NATIONAL ADVISORY COUNCIL FOR HUMAN GENOME RESEARCH
SUMMARY OF MEETING[1]
May 18, 2009

The Open Session of the National Advisory Council for Human Genome Research was convened for its fifty-sixth meeting at 8:32 A.M. on May 18, 2009 at the Fishers Lane Conference Center, Rockville, MD. Alan Guttmacher, Acting Director of the National Human Genome Research Institute, called the meeting to order.

The meeting was open to the public from 8:32 A.M. until 3:35 P.M. on May 18, 2009. In accordance with the provisions of Public law 92-463, the meeting was closed to the public from 3:35 P.M. on May 18, 2009 until adjournment for the review, discussion, and evaluation of grant applications.

Council members present:

Michael Boehnke, *ad hoc*
Eric Boerwinkle
Mark Chee, *ad hoc*
Rex Chisholm, *ad hoc*
Richard Cooper
Jorge Contreras Jr.
Richard Gibbs
Geoffrey Ginsburg
Caryn Lerman
Patrice Milos
Richard Myers
Pearl O'Rourke
Pilar Ossorio
David Page (by teleconference)
Paul Sternberg Jr.
David Valle
Richard Weinshilboum

Council members absent:
Claire Fraser-Liggett

Ex officio members absent:
None

[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".

Staff from the National Human Genome Research Institute:

Ajay, DER
Sanja Basaric, OD
Tsegahiwot Belachew, DER
Vivien Bonazzi, DER
Vence Bonham, OD
Ebony Bookman, OD
Joy Boyer, DER
Lisa Brooks, DER
Comfort Browne, DER
Joseph Campbell, DER
Debbie Chen, DER
Cheryl Chick, DER
Monika Christman, DER
Priscilla Crockett, DER
Christine Cutillo, DER
Camilla Day, DER
Karen DeLeon, OD
Elise Feingold, DER
Adam Felsenfeld, DER
Barbara Fuller, OD
William Gahl, OD
Jonathan Gitlin, OD
Mary Glynn, OD
Peter Good, DER
Bettie Graham, DER
Eric Green, DIR
Alan Guttmacher, OD
Mark Guyer, DER
Linda Hall, DER
Sarah Harding, OD
Lucia Hindorff, OD
Christopher Juenger, DER
Heather Junkins, OD
Rebecca Kolberg, OD
Rongling Li, OD
Carson Loomis, DER
Teri Manolio, OD
Jean McEwen, DER
Keith McKenney, DER
Lisa McNeil, OD
Enrique Michelotti, DER
Janis Mullaney, OD
Anita Nagwani, OD
Ken Nakamura, DER
Brad Ozenberger, DER
Jane Peterson, DER
Rudy Pozzatti, DER
Ed Ramos, OD
Jacqueline Reindl, DER
Cristen Robinson, DER
Laura Rodriguez, OD
Jeff Schloss, DER
Geoff Spencer, OD
Jeff Struewing, DER
Larry Thompson, OD
Elizabeth Thomson, DER
Susan Vasquez, DER
Lu Wang, DER
Christopher Wellington, DER
Kris Wetterstrand, DER
Rosann Wise, OD
Julia Zhang, DER

Others present for all or a portion of the meeting:
Diane Baker, Genetic Alliance
Joann Boughman, American Society of Human Genetics
Sharon Olsen, International Society of Nurses in Genetics
Rhonda Schonberg, National Society of Genetic Counselors
Mike Watson, American College of Medical Genetics

INTRODUCTION OF NEW MEMBERS AND STAFF, LIASONS AND GUESTS

Dr. Guyer noted that the new Council slate has been approved, but three of the new members have not completed their paperwork and are participating at this meeting as *ad hoc* Council Members: Michael Boehnke, Mark Chee, and Rex Chisholm.

Dr. Guyer introduced new NHGRI staff: Ebony Bookman, Epidemiologist on detail with the Office of Population Genomics; Joseph Campbell, DER; Jonathan Gitlin, Program Analyst, Policy Branch, OD; Rongling Li, Epidemiologist, Office of Population Genomics; Enrique Michelotti, Medicinal Chemist, DER; Jacqueline Reindl, Program Analyst, DER.

Dr. Guyer welcomed members of the press and liaisons from professional societies:
Diane Baker, Genetic Alliance
Joann Boughman, American Society of Human Genetics
Sharon Olsen, International Society of Nurses in Genetics
Rhonda Schonberg, National Society of Genetic Counselors
Mike Watson, American College of Medical Genetics

APPROVAL OF MINUTES

The minutes from the February 2009 Council meeting were approved as submitted.

FUTURE MEETING DATES

The following dates were proposed for future meetings: September 14-15, 2009; February 8-9, 2010; May 17-18, 2010; September 13-14, 2010; and February 7-8, 2011; May 16-17, 2011

DIRECTOR'S REPORT

I. GENERAL ANNOUNCEMENTS

Kathleen Sebelius Confirmed as Secretary of HHS
Kathleen Sebelius was sworn in as Secretary of HHS on April 29, 2009.

Applications Invited for NHGRI Director
NIH is accepting applications for the position of Director, NHGRI. The application deadline has been extended to July 17, 2009. For more information, see http://www.genome.gov/27529636 or contact Regina Reiter at (301) 402-1130. Applicants must possess an M.D., Ph.D., or comparable degree in the health sciences field; should have senior-level experience and comprehensive scientific knowledge of research programs in an area relating to genetics or molecular biology; and should have expertise in policy and ELSI issues relating to genetic research.

2009 Service to America Medals
Dr. Jeffery Schloss of NHGRI's Division of Extramural Research was one of only 30 federal employees nationwide who were named today as finalists for the "Service to America" 2009

awards (http://servicetoamericamedals.org/SAM/finalists09/stm/schloss.shtml). This prestigious award "pays tribute to America's dedicated federal workforce, highlighting those who have made significant contributions to our country (see http://servicetoamericamedals.org/SAM/). Honorees are chosen based on their commitment and innovation, as well as the impact of their work on addressing the needs of the nation." The Service to America awards recognizes achievement in each of eight categories. That Jeff is one of only three finalists for the Science and Technology Medal is testimony to the quality of his work and – as Jeff would be the first to point out - that of his colleagues at NHGRI. Award winners will be announced in September 2009.

New Members Elected to the NAS

On April 28th, NACHGR member Paul W. Sternberg was among the 72 new members, including and 18 foreign associates from 15 countries, elected to the National Academy of Sciences in recognition of their distinguished and continuing achievements in original research. The election was held during the business session of the 146th annual meeting of the Academy. Those elected bring the total number of active members to 2,150.

Stem Cells

In March, President Obama issued an executive order removing barriers to the responsible scientific research involving human stem cells (hESC). NIH draft hESC guidelines are out for public comment and will be issued in final form by July 2009.

NHGRI Planning Process for Future of Genomic Research

At the February 2008 meeting, Council approved a staff recommendation that NHGRI embark upon a new long-range planning process. This began in April 2008 and is tentatively scheduled to be completed in late 2010, with the articulation of a new vision for genomics research. The process will involve a wide-ranging assessment of the state of the art in genomics and discussion of where the field should go in the next several years. This is intended to help NHGRI and others plan their research investments to further the use of genomics to improve human health and other applications. The planning process will involve a range of activities, including on-line opportunities, workshops, and other forums, through which the research and medical communities, and the public, can provide input.

In December 2008, NHGRI developed four draft white papers that posed specific questions for broad community input. The draft questions were posted on the web through February 2009 for community comment, and those received were used to modify the questions. In April 2009, revised white papers were posted, with a request for community response to the questions. The input received was received through June 30, 2009 will feed into future planning activities and workshops. The four white papers are:

- Applying Genomics to Clinical Problems – Diagnostics, Preventative Medicine, and Pharmacogenetics, written by David Valle, M.D., and Teri Manolio, M.D., Ph.D.
- Applying Genomics to Clinical Problems – Therapeutics, written by Harry Dietz, M.D., and Christopher Austin, M.D.
- A Vision for the Future of Genomics: Education and Community Engagement, written by Vence Bonham, J.D., and Sharon Terry, M.A.
- The Future of Genome Sequencing, written by Adam Felsenfeld, Ph.D. and Mark Guyer, Ph.D.

Funding Opportunities
See TAB F

II. NHGRI – EXTRAMURAL PROGRAM

Sequencing
An international research consortium, funded by multiple sources including NHGRI, published an analysis of the domestic cattle (Hereford breed) genome sequence in the journal *Science* on April 23, 2009. The project estimated that the genome of the domestic cattle (*Bos taurus*) contains approximately 22,000 genes and shares about 80 percent of its genes with the human genome. Chromosomal rearrangements were found to affect genes related to immunity, metabolism, digestion, reproduction and lactation. The bovine HapMap, which was published in the same issue of *Science,* indicates that present day cattle came from diverse ancestral populations from Africa, Asia and Europe, but have undergone a recent rapid decrease in effective population size, presumably due to domestication. See:
http://www.sciencemag.org/cgi/content/short/324/5926/522

TCGA and Cancer Genomics
NHGRI and NCI continue to work together closely to conduct comprehensive genomic analyses of cancers in The Cancer Genome Atlas program (TCGA). The TCGA research network is currently assembling and analyzing data on ovarian cancer. Gene expression, copy number variation and methylation data from ~200 specimens are available already from the TCGA data portal. These same specimens are being investigated at the NHGRI genome centers by both targeted and whole genome sequencing approaches. Of particular note, genomes of 3 ovarian and 3 glioblastoma tumor/normal pairs have been sequenced in their entirety, revealing rich new information, such as small rearrangements and novel mutations, that would be missed by any other approach. Many additional whole cancer genome studies are in the queue. Looking ahead, the TCGA program expects to complete interim analyses on ovarian cancer during the summer and begin ramping up for several new projects in the second half of this year. In addition to the TCGA program, there are smaller complementary studies continuing in the large-scale centers under the auspices of the Tumor Sequencing Project Consortium. Furthermore, the opportunity to apply next-generation sequencing methods to cancer genomics is not limited to the U.S., but is also being pursued by the global cancer and genomics communities. The International Cancer Genome Consortium, founded to coordinate projects around the world, is gaining momentum. Members are meeting face-to-face next month at the Sanger Institute to renew commitments to investigate specific cancers and to formalize agreements on principles and standards.

Sequencing Technology Development
The fifth annual grantees meeting was held in La Jolla at the end of March 2009. 110 investigators and students attended. Each awardee gave a talk and presented a poster. This meeting offers grantees an important way to establish collaborations and obtain a sense of current research. Mark Chee attended part of the grantees meeting as a program advisor. An open public meeting was held the day after the grantees meeting.

ENCODE and modENCODE

A joint meeting of the ENCODE and modENCODE Consortia was held on March 25-27, 2009. The meeting focused on data integration and the identification of production bottlenecks. A marker paper describing the scope and plans of the modENCODE Consortium has been accepted in principle for publication; it is currently undergoing editing and awaiting final acceptance. ENCODE has selected a series of common cell lines for all groups to work on. Tier 1 consists of two cell lines. Tier 2 has five, including one hES cell line, which is the same cell line being used by the Epigenomics Roadmap project. At an ENCODE Analysis Working Group workshop planned for July, the integration of the various data types from the Tier 1 cell lines will be worked on. The modENCODE project has plans for an Analysis workshop in September.

CEER Meeting

From March 4-6, 2009, there were two Centers for Excellence in ELSI Research (CEER) workshops. The first was a Trainee Workshop that focused on research budgets and work/life balance. The second was a PI Workshop that focused on the role of the CEERs in ELSI research & policy development. Several outside experts were invited to participate to discuss emerging issues, what ELSI research will be needed, and how the CEERs can contribute.

Pharmacogenomics

In a large-scale study and an upcoming clinical trial, scientists supported by the National Institutes of Health will address the ability of genomic analysis to help with one of the trickiest issues in prescribing medicine -- how to quickly optimize each patient's dosage of the common blood-thinning drug warfarin. Using information from thousands of genetically and geographically diverse patients, an international team of researchers, funded in part by NHGRI, has developed a way to use genetic information from patients that could help doctors better determine optimal warfarin doses. The results of the analysis are published in an article titled "Warfarin Dosing Using Clinical and Pharmacogenetic Data" in the Feb. 19 issue of *The New England Journal of Medicine* (http://content.nejm.org/cgi/content/short/360/8/753). Also, NIH is launching a large prospective, multi-center, randomized clinical trial in the United States to test whether a gene-based strategy for prescribing the initial warfarin dose will improve patient outcomes. The clinical trial will use a dosing strategy similar to that developed in the international study. The trial will enroll 1,200 participants of diverse backgrounds and ethnicities at twelve clinical sites, and is scheduled to begin next month.

III. NHGRI – INTRAMURAL PROGRAM

Skin Cancer Study Uncovers New Tumor Suppressor Gene

A collaborative group from NIH, led by NHGRI intramural researchers, has identified a gene that suppresses melanoma tumor growth. The finding was reported in *Nature Genetics* (http://www.nature.com/ng/journal/v41/n5/full/ng.340.html) as part of a systematic genetic analysis of a group of enzymes implicated in skin cancer and many other types of cancer.

This analysis found that one-quarter of human melanoma tumors had changes, or mutations, in genes that code for matrix metalloproteinase (or "MMP") enzymes. The collaborative team also found that *MMP-8* actually serves as a tumor suppressor gene in melanoma. Consequently, in the estimated 6 percent of melanoma patients whose tumors harbor a mutated *MMP-8* gene or related tumor suppressor(s), it may not be wise to block all MMPs. The study suggests that a

better approach may be to look for drugs that restore or increase MMP-8 function or for drugs that block only those MMPs that are truly oncogenes.

Researchers Devise New Way to Explore DNA
A team that includes the NIH, including researchers from NHGRI, has found a new way of detecting functional regions in the human genome. The novel approach involves looking at the three-dimensional shape of the genome's DNA, rather than just reading its sequence.

In a paper published in the early online edition of *Science* (http://www.sciencemag.org/cgi/content/full/324/5925/389), a team led by Thomas Tullius, Ph.D., of Boston University and Elliott Margulies, Ph.D., of NHGRI, described an innovative approach for detecting functional genomic regions. By combining chemical and computer analyses, the researchers survey the landscape, or topography, of DNA structure for areas likely to play a key role in biological function. The method involves identifying all of the grooves, bumps and turns of the DNA that makes up the human genome and then comparing those structural features to those seen in the genomes of other animal species. Structural features that have been preserved across many species are likely to play important roles in how the human body functions.

Familial Lung Cancer Gene Located
A consortium that included scientists from the NHGRI has identified a gene associated with an increased susceptibility for lung cancer in members of families with a history of the disease. The new finding is reported in the April 15, 2009 issue of the journal *Clinical Cancer Research* (http://clincancerres.aacrjournals.org/cgi/content/abstract/15/8/2666).

The investigators conducted fine-mapping of the suspect region of chromosome 6 in members of families in which five or more individuals over multiple generations had been diagnosed with lung cancer. The region contains approximately 100 genes. Precise computational analysis uncovered similar SNPs in the DNA sequence for members of the families with lung cancer that directed them to the gene, *RGS17*.

Lung cancer samples were more likely to have a version of the *RGS17* gene that produces high levels of the encoded protein than were normal tissue samples from individuals with no cancer. The conclusions of this analysis are that *RGS17* plays a major role in lung cancer susceptibility, and individuals who carry the higher-risk version of this gene have an increased susceptibility to lung cancer when exposed to environmental risk factors, such as smoking.

IV. ROADMAP PROGRAMS

Molecular Libraries Probe Production Centers Network (MLPCN)
The MLPCN will complete the first year of the production phase next month. The first year has been a building and organizational year for the screening centers as they ramp up to a maximum probe production rate of 2 assays per month against a 300,000 compound library. Two specialized chemistry centers met first-year milestones of receiving and starting work on 15 chemistry projects transferred from the screening centers.

An evaluation of the three years of the pilot phase showed that the pilot screening centers completed 283 HTS assays averaging 93,000 compounds screened per assay. Over this period, 90% of the HTS assays found tractable hits for follow up chemistry and 25% of the assays produced a probe.

Human Microbiome Project (HMP)
Awards for the demonstration projects are expected to be made by June 1.

V. NHGRI OFFICE OF THE DIRECTOR

Population Genomics.
The GENEVA consortium of 14 genome-wide association studies is setting new standards for cleaning of GWAS genotype data and identification of chromosomal abnormalities, with plans to make these tools widely available to the scientific community. The NHGRI GWAS catalog is maintaining a turnaround time of two weeks from publication date to posting through the outstanding efforts of Lucia Hindorff and Heather Junkins; it now includes over 300 publications and over 1,400 SNPs associated at $p < 10^{-5}$ in over 95 diseases and traits. Erin Ramos and Laura Rodriguez have also finalized a valuable online resource of materials related to informed consent for genomic research; this was previously reviewed by Council and has been vetted with the scientific community. It includes specifics of elements tailored to genomic research and examples of consent forms for the GENEVA, Medical Sequencing, and 1000 Genomes projects.

Free Online Toolkit Provides Standard Measures for Genome and Population Studies
In mid-April, NHGRI announced release of the first products from the "Consensus Measures for Phenotypes and EXposures (PhenX) initiative." PhenX is supported by a $6.8 million cooperative agreement from NHGRI and is coordinated by RTI International in Research Triangle Park, N.C. The three-year project will engage domain-specific expert working groups to develop a set of standard measures across 20 research categories related to health and common diseases. This initial release contains standard measures selected by the project's working groups in three categories: demographics, anthropometrics, and use of alcohol, tobacco and other substances. Additional domains are under development and will be released over the next two years.

Researchers Uncover Genetic Clues to Blood Pressure
In a genome-wide association study of over 29,000 participants, researchers scanned millions of common genetic variants of individuals from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium to find variants associated with blood pressure and hypertension. This extensive resource includes white men and women from the Framingham Heart Study, Atherosclerosis Risk in Communities study, Cardiovascular Health Study, the Study, the Rotterdam Extension Study, and the Age, Gene/Environment Susceptibility Reykjavik Study.

The investigators identified a number of SNPs associated with systolic blood pressure, diastolic blood pressure, and hypertension. When they jointly analyzed their findings with those from the GWAS of over 34,000 participants in the Global BPgen Consortium (whose results are presented in an accompanying paper in the same issue of Nature Genetics

http://www.nature.com/ng/journal/vaop/ncurrent/abs/ng.361.html), they identified 11 genes showing significant associations across the genome: four for systolic blood pressure, six for diastolic and one for hypertension.

National DNA Day
NHGRI Ambassadors traveled to high schools in DC, Maryland, Virginia, Minnesota, New Mexico, Texas, Utah and Colorado. The DNA Day Facebook page has over 950 friends. This year's chatroom featured 18 experts (including experts from the partnering organization National Society of Genetic Counselors) answering questions from various locations in the US and 40 NIH experts located on the main campus of NIH. The experts answered 99% of the almost 900 vetted questions received.

Office Of Ethics – NHGRI
There was a recent Program review by DHHS Office of General Counsel. The report was extremely positive; the NHGRI Office was seen to be an exemplary program with many elements that exceeded regulatory requirements and a number of best practices in place. The program, which is led by Barbara Fuller, will be used as a model across HHS.

VI. NHGRI – POLICY

Intellectual Property and Human Genes
The draft SACGHS IP report has been out for comment; the comment period closed on May 15th.

On May 12th, the American Civil Liberties Union and the Public Patent Foundation at Benjamin N. Cardozo School of Law filed a lawsuit charging that patents on BRCA1 and BRCA2 are unconstitutional and invalid. The lawsuit was filed on behalf of four scientific organizations, the Association For Molecular Pathology, the American College Of Medical Genetics, The American Society For Clinical Pathology and the College Of American Pathologists, Breast Cancer Action, representing more than 150,000 geneticists, pathologists, and laboratory professionals, as well as individual researchers, breast cancer and women's health groups, genetic counselors and individual women. The lawsuit, *Association for Molecular Pathology, et al. v. United States Patent and Trademark Office, et al.*, was filed in the United States District Court for the Southern District of New York in Manhattan against the Patent and Trademark Office, Myriad Genetics and the University of Utah Research Foundation, which hold the patents on the BRCA genes.

Council discussed the ACLU lawsuit challenging the patent of the BRCA genes. Mike Watson from ACMG was asked to provide comment as one of the plaintiffs in the lawsuit. The ACMG was asked by the ACLU to join the case, but Dr. Watson was unable to comment further. Council member Pilar Ossorio was asked to comment on the historical precedence of the case. Patents have never been tested in court, in part because of the deterrent presented by cost; it takes approximately $1.5-2.5 million dollars to challenge a patent. The U.S. Patent Office views genes as natural matter (like a chemical), so that purification and isolation represent an inventive activity. The Supreme Court has not given any indication about its stance on patenting genes. If the Court were to say that genes are not patentable, it would negate many of the current gene

patents. If this case were to go to the Supreme Court, the estimated time before a ruling could be as long as five years.

Dr. Guttmacher suggested that if Council would like a longer presentation about patent law and this particular case, this could be considered for next Council round.

Appropriations Update
The Federal government operated for the first six-months of the fiscal year under a Continuing Resolution. A final omnibus agreement for the FY 2009 budget was signed into law on March 12, 2009. The FY2009 enacted level for the NIH was $30.5 billion. For the NHGRI, it was $502.4 million, an increase of $15.6 million over FY2008. Included in the FY2009 Appropriations for the NIH was $24 million to the Office of the Director, NIH for initiation of a research program, to be coordinated by the Office of Rare Diseases Research (ORDR), focused on the development of therapeutics for rare and neglected diseases. The NHGRI is working closely with the ORDR to develop program plans for this exciting new focus area. More details will be presented at future Council meetings.

President Obama sent the FY2010 budget request to Congress on May 7, 2009. Approximately $31 billion was requested for the NIH, including $509.6 million for the NHGRI. This would be an increase of $7.2 million for the Institute. The House of Representatives has already held a series of Appropriations hearings on the NIH Budget, and the Senate will begins its deliberations on Thursday of this week with testimony from Dr. Raynard Kington, Acting Director, NIH about the FY2010 NIH budget and proposed programs.

Genetic Information Non-Discrimination Update
On Thursday May 21, 2009, the provisions within the Genetic Information Non-Discrimination Act (GINA) pertaining to health insurance decision-making will go into effect. This law provides a baseline of protection for all Americans against discrimination in health insurance or employment decisions on the basis of their genetic information.

Several Departments are expected to promulgate regulations pertaining to their jurisdictions later this week. The regulatory issuance will include provisions from HHS (including the Center for Medicare and Medicaid Services and the Office of Civil Rights), the Department of Labor, and the Department of Treasury. Due to the short timeline under the statute of only twelve months for regulatory development, many of the regulations will be released as Interim Final Rules and will include a public comment period after publication for members of the public to share their feedback. Dr. Guttmacher urged the Council members to review the regulations when they are released and to share their comments with the respective agencies based on their technical and practical experience in genetics and related fields.

The provisions of the law relevant to employment practices will go into effect on November 21, 2009. The Equal Employment Opportunity Commission is actively working to finalize the regulations pertaining to GINA's protections within the employment realm, and they are expected to be released in advance of the November effective date.