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.

In addition to the direct work that has been underway to develop the GINA regulations, important discussions have also been taking place about the implications of GINA for those conducting and overseeing research with human subjects. These discussions culminated in the release of two documents on March 24, 2009. The first is a Guidance document from the Office for Human Research Protections for Investigators and IRBs; the second is a series of FAQs for researchers and health care providers. The latter was developed with strong input from NHGRI staff. The documents were developed concurrently and include an overview of the bill and its provisions, as well as the Guidance that provides input from the OHRP on considerations for IRBs in reviewing genetics protocols and informed consent documents.

INTERNATIONAL DATA RELEASE WORKSHOP

Dr. Mark Guyer presented a summary from the May 12-13, 2009 International Data Release Workshop, held in Toronto, Canada. The meeting was organized by several funding agencies, including Genome Canada, NHGRI, Wellcome Trust, NSF, the European Commission, and the Biotechnology and Biological Sciences Research Council of the UK (BBSRC). The meeting was co-chaired by Ewan Birney of the European Bioinformatics Institute and Tom Hudson of the Ontario Institute for Cancer Research. Approximately 100 people from a broad swath of the biological and biomedical research communities were in attendance. Three Council members, Jorge Contreras, Rex Chisholm, and David Valle, were among the attendees. The purpose of the meeting was to update previous discussions about pre-publication data release from community resource projects. These are projects that are initiated to create data resources of widespread broad utility, and one of the goals of mandating rapid release of data from them is to maximize utility and community benefit.

The vast majority of the attendees supported the fundamental tenets from the earlier Fort Lauderdale, Bermuda and Amsterdam meetings. They strongly supported data release no later than time of publication (or end of project) as a general rule for scientific research. Beyond that, rapid pre-publication release was deemed to be desirable and thought to be mandatory for projects that have certain characteristics, such as being of large-scale, broad utility, that produce a reference data set, and that have prior community buy-in. It was also strongly recommended that to enable such a system to work, funding agencies must set clear policies about data release in any Call for Proposals and timelines should be established by time of funding. It was recommended that the proposed data release policy be addressed in the peer review of proposals.

There was considerable discussion at the Toronto meeting about best practices for data users and producers. The meeting concluded that data users should use the data as extensively as possible but must be aware that pre-publication data can change; users should also respect the opportunity of the producers to publish a first global analysis of the resource data set. Communication between users and producers was seen as being beneficial and potentially reducing the possibility of publication conflict. Users were also reminded that they should always cite the source of data. Data producers, in turn, were seen to have the responsibility to make the data readily available, to describe the project in a citable manner, such as in marker paper or on a project website, to inform users of their production and analysis plans, and to provide contact information. It was noted that best practices for data release that involves data from human participants have

additional aspects, such as being under a controlled access process, to protect the identity of participants.

Other points that were raised in the discussion were that the scientific community needs to recognize that we are in a very rapidly changing environment and that best practices for data release are evolving, that some projects need to be exempted from these best practices (e.g., when consent forms do not allow for data release or if a project has only a small number of participants who could potentially be identified through use of the data). It was thought that the issue of incentives for investigators to adopt these best practices more widely needs more thought and attention and that the culture of science and how it relates to the idea of rapid data release needs to be examined closely.

The conclusions from the meeting are being written up and a manuscript will be submitted to a peer- reviewed journal. A formal meeting report will also be developed for circulation to funding agencies.

The Council members who were at the meeting also noted that there were differences of opinion among the attendees about the goals of the meeting. Some participants indicated ambivalence about pre-publication data release in general, while others expressed concern about clinical researchers being possessive of their data and not willing to share with the greater community. Meeting attendees who were from scientific journals made it clear that the journals did not want the role of enforcer of data release policies. The concept of intellectual property was discussed and the potential problem, as data get more and more relevant to human medicine, that institutions will be reluctant to allow data to be shared due to patent issues. It was acknowledged that, with only 100 attendees, not all relevant areas were represented at the meeting and a great deal of additional input is needed.

Council asked where the clinical data should be released in certain cases. Dr. Guyer replied that were was no specific discussion about this. Council member Rex Chisholm mentioned that a subgroup discussion in which he participated mentioned clinicaltrials.gov, but agreed that the focus was on providing guidance to funding agencies and changing the scientific culture, which can often act as a barrier to data release.

One Council member, noting that data release can actually cost money, particularly for clinical data, because of their complexity, suggested that funding agencies offer incentives for appropriate funding if investigators are required to release data. The size of the grant should not matter; all grants needs to be considered. It was also noted that the GAIN and ENCODE projects had specific data release policies in place before the funded research started, and that these projects could be used as good examples of how to facilitate data release.

Finally, the Toronto meeting organizers, noting that there was a long time between the Fort Lauderdale and the Toronto meeting, that data production is increasing at an accelerating rate, and that data release issues are becoming more complicated, proposed that there needs to be continuing discussion in the community and that another meeting should be held reasonably soon.

ANNUAL REPORT ON THE DIVISION OF INTRAMURAL RESEARCH, NHGRI (DIR) and INTRAMURAL CLINICAL RESEARCH PROGRAM

Dr. Eric Green, Scientific Director, NHGRI, presented the annual DIR update to Council.

There are currently 45 research faculty in DIR -- 20 senior investigators, 8 tenure-track investigators, 17 associate investigators, and 4 adjunct investigators from other NIH ICs. NHGRI DIR faculty members are a full decade younger than the typical NIH intramural investigator (average age: 57 years old).

DIR is composed of seven branches. Every branch undergoes an external review every four years under the auspices of the Board of Scientific Counselors.

The DIR has a budget of $100.3M, of which half goes to infrastructure, and the remaining portion covers personnel, operating costs and discretionary funds. There can be no mixing of extramural and intramural funds. Intramural funding varies across the NIH ICs with the total for intramural research currently representing approximately 10% of the entire NIH budget [Note added: Since the OD and a few ICs have no intramural programs, the average among ICs with intramural programs is somewhat higher].

DIR faculty published more than 200 papers in the past year, reflecting a diverse portfolio. The collection demonstrates the highly collaborative nature of the DIR. Eighty-percent of papers involved at least one investigator outside of DIR, 60% with a non-NIH investigator, and 20% included two or more DIR investigators.

In late 2008, the intramural faculty developed a new vision and mission for DIR.

The ClinSeq program serves as a bridge for activities between the NIH Clinical Center and the NIH Intramural Sequencing Center (NISC). This effort is led by Dr. Les Biesecker and aims to enroll 1,000 subjects who will consent to whole genome sequencing.

DIR has also been actively involved in other trans-NIH projects, including the Human Microbiome Project. Dr. Julie Segre is spearheading the NIH Intramural Skin Microbiome Consortium (NISMC). The first paper from this group was published in the May 2009 issue of *Science* and received coverage on the front pages of the New York Times and Wall Street Journal.

CLINICAL RESEARCH IN THE NHGRI INTRAMURAL PROGRAM

Dr. William Gahl, NHGRI Clinical Director, gave a presentation on the NHGRI clinical research program and the NIH Undiagnosed Diseases Program.

The NIH Clinical Center (CC) opened in 1953 and has seen more than 350,000 patients since then. The new Clinical Research Center opened in April 2005 with 234 beds, 1,850 employees, 1,222 credentialed physicians, and nearly 1,500 active protocols. The CC is funded by a tax on

the NIH ICs based on their intramural budgets. The total budget is $350 million and NHGRI is taxed $12 million. In return, ICs have free access to beds and CC infrastructure such as PET scans. The ICs contribute expertise in running the various laboratories and programs throughout the CC. The Medical Executive Committee, composed of department chiefs, sets CC policy. The majority of the protocols in the CC are early stage clinical trials and the remaining portion includes screening and training.

The NHGRI Office of the Clinical Director is responsible for an Institutional Review Board, bioethics core and training program, as well as credentialing, quality controls, CC ward control, consults, inquiries and reports. NHGRI has 91 protocols (53 active), 11 clinical investigators. The institute's program had 1,032 inpatient days and 1,896 outpatient days in 2008, but NHGRI only used $7 million of the $12 million 'tax' dollars that were provided to the CC. Nonetheless, NHGRI has a substantial clinical presence within the Clinical Center and its experts are involved in research on a number of rare diseases.

At a June 2007 retreat, IC Directors met to discuss ways of reinvigorating the NIH Clinical Center. One of the ideas was to create a clinic where experts can work with patients that have unknown diagnoses. The Office of Rare Diseases (ORD) receives thousands of calls per year, approximately six percent of which are patients who have never received a diagnosis. The program needed an intramural connection to enroll patients, leading to the establishment of the Undiagnosed Diseases Program (UDP). This new program is widely endorsed by NIH and NHGRI leadership. There was an initial commitment of $280,000 from ORD, and the NIH has promised more funds towards the program in Fiscal Year 2010. NHGRI has agreed to administer the program, which will be housed in the Clinical Center.

Applicants to the UDP program submit their complete medical records with a summary letter from a referring physician. The UDP Director triages the records and coordinates with NIH senior consultants to review together. It takes an average of five hours to complete the medical record review. The Director synthesizes recommendations and makes final disposition. Accepted patients come to the Clinical Center for one week, meet with the medical team, and undergo additional tests and evaluation.

In the past twelve months, the UDP has received approximately 2,000 inquiries and reviewed 750 medical records; 350 were rejected, 130 were accepted (45 children), 250 are active, and 10 patients have died. Roughly half of the cases are neurological and 100 cases are complex pediatric genetic disorders. The program receives referrals from elite medical centers across the country. Cases are rejected if the program feels that it cannot help the applicant. So far, there has been a success rate of 10-15% in finding a diagnosis, and patients are made aware of this from the beginning. Before accepting a patient, the UDP needs assurance from the referring physician that will he or she will take the patient back for follow-up care.

So far, the UDP has solved some cases, identified some new diseases and, with so many specialists coming together, has developed new protocols. The program also offers tremendous training opportunities for the medical community. It has re-established the NIH Clinical Center as the place to send fascinating clinical cases. The downsides have included complaints when

patients are turned down from the program, and the program often misses its goal of a 6-8 week response.

The need for a basic research arm for genomic analysis has been identified and several UDP cases are using cutting-edge genomic tools, such as SNP arrays and targeted and/or whole genome sequencing. In the future, the program plans to engage a larger set of NIH intramural researchers as well as international consultants via the web, and is considering creating UDP clinics at other U.S. medical centers to serve as satellites.

This program would not exist without the immense support from the NIH Director, NHGRI, and the Office of Rare Diseases. The program has received much attention in various media outlets with pieces featured on the NBC Nightly News, Newsweek, and The New York Times Magazine.

Council was supportive of the new program, pointing out that some diseases are Mendelian but that the majority are complex and this area needs more research. As for the potential expansion plans, Council was concerned that only seasoned professionals would be qualified to participate. This could make finding candidates very difficult. With satellite centers, the cost is in the support staff to review and maintain records and coordinate patients. Council suggested that the program should try to disseminate knowledge through forums and publish case studies. The program could also serve as a model for the extramural world (e.g., CTSAs).

AMERICAN RECOVERY & REINVESTMENT ACT (ARRA)

The ARRA appropriated $10 billion over two years to NIH for economic stimulus, to create and preserve jobs, and to advance biomedical research. An additional $400 million was transferred to NIH to support comparative effectiveness research (CER). Each IC was allocated a proportional amount based on the size of its extramural budget. NHGRI received a total of $127 million, over FY09 and FY10. 5% ($6.351 million) will be used for ELSI research and $0.9 million for management and administrative support. Thus, the total available for non-ELSI research support will be $119.8 million for the two years.

The NIH's emphases for the use of ARRA funds are to accelerate research using both existing mechanisms and new NIH-wide and IC-specific programs. The NIH-wide ARRA programs include two new funding mechanisms, Challenge Grants (RC1) and Grand Opportunities ("GO" Grants, RC2). NHGRI will also participate in a program from the NIH Director's Office to provide summer jobs for high school and college students to work in laboratories.

NHGRI is still considering several ways to use its ARRA funds, including extending the paylist, supplementing existing grants, and awarding Grand Opportunity and Challenge Grants. The NHGRI has identified several areas of high priority for each of these, as well as for requests for supplements. These are all detailed on the NHGRI web site (http://www.genome.gov/27530304).

For the Challenge Grants, the areas of interest include enabling technologies through computational and statistical methods, technology and resources for functional analysis,

development of new information technology to address disease prevention and personalized medicine, and bioethics, including informed consent, direct-to-consumer personal genomics, and ethical issues raised at the interface between research and treatment. One note of interest is that nine other ICs have identified genomic technology as a priority area for Challenge Grants. The RC1 mechanism has a ceiling of $500,000 total costs per year for up to two years. The Office of the NIH Director will also use ~$200 million of its allocated funds ($800 million) to fund Challenge Grants. Building 1 hopes that the ICs will fund an equivalent number of Challenge Grants. There have been over 20,000 applications received and CSR will be using a new two-phase editorial review process as well as the new scoring system.

The Grand Opportunity Grants allow investigators to address large biomedical and behavioral research questions that will benefit from two-year funds without the expectation of NIH funding beyond two years. These grants start at $500,000 direct costs with no upper limit. NHGRI has identified seven areas of research for the GO Grants:

- Enhancing the ENCODE the modENCODE Projects,
- Development and application of statistical and computational data analysis for genomic data sets,
- Software development for sequence data,
- Development of a Data Analysis and Coordination Center for cancer genomics,
- Sequencing technology development,
- Cellular responses to perturbations, and
- Medical sequencing discovery projects.

The medical sequencing discovery research projects were included as part of the NHGRI response to the recommendations from the March 2009 sequencing workshop to support sequencing projects outside of large-scale sequencing centers that use next-generation sequencing technology in a vertically integrated setting. NHGRI also took the ARRA opportunity to introduce and pilot a new area of cellular response to perturbations.

In addition to the new funding mechanisms set forth by NIH, NHGRI has set priorities for ARRA-funded administrative supplements:

- Development and application of statistical and computational data analysis methods for DNA sequencing and other genomic data,
- Sequencing technology development,
- ENCODE/modENCODE,
- Model organism database enhancement,
- Population Genomics collaborative programs (eMERGE, GENEVA, PAGE, PhenX), and
- ELSI.

Administrative supplements do not need Council approval, unless the amount requested exceeds staff's delegated authority. There will be a teleconference scheduled for July to review the supplements.

Another trans-NIH ARRA program, support for summer jobs in research for students and teachers, will be awarded as administrative supplements to existing grants using funds from the NIH OD's ARRA allocation. The funding decisions will be made by the OD.

The NHGRI Grand Opportunity grants will be reviewed by NHGRI review staff and the Challenge Grants will be reviewed by CSR. Council was asked how they want to be involved in the review of ARRA applications; it was agreed that conference calls would be most effective. Therefore, to expedite the award process, NHGRI will use the approach of early Council concurrence. A Council teleconference is being planned for August 17 for the second-level review of GO grants and Challenge Grants. At the September 14 Council meeting, any additional ARRA-related grant issues will be taken up. By September 30, all FY 2009 ARRA spending will be completed.

Council asked about the budgets for the Grand Opportunity grants. Dr. Guyer replied that at the NIH level there is no ceiling, although ICs are allowed to implement ceilings as appropriate.

Council expressed concern about possible suboptimal review of applications and potential reviewer burnout; Alan Guttmacher encouraged all Council members to consider accepting reviewer invitations.

Council expressed concern that Congress will not supply enough funding for FY11 to prevent a rapid descent from the ARRA funding. Dr. Guttmacher stated there is reason to be concerned and he and many others at NIH have been engaged in conversations about this potential shortfall. Similarly, Council expressed concern that ARRA applications that fail to be funded will turn around and apply for other grants. Dr. Guyer commented that many academic institutions are apparently encouraging investigators to recycle unfunded ARRA applications.

Council expressed concern about closing out the record number of grants in the next two years and accounting for every dollar. There is an unprecedented amount of tracking of funds during this two year period. Dr. Guyer commented that there will be more discussion about ARRA funding during the closed session.

PROJECT UPDATES

Informatics for Large-Scale Sequencing. Dr. Vivien Bonazzi presented on the informatics challenges for next-generation sequencing. Next-generation sequencing experiments are already generating huge volumes of data and that will increase enormously, even in the near future. Accordingly, we need to change our thinking about how to handle the data from reads to data sets and from kilobytes to terabytes. In a presentation to Council in February 2009, Dr. Bonazzi had presented an initial review of informatics infrastructure needs related to handling large volumes of data including: storage, computing capacity, data transfer rates and data representation. In addition, there is a need for efficient analysis tools.

At a March 2009 conference of the Genome Informatics Alliance, attendees discussed computational challenges and potential solutions concerning data from next-generation sequencing. Attendees at that meeting included experts from the fields of high performance

computing, sequencing instrumentation, high-energy physics, and cloud computing. There were several outcomes of the meeting:

- Computational infrastructure is already a bottleneck. The cost of maintaining and expanding large, stand-alone IT centers is high. Several groups are thinking of using distributed or "cloud" computing as a way to deal with this problem. Cloud computing is access to informatics resources acquired over the Web and paid for via subscription. It allows increased capacity to be added on the fly, without investing in additional machines. This method also avoids the need to train personnel for maintenance and paying license fees.

- Two pilot cloud computing projects are already planned. The first, being carried out by the Wellcome Trust Sanger Institute and Amazon will serve as a prototype for handling large genome sequence data via a cloud environment. In the second pilot, NCBI and EBI will load 1000 Genomes data to Amazon's S3 storage clusters. Both projects will use computing clouds to record CPU time for analysis and allow for rapid, correct and secure data downloads.

There are already several large public data sets that are being hosted by various vendors. Amazon is hosting ENSEMBL (human), GenBank, Unigene, PubChem, influenza virus, and census data. Google is hosting Census data, unemployment statistics, urban development and population statistics
NHGRI is planning another informatics workshop in September 2009. Discussion at that meeting will revolve around the pilot project results and the cloud requirements for each of sequencing centers. An NSF initiative with Google and IBM for the Cluster Exploratory (CluE) project will be discussed as a possible way to provide funds to researchers for cloud computing. The HMP Project will discuss their experience with cloud computing. The many challenges involved with cloud computing will be discussed, including security (a group from DOE is working on Amazon Federal and compliance issues), scalability, availability, performance, cost-effectiveness (financial cost, time, and resources), acquiring resources on demand, integration, and avoiding vendor lock-in. The invitees to this meeting will include groups dealing with large sequence data sets, including all genome sequencing centers; analysts from the TCGA, ENCODE, HMP, and 1000 Genomes Projects; staff from NCBI, EBI, UCSC, staff from other NIH Institutes, and representatives from sequencing instrumentation companies and other developers. Groups that have handled large sets using computing clouds will also be present to discuss lessons learned. These will include individuals from the NSF supercomputing centers (CluE), DOE, NIST, Google, IBM, SUN, and Aspera. The workshop planning committee is a small group of individuals with a balance of biology and computing skills.

Council asked about the costs involved with cloud computing. Dr. Bonazzi agreed that there is a need to understand the costs, which will vary from project to project. There were also comments about permanent storage and graphic processing capabilities of clouds; these are all worth consideration. There was a suggestion to move 1000 Genomes data from one protected server to another public server hosting the cleaned up data. Council suggested that the genomics community engage and consult with the physics community who seem to have more experience with cloud computing.

1000 Genomes. Dr. Lisa Brooks presented an update on the 1000 Genomes Project. Nine groups have produced data using three platforms -- Solexa, SOLiD, and 454. The April data release contained 3.8 terabases of data. Several steps are involved in data processing: cleaning the read data, recalibrating the read quality, aligning to the reference sequence, and calling variants. The data processing is done by NCBI and EBI of the DCC, as well as by groups at Sanger, Michigan, Broad, Boston College, Baylor, and TGen. Goncalo Abecasis at the University of Michigan is responsible for much of the data quality control.

The coverage of the samples in the two trios (pilot 2) ranges from 20X to 60X, and 5.1 million new SNPs were found in these samples. The low-coverage pilot (pilot 1) found 15 million new SNPs in 172 samples. In the gene region pilot (pilot 3), about 2.2 megabases were sequenced in 398 samples; additional samples are being sequenced. The Yoruba and Luhya populations have a higher proportion of rare SNPs than do the other populations, as expected. Ten groups are looking at structural variants and comparing their methods.

The full-scale 1000 Genomes Project will use 4X coverage, and will sequence 1,200 samples by end of 2009 and 800 samples during 2010. Many samples from the extended set of HapMap samples will be used -- Han Chinese, Japanese, CEPH, Tuscan, Yoruba, Luhya, African-American in the southwest U.S., Mexican-American in Los Angeles, and possibly some samples with Indian ancestry (Gujarati). In addition, samples are being collected from the Dai Chinese, Southern Han Chinese, Kinh Vietnamese, UK, Finnish, Mandinka (Gambia), Northerner (Ghana), Blantyre (Malawi), African-Americans, African-Caribbeans, Puerto Ricans, Colombians, and Peruvians.

GWAS studies have used the 1000 Genomes data to impute untyped variants; this strengthens the GWAS signal for some regions. The Wellcome Trust Case Control Consortium (WTCCC) decided to use 1000 Genomes data rather than sequence in 80 samples to find variants. The 1000 Genomes data will allow GWAS groups to save the cost of sequencing if they are looking for variants with frequencies above 1%; sequencing would be needed in disease-associated regions if they want to find rarer variants.

MEETING REPORTS

Future of Large-Scale Sequencing Workshop. Dr. Adam Felsenfeld presented a report on the March 23-24, 2009 workshop, which is one component of the new NHGRI planning process. The major questions that were posed to the attendees included: what important biomedical questions can be addressed by large-scale sequencing? What are the most compelling sequence-based community resources that should be created? What will be the consequences of the rapid increase in sequencing technology and the rapid decrease in cost of platforms?

The general conclusions of the workshop were:

- NHGRI is uniquely positioned within NIH to undertake the development, assessment, and implementation of a wide range of projects involving very large-scale application of genomic technologies.

- NHGRI should maintain a large-scale sequencing program; there are many compelling projects that can only be done at a very large scale.
- Several areas, such as computational biology methods, resources, infrastructure, tools and expertise, have not kept pace with the improvements in sequencing technology.
- There is a growing need to integrate sequence data with biological and biomedical information and NHGRI needs to play a role in facilitating this within NIH.
- Large scale centers contribute more than just data; they provide knowledge about designing projects, software tools and methods, new technology platforms, as well as set quality standards and provide intellectual leadership for the field.
- NHGRI is in a unique position to encourage wider dispersion of tools and knowledge for genomic projects that will benefit a wide range of topics.
- There is a need to provide opportunities for smaller, more specialized groups to apply "next-generation" sequencing to well-defined projects that address biological or biomedical problems. NHGRI should consider funding such smaller groups and encourage co-funding with other funding sources.
- The new sequencing platforms excel in data production but do not produce a "finished" genome, and NHGRI should not neglect the production of finished genomes.
- In the future NHGRI should consider "flagship" projects and design studies that encompass all aspects (sequencing, analysis, and genome maintenance).
- There also needs to be improved project tracking that is up-to-date and transparent to the public.

Dark Matter Workshop. Dr. Teri Manolio presented a report on the February 2-3, 2009 Dark Matter of Genomic Association with Complex Diseases workshop.

A number of common diseases have been examined in genome wide association studies (GWAS) with a growing number of associated genetic loci identified. Thirty-two loci have been identified for Crohn's disease, six loci for systemic lupus erythematosus (SLE), eighteen loci for type 2 diabetes, and twenty-two for lipid levels. The percent of disease that can be explained via genetic variants varies from a few percent for heart disease to 50% for age-related macular degeneration (AMD). GWA studies have demonstrated that GWA-defined variants associated with many common diseases account for a small percentage of heritability.

The workshop goals were to examine current estimates of heritability for common diseases following the initial yield of GWA findings of small effect, explore the reasons for the unexplained heritability, and develop strategies for investigating the problem.

Several explanations for missing heritability were identified: larger numbers of variants of smaller effect yet to be found; rarer variants (possibly with larger effects) that are poorly detected by available genotyping arrays; structural variation poorly captured by existing arrays; low power to detect gene-gene interactions; and inadequate accounting for shared environment among relatives.

The most promising explanation may be that we have not been able to explore low frequency intermediate penetrance variants since many common variants and a few rare alleles have been

identified for common diseases. Copy number variants and other forms of structural variation may also be important contributors.

Recommended approaches for finding missing heritability include: targeted or whole-genome sequencing, especially in persons with extreme phenotypes; use of expanded reference panels of genomic variation such as 1,000 Genomes to enhance coverage of existing and future GWA studies; mining of existing GWA studies for associations with structural variants and evidence of gene-gene interactions; improved methods for detection of CNVs and other structural variants; and expansion of sample sizes for complex disease studies, including persons of non-European ancestry.

Council asked if there is a sense that epigenetics may play a role in missing heritability. Dr. Manolio commented that there are some people who believe that epigenetics is the answer, but the technology to measure its effect is not there. There is also the issue of what affected tissue to collect for potential epigenetic studies. Council inquired about how the fly field partitions heritability; one can control flies' environment, this is much harder to measure in humans.

Sequencing Follow-up to GWAS. Dr. Lisa Brooks presented a report from a GEI-NCI March 24-25, 2009, meeting on "The Challenge of Exploring GWAS Signals."

GWA studies identify genomic regions that are associated with disease. The 1000 Genomes data will be valuable for providing the common to moderately rare variants in these regions, but sequencing will be needed to find the rare variants. Sequencing will allow the discovery of the comprehensive sets of variants in these regions, thus providing the set that will include the causal variants, although the many highly associated variants mean that experimental studies are needed to identify which of the variants are causal. This meeting was held to address how to design the sequencing and genotyping experiments to follow up on GWAS signals. A conclusion of the meeting was that genetic contributions come from alleles across the range of frequencies (common to rare) and with a range of effect sizes. With this variety of genetic architectures, the designs for sequencing studies that are appropriate for these differences are not clear. Potential study designs for sequence follow-up studies of GWAS signals include sequencing only exons or entire regions, using samples from just the extremes of the phenotype distribution or from the entire distribution (including samples with the entire set of haplotypes in the regions), and including a diversity of ethnicities. The meeting concluded that it would be valuable to generate data sets that would allow researchers to test alternative experimental designs as well as to develop analysis methods. These studies will need to include many samples and multiple ethnicities with good phenotype and environmental exposure data.

CONCEPT CLEARANCE

Sequencing Follow-up to Genome-Wide Association Studies. Dr. Lisa Brooks presented a concept clearance for a proposed joint NHGRI-GEI RFA.

The concept proposed an RFA to solicit proposals for following up GWAS signals by sequencing the disease-associated regions, and for comparing design strategies for this

sequencing. The NHGRI large-scale sequencing centers would do the sequencing, and GEI would fund analysis of the data. The program would use the U01 cooperative agreement mechanism and the participating investigators, sequencers, analysts, and program staff would work collaboratively to design the broad initial sequencing strategy, analyze the individual studies for which variants should be studied more in later experimental studies, and compare the various possible design strategies within and across the GWA studies to try to draw conclusions about which strategies are most appropriate for particular genetic architectures. The GWA studies would be chosen based on disease significance, strength of evidence for genetic contribution to the disease, richness of phenotype and exposure data, breadth of consent to study many diseases, balance of genetic architectures across the set of studies, and study population diversity.

Funding decisions are planned to be made in the late spring of 2010; sequencing would be expected to start that summer and the analysis carried out during the fall. NHGRI and GEI would be able to support three to four projects, and efforts would be made to obtain co-funding from other ICs to allow an additional three to four (six to eight projects total).

In the discussion, Council noted the need for large sample sizes to make this approach informative and the need for good measures of the relevant environmental exposures. They recognized, that the bigger the study, the more funds needed for sequencing and analysis. Council expressed some concern about the availability of datasets with exposure data and robust consent. Council also noted the importance of ensuring that the signals chosen for follow-up are genuine.

COUNCIL-INITIATED DISCUSSION

Potential agenda items for the September 2009 Council:

1. Update on the new, rare and neglected diseases program
2. Council visit with the new NIH director
3. Update on the progress of developing the new vision for NHGRI
4. Update on status of ARRA grant applications pertaining to NHGRI
5. Update on the BRCA gene patent issues

ANNOUNCEMENTS AND ITEMS OF INTEREST

Dr. Guyer directed Council to the Council folders containing items of interest. Please look at Tabs O, P, Q, R and reports from liaisons. Tab S has information on the FY 2010 budget.

CONFLICT OF INTEREST

Dr. Guyer read 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 $84,797,029. The applications included 68 research projects, 28 ELSI grants, 1 research center grant, 5 conference grants, 1 institutional training grant, 8 SBIR Phase I grant, 6 SBIR Phase II grants, 2 STTR Phase 1 grant, 7 individual training grants, 1 continuing education training award, and 10 resource access awards. A total of 131 applications totaling $45,775,113 were recommended.

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

9/23/09
Date

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

9/17/09
Date

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