related to the development of new methods for analysis of genome-wide genetic data. Over the past eleven years, 69 distinct awards have been made to 66 PIs in 46 institutions. The total number of awards and the average award value are both rising, producing a strong but spread out community. One concern is that cutbacks, always possible in this funding climate, often force PIs to cut students, thereby reducing the future pool of researchers in this field. However, these grants do tend to be quite competitive in review and NHGRI has been

able to fund many of the strong proposals that have been submitted. The continuing challenge is to bring researchers from a wide variety of disciplines into this field.

This RFA is prompted by these concerns at a time of a great outpouring of GWA data and a large number of GWA discoveries. This has led to a series of new challenges in dealing with copy number information, rare variants, whole genome sequence data, and other information types. These challenges have led to significant programmatic needs in these areas to ensure properly nuanced analyses. It is becoming clear that a single variant may be only a small contributor to risk, and yet methods for measuring environmental modifiers, diversity, and other factors are lacking. Current investigator-initiated programs have been powerful, but NIH funding tends to be behind the curve and to miss the most exiting opportunities. Launching a Center at the heart of a consortium would allow NHGRI to rapidly respond to advances in the community, much as the Sequencing Centers have done. By bringing together a critical mass of researchers will make it possible to encourage robust development of analysis tools and approaches. After considerable discussion, Council encouraged NHGRI to articulate clearly the goals and needs and make the Institute's interest widely known without employing an RFA.

Minority Action Plan

Though there are a significant number of grantees participating in the NHGRI's Minority Action Plan (MAP), there has not been any systematic effort to analyze their efforts to determine which approaches have been successful. MAP grantee meetings have not served this purpose, since it is not an easy problem to compare different approaches with differing numbers of students and resources. NHGRI proposes to issue an RFA to solicit applications to collect and analyze outcomes of the MAP. Council supported the release of an RFA in this area.

Protein Sequence and Function Resource

Protein sequence and function resources have become key tools of biologists. Currently, NHGRI funds the UniProt Consortium, but this is a rapidly-changing field with a vast influx of new data. To continue to be successful, the database that meets these needs in the future needs to be able scale with increasing amounts of data while balancing manual and computational annotation. NHGRI staff plan to hold a workshop to address the current state of the field, the requirements for new data types, the need for scaling with increasing data volumes, community input, and training. The goal of the workshop will be to collect the input necessary to formulate an RFA to solicit proposals for a protein sequence and function database at approximately 5 million dollars per year via a U01 cooperative agreement mechanism. Since the UniProt grant terminates in September 2009, it will be necessary to move forward with developing and issuing an RFA shortly after the workshop. Council agreed with the need for a resource in this area, and approved the concept clearance pending an e-mail consultation providing more details following the workshop.

PROJECT UPDATES

Population Genomics Workshop Recommendations: Frontiers in Population Genomics Research

The Frontiers in Population Genomics Research workshop was held in December 2007 to review the current status of research in the field of population genomics and to identify new areas of emphasis for future work. The strongest recommendations were to increase community involvement, to increase minority participation, to standardize phenotype data, to document environmental exposures, to make full use of existing studies, and to translate the findings to practice. Particular areas to address were large cohort studies, follow-up to GWA studies, and the development of new database and data analysis techniques. The development of informed consent processes that engage the community remains a major challenge. NHGRI is working to develop a standard consent form template to be distributed this coming summer that would address some of these issues.

1000 Genomes

The purpose of the 1000 Genomes Project is to create a much more complete catalogue of variations in the human genome to further simplify the process of moving from a GWA hit to a causal variant. There are currently multiple pilots being performed or planned as part of 1000 Genomes. Pilot 3, the Gene-Region Pilot, will obtain deep coverage of 1000 gene regions in 900 samples to evaluate how well the new capture technologies work. Pilot 2, the Trio Pilot, will generate deep coverage of the six individuals (two trios from the YRI and CEU HapMap samples) to evaluate the depth of coverage from the new sequencing technologies that is necessary to completely characterize a genome. Pilot 1, the Low Coverage Pilot, will sequence 1000 individuals lightly, initially at 2x coverage, to see how much information can be derived from this amount of data. The HapMap samples will be used in these pilots. The full project, as currently envisioned, will involve between 1,200 and 1,500 samples and produce approximately 18,000 Gb of sequence data. The unprecedented amount of data will require a novel analysis framework that is currently under development. To date, approximately 236 Gb of data have been produced.

Informatics

With informatics playing an ever-larger role in biology, it is necessary to organize the NHGRI informatics portfolio in a way that optimizes its efficiency. There are short-term steps that can be taken to this end, such as increasing interpretability and developing data standards, and longer-term steps, such as the development of metrics by which the informatics resources can be measured and compared. In order to begin working on these goals, the PIs of the P41 and U01 NHGRI informatics grants have been brought together to form the steering committee of the Genome Research Informatics Network (GRIN). GRIN will convene various sub-groups to deal with these and other issues. In order to provide guidance to the GRIN, the Informatics Advisory Panel (IAP), a sub-committee of

this Council, has also been formed. Charter documents for both of these groups have been developed and GRIN has met by teleconference three times and IAP once. Initial progress of the GRIN has been slow, due both to the complexity of the problems and a low level of PI involvement, but the calls are continuing and one of the PIs will co-chair the meetings each quarter. Resources not included in the NHGRI portfolio have expressed interest in becoming part of this group, so it may eventually be expanded to include these other informatics resources.

GTEX

The Genotype-Tissue Expression (GTEX) Resource, a new proposed Roadmap project, is preparing to move forward. The goal of this project is to facilitate the discovery of causal variants from GWA studies, by providing investigators with information about the RNA expression levels of genes across many tissues in densely genotyped individuals and to discover those genes whose expression level varies with genotype (so-called expression quantitative trait loci or eQTLs). As was recently demonstrated in an asthma study, finding intersections between GWAS hits and eQTLs can help to identify putative causal variants. A workshop will be held soon to address a number of initial questions, such as which tissues would be the most important to analyze, the feasibility of obtaining tissues, and the appropriate number of donors.

COUNCIL-INITIATED DISCUSSION

Council suggested that Dr. Kathy Hudson be invited to make a presentation about what she has learned in conducting town meetings and surveys about public receptivity for a large, population-based longitudinal study. The presentation could also address the question of public receptivity for genetic and genomic research in general.

The Council also requested updates or presentations on TCGA and the ICGC.

Council expressed continued interest in hearing a presentation on informatics when the new sequencing technologies are farther down the implementation pipelines.

ANNOUNCEMENTS AND ITEMS OF INTEREST

Dr. Guyer directed Council to the Council folders containing items of interest.

CONFLICT OF INTEREST

Dr. Guyer reads the Conflict of Interest policy to Council and asked them to sign the forms provided.

REVIEW OF APPLICATIONS

In closed session, the Council reviewed 188 applications, requesting \$72,987,422. The applications included 70 regular research grants, 15 ELSI grants, 77 RFA grants, 2 center grants, 1 conference grant, 1 career transition award, 1 institutional training grant, 4 individual training grants, 1 continuing education training program grant, 11 SBIR Phase I grants, 2 SBIR Phase II grants, 1 STTR phase I grant, and 2 STTR phase II grants. A total of 107 applications totaling \$45,594,562 were recommended.

I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.

Date Mark Guyer, Ph.D.
 Executive Secretary
 National Advisory Council for Human Genome Research

Date Alan Guttmacher, M.D.
Acting Chairman
National Advisory Council for Human Genome Research