NATIONAL ADVISORY COUNCIL FOR HUMAN GENOME RESEARCH
SUMMARY OF MEETING[1]
May 16, 2011

The Open Session of the National Advisory Council for Human Genome Research was convened for its sixty-second meeting at 8:30 A.M. on May 16, 2011 at the Fishers Lane Conference Center, Rockville, MD. Eric Green, Director of the National Human Genome Research Institute, called the meeting to order.

The meeting was open to the public from 8:30 A.M. until 3:30 P.M. on May 16, 2011. In accordance with the provisions of Public law 92-463, the meeting was closed to the public from 3:30 P.M. on May 16, 2011 until adjournment for the review, discussion, and evaluation of grant applications.

Council members present:
Michael Boehnke
Mark Chee
Rex Chisholm
Neal Copeland, *ad hoc*
Claire Fraser-Liggett
Geoff Ginsburg
Ross Hardison
David Kingsley
Howard McLeod
Deirdre Meldrum
Jill Mesirov
Richard Myers
Pearl O'Rourke
Pamela Sankar
Joseph Takahashi, *ad hoc*
David Valle
David Williams
Richard Wilson

Council members absent:
Richard Cooper
Pilar Ossorio

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:

Leslie Adams, DER
Maggie Bartlett, OD
Vivien Bonazzi, DER
Vence Bonham, OD
Ebony Bookman, OD
Joy Boyer, DER
Lisa Brooks, DER
Comfort Browne, DER
Zieanna Chang, DER
Cheryl Chick, DER
Monika Christman, DER
Nicholas Clemm, DER
Christine Cutillo, DER
Chris Darby, DER
Karen Deleon, OD
Corina Din-Lovinescu, OD
Elise Feingold, DER
Adam Felsenfeld, DER
Colin Fletcher, DER
Tina Gatlin, DER
Jonathan Gitlin, OD
Peter Good, DER
Bettie Graham, DER
Eric Green, OD
Mark Guyer, DER
Lin Gyi, OD
Linda Hall, DER
Lucia Hindorff, OD
Jason Hotten, DER
Heather Junkins, OD
Rongling Li, OD
Carson Loomis, DER
Rebecca Lowdon, DER
Jean McEwen, DER
Keith McKenney, DER
Michelle Milligan, DER
Janis Mullaney, OD
Ken Nakamura, DER
Cathy Ng, DER
Vivian Ota-Wang, DER
Brad Ozenberger, DER
Michael Pazin, DER
Jane Peterson, DER
Ajay Pillai, DER
Rudy Pozzatti, DER
Lita Proctor, DER
Erin Ramos, OD
Laura Rodriguez, OD
Jeff Schloss, DER
Heidi Sofia, DER
Geoff Spencer, OD
Jeff Struewing, DER
Elizabeth Thomson, DER
Susan Vasquez, OD
Simona Volpi, DER
Lu Wang, DER
Chris Wellington, DER
Kris Wetterstrand, OD
Anastasia Wise, OD
Rosann Wise, OD
Julia Zhang, DER

Others present for all or a portion of the meeting:
Adam Berger, Institute of Medicine
Karin Helmers, Center for Scientific Review, NIH
Michael Meder, American College of Medical Genetics
Brian Oliver, National Institute of Diabetes and Digestive and Kidney Diseases, NIH
Karen Rothenberg, University of Maryland School of Law
Rhonda Schonberg, National Society of Genetic Counselors
Lonnie Welch, Ohio University

INTRODUCTION OF NEW MEMBERS AND STAFF, LIASONS AND GUESTS

Dr. Guyer noted that there are no new NHGRI staff members to introduce.

APPROVAL OF MINUTES

The minutes from the February 2011 Council meeting have not been submitted to the group. There will be an e-mail vote to approve them once they are finished.

FUTURE MEETING DATES

The following dates were proposed for future meetings: September 12-13, 2011; February 13-14, 2012; May 21-22, 2012; September 10-11, 2012; February 11-12, 2013; May 20-21, 2013.

DIRECTOR'S REPORT

NHGRI staff have created an electronic resource for the Director's Report and associated supplemental material available at http://www.genome.gov/directorsreport. In addition, Dr. Green reminded participants that the Open Session of the Council meeting is Webcast live, with plans to Webcast and Web-archive all future Council meetings.

I. GENERAL NHGRI UPDATES

NHGRI's New Strategic Plan for Genomics. The strategic plan for the field of genomics was published on February 10 in *Nature*, the culmination of the two-year strategic planning process, which had included substantive contributions from Council. There was significant press coverage, in approximately 75 different media outlets including scientific blogs and news websites. NHGRI reached out to science and genomics bloggers to present an opportunity to discuss the new strategic plan with Dr. Green.

Symposium: A Decade with the Human Genome Sequence. On February 11, NHGRI hosted a Symposium celebrating the tenth anniversary of the human genome sequence, and coinciding with the publication of the strategic plan. Symposium speakers included Francis Collins, James Watson, and Eric Lander, among others. The event was webcast and garnered approximately 2000 live viewers. The entire symposium broadcast is archived on the GenomeTV channel on YouTube.

Appointment of NHGRI OPCE Director. Dr. Laura Lyman Rodriguez, PhD, previously the Acting Director of the Office of Policy, Communication, and Education (OPCE) in the Office of the Director, NHGRI, has been appointed as the Director of OPCE. Dr. Rodriguez will be a key advisor to the NHGRI Director on numerous topics, including the federal budget and policy.

Extramural Program Director Retires. Dr. Gary Temple, MD, PhD retired on March 31, 2011. Dr. Temple joined NHGRI late in his career and made substantive contributions to a number of DER research programs. He managed the Mammalian Gene Collection (MGC), and helped to initiate of the Genotype-Tissue Expression (GTex) Program.

Special Advisors to NHGRI Director. Starting in June 2011, Dr. Marc Williams, MD will be spending one week per month at NHGRI as a special advisor to Dr. Green in the area of genomic medicine. Dr.

Williams is currently the Director of the Intermountain Healthcare Clinical Genetic Institute in Salt Lake City, UT. His advice will help in the development of new areas for NHGRI involvement, including the interface of genomics with electronic health records, and clinical genomics information systems. Dr. Williams also assisted during the development of the new strategic plan and participated in several subsequent workshops.

Dr. Karen Rothenberg, JD, MPA, is taking a one-year sabbatical from the University of Maryland, during which she will serve as a part-time Special Advisor to the Director, NHGRI, starting this summer. Dr. Rothenberg will be working on various projects with NHGRI related to the development of new opportunities in the societal aspects of genomics. During this year, she will also work with the Bioethics Department in the NIH Clinical Center.

UMD Law School Workshop on the Regulation of Genomic Research. In a recent outreach program, a small group of senior University of Maryland law school students participated in a course and subsequent workshop focusing on issues raised by next-generation genome sequencing research. Dr. Karen Rothenberg and NHGRI's Ben Berkman led the workshop, in which the students collaborated with NHGRI bioethicists and policy makers to analyze legal, ethical, and regulatory questions that are emerging in the field of genomic research. The students prepared a series of policy papers about a range of issues (e.g., CLIA, group harm, and incidental findings), which were presented to NHGRI leadership in April 2011. The workshop participants are now completing a consensus document that will be forwarded to NHGRI for final review.

Meeting on Genomics and Health Information Technology Systems. During the Airlie finale planning meeting last summer, there was a significant debate over the importance of NHGRI fostering research at the interface of electronic health records and genomics. Accordingly in April, NHGRI hosted a meeting entitled Genomics and Health Information Technology Systems to explore the broad spectrum of issues facing the intersection of clinical informatics systems and genomics. See below for specifics.

Workshop on The Collection, Storage, Management, and Distribution of Next-Generation Sequence Data. In May, the NHGRI and NCI convened a workshop entitled The Collection, Storage, Management, and Distribution of Next-Generation Sequence Data. The workshop considered a number of issues related to the prodigious increase in the amount of genomic sequence data that has been and will continue to be generated by the use of next-generation sequencing technologies, and the issues involved in making large datasets available to the scientific community in a cost-efficient and scientifically useful fashion. See below for specifics

II. GENERAL NIH UPDATES

Fiscal Year 2011 Appropriations Update. On April 15, 2011, President Obama signed a bill to fund the federal government through the end of Fiscal Year 2011. This included an NIH appropriation of $30.7B, 0.8% less than in FY2010. As a result, overall success rates for NIH grant applications may fall to 17-18%. Furthermore, biomedical inflation has reduced NIH purchasing power to its 2001 levels. The 2011 NHGRI budget will be finalized by DHHS and OMB, but is similarly projected to be 0.8% less than the FY2010 budget.

FY2011 Extramural Award Guidelines. The 0.8% cut in the FY2011 appropriation will mainly affect the NIH extramural budgets. Intramural budgets are less flexible this late in the fiscal year and cannot take such a cut. To accommodate the reduction, NIH has decided to reduce non-competing awards to 1% below the FY2010 award level. Each NIH Institute/Center will manage its competing awards. For R01-equivalent awards, NIH will strive to continue to support new investigators at success rates equivalents to those for established investigators. NIH will implement a 2% increase at all stipend levels for the Ruth L. Kirschstein National Research Service Awards (NRSAs).

President's FY2012 Budget. The President's FY12 Budget proposes a $32B budget for NIH, a 2.4% increase. The proposed NHGRI budget is $525M, a 1.7% increase. Dr. Green noted that NHGRI's budget distribution is significantly different from NIH as a whole -- NHGRI has the largest intramural

program relative to the Institute budget, and the proportion of extramural research and development grants is smaller than the NIH average. Consequently, the NHGRI response to the budget changes will vary from the NIH response as a whole.

House FY2012 Budget Resolution. The House passed Representative Paul Ryan's budget resolution on April 15, 2011 which aims to cut government spending from 24% to 20% of GDP. The Budget Resolution is a high-level framework from which the Appropriations Committee takes its lead and sets the actual dollar levels allocated to each Appropriations Subcommittee. Therefore, the budget resolution did not include a specific numbers for NIH, but some projections anticipate cuts to about the FY2002 level.

Senate Appropriations Hearing. The Senate Subcommittee on Labor, HHS, Education and Related Agencies held an NIH hearing on May 11, 2011. Francis Collins, Harold Varmus, Tony Fauci, Griff Rodgers and Susan Shurin participated in the hearing. Dr. Collins highlighted four themes -- accelerating discovery through technology, applying science to prevention, enhancing the US economy and global competitiveness, and advancing translational sciences. Genomics was a central feature of the NIH message, as reflected in Dr. Collins' discussions of sequencing costs, The Cancer Genome Atlas (TCGA), the Beijing Genomics Institute (BGI), and genome sequencing as part of clinical care.

Proposed National Center for Advancing Translational Sciences (NCATS). The primary goal of NCATS is to establish the discipline of translational science and to catalyze the development and testing of novel diagnostics and therapeutics across a wide range of human diseases and conditions. The Center will facilitate, rather than duplicate, other translational research activities supported by NIH; will complement the private sector; and will reinforce NIH's commitment to basic research. It is planned that NCATS will be operational on October 1, 2011.

The research programs at NCATS will include components of the Molecular Libraries Program, the Therapeutics for Rare and Neglected Diseases program, the Rapid Access to Interventional Development (RAID) program. the Clinical and Translational Science Awards (CTSAs), as well as the Office of Rare Diseases Research (ORD), the FDA-NIH Regulatory Science program and the Cure Acceleration Network (CAN). The first three programs are currently housed within NHGRI and will be transferred to NCATS on October 1. NHGRI will lose approximately 125 personnel to this transfer.

Associate Director for Science Policy, NIH. Dr. Amy Patterson, PhD was appointed as Associate Director for Science Policy, NIH. Dr. Patterson had been serving as the Acting Associate Director since Fall, 2008. Previously, she has served multiple roles as the Director of the Office of Biotechnology Activities, within OSP, as the Deputy Director of the Division of Cellular and Gene Therapies, and as a Senior Medical Officer in the Center of Biologics Evaluation and Research at the FDA.

NCI Interim Director for Center for Cancer Genomics. Dr. Barbara Wold, PhD, will serve as Interim Director of NCI Center for Cancer Genomics starting this Fall, while on sabbatical from Caltech where she is the Bren Professor of Molecular Biology and the director of the Beckman Institute. Dr. Wold is a former member of the NACHGR and has served the NHGRI in numerous other advisory roles.

New Look for the NIH Website. The NIH website has been recently redesigned.

III. GENOMICS UPDATES

Mourning the Loss of Charles Epstein. Dr. Charles Epstein passed away in February 2011 after a protracted battle with pancreatic cancer; he was 77 years old. Dr. Epstein conducted groundbreaking research on Down syndrome and led the production of a mouse model for the disease. He was awarded the McKusick Leadership Award at the 2010 ASHG meeting. Also notable, Dr. Epstein was a survivor of an attack by the Unabomber.

Awards, Recognitions and Prizes to NHGRI-associated Scientists

- Jo Handelsman was awarded a Presidential Award for Excellence in Science, Mathematics, and Engineering Mentoring for her work in metagenomics. She is the PI. of the NHGRI training grant at Yale University.
- Stephen Quake was awarded an American Society of Microbiology 2011 Promega Biotechnology Research Award. Dr. Quake is the Professor of Bioengineering and Applied Physics at Stanford University, an investigator in the Howard Hughes Medical Institute, and an NHGRI grantee. The award honors his "outstanding contributions to the application of biotechnology through fundamental microbiological research and development."
- David Page was awarded the 2011 March of Dimes Prize in Developmental Biology. One of two investigator awardees, Dr. Page was honored for his work on the biology of sex chromosomes. His studies of the Y chromosome revealed its role as a complex genetic system with many specialized functions. Dr. Page is the Director of the Whitehead Institute and is an HHMI Investigator. He is a former member of the NACHGR and is an NHGRI grantee.
- David Page and Robert Kingston were inducted into the American Academy of Arts and Sciences. Dr. Kingston was recognized for his work in understanding the fundamental mechanisms of enzymatic chromatin modification. He heads the Department of Molecular Biology, Massachusetts General Hospital, and is Vice Chair and Professor of the Department of Genetics at Harvard Medical School. He is also a former ENCODE technology grantee.
- Several geneticists and genomicists were elected to the National Academy of Science in 2011, including NACHGR member David Kingsley and several other current and former NHGRI grantees.
- Several geneticists were recognized in Reuters' Science Watch for the Hottest Research of 2010. The list, which recognizes individuals authoring the largest number of "Hot Papers' over the preceding two years, includes Richard Wilson and Eric Lander (Dr. Lander for the seventh time).
- *Technology Review* annually selects ten emerging technologies of the past year that have the greatest scientific impact, and this year recognized the work of both Stephan Quake and Elaine Mardis.

Pulitzer Prize for 'One in a Billion' Series. In April 2011, the authors of a three-part series in The *Milwaukee Journal Sentinel* won a Pulitzer Prize for explanatory reporting. The series, "One In A Billion: A boy's life, a medical mystery" reported the story of 6-year-old Nicholas Volker, who suffered from a mysterious condition that attacked his intestines. Whole-exome sequencing was used to pinpoint the causative mutation, leading to a bone marrow transplant and significant improvement of his condition. In the recent Senate Appropriations hearings, NIH Director Francis Collins described Nicholas' experience as an example of a genomics advance applied to improving human health.

NCBI's Sequence Read Archive to be Discontinued. NCBI is discontinuing the Sequence Read Archive (SRA) database and a few other resources due to budgetary constraints this year. The SRA and Trace archives will be closed in phases; the expected final closure date is November 2011. NCBI plans to make SRA data available as a public archive for 12 months after it is decommissioned; after this time usage will be reevaluated periodically in determining a final plan. NCBI plans to continue the Database of Genotypes and Phenotypes (dbGaP). NHGRI staff have been in active discussion with NCBI to determine the best path forward. As a basis for this discussion, an inventory of funded projects was compiled as a basis for an estimate of the data volumes from all NHGRI projects for the next 12 months; similar inventories have been compiled at other NIH Institutes. NHGRI staff managing large genome projects are actively working to determine alternative course(s) of action for their projects.

CDC Office of Public Health Genomics. The CDC Office of Public Health Genomics, which was established in 1997, is being downsized by more than 90% in FY2011-FY2012. The Office funded knowledge synthesis, translational research and population data studies. The Office also funded both the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) effort, as well as the Genomic Applications in Practice and Prevention Network (GAPpNet). NHGRI is in communication with the CDC group to explore the implications of the downsizing.

SACGHS. The Secretary's Advisory Committee on Genetics Health and Society (SACGHS) has been disbanded, with the release of its final report, which is available for public comment until June 30, 2011. The topic of the report was genetics education and training of health care professionals, public health providers and consumers. Some the recommendations in the report intersect with elements of NHGRI's new strategic plan, and are also relevant to outcomes of the Genomics and Health Information Technology Systems meeting.

Presidential Commission for the Study of Bioethical Issues. Participants at the recent meeting of the Presidential Commission for the Study of Bioethical Issues discussed emerging technologies for diagnostic and predictive tools, particularly in the genetics and neuroimaging fields. NIH Director Francis Collins was the first speaker, and he highlighted three areas -- genetic discrimination, incidental findings and return of results, and forensic uses with civil liberties implications. NHGRI staff are in communication with the Commission staff about possible directions that their studies of genetic technologies might take. The Commission is also focusing attention on human subjects research in light of revelations about the Guatemalan STD experiments and the book about Henrietta Lacks. The Commission will be conducting a study of the ethics surrounding contemporary clinical trials; that study will be released in the Fall of 2011.

International Rare Disease Research Consortium (IRDiRC). . A workshop was held in April 2011 to consider the organization of an International Rare Disease Research Consortium (IRDiRC). Funding agencies, patient advocacy groups, researchers, industry members and regulatory agencies all participated in the workshop. The Consortium's proposed goals include delivering diagnostic tests for most rare diseases by 2020, and new therapies for 200 rare diseases. Coordination at the international level is necessary to meet the Consortium goals. It has not been decided whether the NIH will join IRDiRC as a single entity or whether ICs will join individually. Seven Consortium working groups have been established, and NHGRI is well-represented. IRDiRC has significant relevance to NHGRI's extramural plans, for establishing Mendelian Disease Sequencing Centers.

New Journal: *Gigascience.* BGI and Biomed Central will launch a new journal for large-scale biology, entitled *GigaScience*, later this year. The journal will publish and serve as a data repository for studies generating large biomedical data sets, including genomic studies. Another unique feature of the journal is that it will provide DOI numbers for large datasets so they can be considered as publications. Dr. Laurie Goodman, formerly editor of *Genome Research* will be the editor of *GigaScience*. The business model for this journal is not yet clear. Dr. Felsenfeld noted that a similarly new and unique journal will be launched by the Genetics Society of America.

ELSI Congress 2011. The Third ELSI Congress was held in April 2011 and attracted more than 350 researchers, trainees, and policy makers. The meeting featured 19 panels, 79 individual papers, 12 focused workshops and 54 posters. Research themes included genomic data sharing, return of clinical and research results, behavioral genetics, health equity, race and genomics, intellectual property, and the implications of microbiome research and epigenomics. Of particular interest to the NHGRI were the number and the quality of the participating trainees from the Centers for Excellence in ELSI Research (CEERs), who came from a variety of disciplines and population groups.

Biology of Genomes Meeting. The 2011 Biology of Genomes Meeting was held on May 11-14 at Cold Spring Harbor Laboratory. The meeting continues to be a primary locus for the presentation of high-quality, cutting-edge research and was very well-attended. Council member Pilar Ossorio led an ELSI panel discussion.

NHGRI Genomic Advance(s) of the Month. NHGRI recently launched a "Genome Advance of the Month" feature on www.genome.gov. This month feature the work of Stephen Quake and Hannah Valantine, "Universal noninvasive detection of solid organ transplant rejection." Dr. Green encouraged Council members to nominate papers and studies for this website feature.

Economic Impact of the Human Genome Project. Last week, the Battelle Memorial Institute released a study of the economic impact of the Human Genome Project (HGP). The goal of the study was to fill a gap in the literature regarding the HGP by assessing its economic and functional impacts. The key

conclusion was that the HGP is arguably the single most influential investment to have been made in modern science and a foundation for future progress in the biological sciences. Another group, United for Medical Research (UMR), released a similar report titled, "An Economic Engine: NIH Research, Employment, and the Future of the Medical Innovation Sector." That study further illustrated how the US economy is stimulated by biomedical research.

IV. NHGRI EXTRAMURAL PROGRAM

Large-Scale Sequencing Program

- Organisms update. The sequencing program funded the recently published draft genome sequence of the parasitic nematode, *Trichinella spiralis*. The sequence was drafted by researchers at the Washington University Genome Institute, and was reported in the March 2011 issues of *Nature Genetics.*

- The Cancer Genome Atlas (TCGA). Post-pilot production for TCGA is approaching the ARRA goal of 3,000 tumor/normal pairs over 22 tumor projects by September 2011. The TCGA analysi of ovarian cancer, the broadest and deepest tumor genome project to-date, is now in press in *Nature*. Other projects now underway include AML, colorectal cancer, breast cancer, kidney clear cell cancer and endometrial cancer.

- 1000 Genomes Project. The 1000 Genomes Project continues to make major progress towards its goals. Major recent achievements include low-coverage sequencing of 1150 samples, exome sequencing of 1000 samples, and OMNI 2.5M SNP genotyping of 1500 samples, including trio children. So far, approximately 39 million SNPs, 100,000 indels, and 84,000 structural variants have been discovered. The project is preparing a manuscript on a data set integrating all the Phase I variant types.

DNA Sequencing Technology. The 2011 Sequencing Technology grantee meeting was held in April 2011 in San Diego. The sequencing technology-related ARRA grantees met together with the $100,000 genome and $1000 genome grantees. The last day of the meeting was open to the public and was attended by, among others, 35 scientists who not supported by the sequencing technology development program. The meeting highlighted how effective partnerships between technology developers and technology users can enhance usability of the new platforms. Progress on physical methods for sequencing, particularly in nanopore sequencing, has been significantly.

ENCODE and modENCODE. The annual joint ENCODE and modENCODE Consortia meeting will be held on May 23-25, 2011 in Washington, D.C. ENCODE is currently focusing on completing an initial analysis of its data, while modENCODE is doing an integrated analysis of the *D. melanogaster* and *C. elegans* data. Several papers have been published since the February Council meeting, including "A User's Guide to the Encylopedia of DNA Elements (ENCODE)" in *PLoS Biology*. Council member Rick Myers led the development of this publication, along with many ENCODE investigators.

V. COMMON FUND PROGRAMS

Human Microbiome Project (HMP). The HMP expects that a global analysis of the primary "healthy cohort" will be submitted for publication soon, along with over 20 companion papers. The International Human Microbiome Congress was held in March 2011 in Vancouver. There were approximately 500 attendees from 20 countries. A brainstorming meeting on future initiatives was held in April 2011 in Bethesda, MD and focused on clinical application outcomes. The American Society for Microbiology meeting to be held in May 2011 will feature major presentations by two HMP investigators.

Genotype-Tissue Expression (GTEx). GTEx is now operational and has funded a Laboratory Data Analysis and Coordination Center (LDACC) at the Broad Institute and three Biospecimen Source Sites, at the National Disease Research Interchange (Philadelphia, PA), Roswell Park Cancer Institute (Buffalo, NY) and Science Care (Phoenix, AZ). The Project Team aims to have the initial sample collections started

by April or May of 2011. A PI meeting is scheduled in June 2011, and there are a new website and brochure to explain the project to the lay public.

Library of Integrated Network-based Cellular Signatures (LINCS). The U54 LINCS production groups published a paper in May 2011 in *Nature Methods* detailing the techniques used to organize microarray data for LINCS project data analysis. In March 2011, LINCS held a meeting of the External Scientific Panel with the U54 centers and NIH Project Team at the Broad Institute. Three administrative supplements have been awarded to R01 investigators to stimulate development and analysis through the LINCS production pipeline of the cell lines and perturbagens they use. The LINCS program expects to fund three to five technology development awards. The program is developing metrics for Phase 1 and 2 of the LINCS project, There will be a Consortium Meeting in October 2011 for investigators from the two production centers and the new supplement and technology development awardees.

Protein Capture. Applications have been received for the Production and Technology Development components of the Protein Capture program. These applications will undergo initial review during summer 2011 and be brought to the September meeting of the NACHGR.

Human Heredity and Health in Africa (H3Africa). H3Africa held a meeting Cape Town, RSA to discuss the white paper authored by the project working groups (www.h3africa.org), which makes a proposal about the scientific scope of the project. A presentation about H3Africa was made to the IC Directors in hopes of attracting additional support for the project, beyond the Common Fund's base support of $5M per year (NHGRI plans to commit $2M per year). In June 2011, the project will be taken to the Council of Councils for concept clearance; the Project Team aims to publish the initial FOAs in July 2011.

Single Cell Biology Workshop. A Request for Information (RFI) published in the NIH Guide in February 2011 elicited 75 responses. A workshop was held in April 2011 to engage experts in a discussion of the range of biomedical and technology opportunities and challenges for single-cell analysis technology. The next step will be to develop a set of goals and milestones for a trans-NIH initiative, which will be submitted in May as a proposal to the Common Fund.

Innovation Brainstorm meeting: Transforming Discovery Into Impact. The NIH Common Fund convened an Innovation Brainstorm Meeting in early May 2011 to identify areas of emerging scientific opportunities in which strategic investment by the Common Fund could accelerate progress. IC Directors had been asked to nominate junior investigators to engage in a discussion focused on a set of highly innovative papers selected by the attendees. Based on the nominated papers and comments, the Common Fund staff organized 8 discussion sessions, which included beyond GWAS, microbiome, proteomics and therapeutics development, and single cell analysis. Participants from NHGRI included Drs. Teri Manolio, Lita Proctor, and Jeff Schloss.

VI. NHGRI OFFICE OF THE DIRECTOR

Office of Population Genomics. The Electronic Medical Records and Genomics (eMERGE) Network continues to demonstrate the value of deriving phenotypes defined by electronic medical records and to capitalize on the eMERGE-funded genotyping to study EMR-defined phenotypes. Two publications, from the Mayo and Vanderbilt sites, "A Genome-Wide Association Study of Red Blood Cell Traits Using the Electronic Medical Record" in *PLoS One* and "Identification of Genomic Predictors of Atrioventricular Conduction" in *Genetics* respectively, were highlighted.

New England Journal of Medicine Genomic Medicine (NEJM) Series. Seven articles have now been published in the NEJM genomic medicine series edited by Drs. Greg Feero and Alan Guttmacher. In January, the sixth installment reviewed the effects that genomic approaches are having on tumor classification, prognostic markers, predictive indicators of drug response, the development of new drug therapies, strategies for monitoring disease, and the management of susceptibility to cancer. The seventh article in March, featuring Dr. Howard McLeod and Dr. Richard Weinshilboum, discussed how

pharmacogenomics facilitates the identification of biomarkers that can help physicians optimize drug selection, dose, and treatment duration, and avert adverse drug reactions.

Genetic/Genomic Competency Center for Education Program (G2C2). G2C2 is a web-based repository of educational resources on genetics and genomics. In February 2011, the G2C2 website was redesigned in response to evaluation by healthcare providers. Genetic counselors will be adding resources to the site this summer. A meeting with pharmacists will be convened in fall 2011 to discuss discipline-specific competencies, to identify resources, and to explore the use of G2C2. A manuscript entitled "Establishment of the Genetic/Genomic Competency Center for Education (G2C2)" has been accepted for publication in the *Journal of Nursing Scholarship*.

OPCE Staff Member Award. Mr. Rocky Rackover will receive the 2011 Paragon Outstanding Physician Assistant of the Year Award. Mr. Rackover is a contract employee in OPCE and is also on the faculty at Philadelphia University. He will honored for his efforts to introduce genetic literacy to physician assistant education, beginning in 2001, during the annual American Academy of Physician Assistants (AAPA) conference in May 2011. Mr. Rackover has previously served on the Board of Directors for the National Coalition for Health Professional Education in Genetics.

DNA Day. NHGRI held its annual DNA Day Chatroom on April 15, 2011 from 8:00 am to 6:00 pm. 45 NHGRI staff answered questions remotely or on-site. The DNA Day Ambassadors Program partnered with the NIH Office of Science Education Speakers Bureau to help connect teachers and speakers. The DNA Day Ambassadors will visit or interact with approximately ten schools during March, April and May.

Johns Hopkins Center for Talented Youth Family Academic Program. NHGRI hosted 200 students and parents from Johns Hopkins Center for Talented Youth (CTY) in April 2011. The event featured keynote addresses from Dr. Jim Mullikin and Dr. Lita Proctor on sequencing the Neanderthal genome and the human microbiome, respectively. Students participated in hands-on activities related to forensics, immunology, and microbiology. Parents received a tour of the NLM and learned about genetic counseling.

VII. NHGRI INTRAMURAL PROGRAM

NIH Intramural Sequencing Center (NISC). NISC has launched a search to identify a new Director. Dr. Jim Mullikin has been the Acting Director of NISC since December 2009. The closing date for applications was May 15, 2011 and the Search Committee plans to identify candidates in the next two months..

Undiagnosed Diseases Program.

- Dr. Bill Gahl presented a TED^{x} talk in April 2011 about the NIH Undiagnosed Diseases Program and on the obstacles faced by patients with rare diseases seeking treatment, including regulatory impediments and possible solutions. The TED^{x} talks are archived and publically accessible.

- Dr. Gahl was named a finalist for the 2011 Samuel J. Heyman Service to America Award in the Science and Environment Category for his founding leadership and success with the NIH Undiagnosed Disease Program. Category winners will be announced in September 2011.

- Dr. Bill and the entire NIH Undiagnosed Diseases Program were selected for the Team Science Award by the Society for Clinical and Translational Science (SCTS).

- An article by Dr. and Dr. Cynthia Tifft titled "The NIH Undiagnosed Disease Program: Lessons Learned" was published in *JAMA* on May 11, 2011.

NHGRI Intramural Research Highlights. NHGRI's whole Intramural Research Program continues to be highly productive, with numerous accomplishments over the last four months. Highlighted publications include a paper from Dan Kastner's group in *PNAS* reporting the genetic cause and a new treatment for a genetic form of recurrent fever in children, a paper from Yardena Samuel's group *Nature Genetics* on a whole-exome sequencing of melanoma that identifyied GRIN2A as the most highly mutated gene, and a

paper from Colleen McBride's group in *Pediatrics* describing the results of studying parents' attitudes toward pediatric genetic testing for common disease risk.

PROJECT PRESENTATION

PheGenI. Dr. Lucia Hindorff presented an overview of the Phenotype-Genotype Integrator (PheGenI) Project. The purpose of the PheGenI resource is to add a layer of genotype-phenotype association data to existing NCBI resources, as the functional implications of genome-wide association studies (GWAS) are rarely transparent. Features include the ability for users to search on phenotype, genes, SNPs or chromosomal range, downloadable data tables, hyperlinks to records in source databases, an interactive sequence viewer, and a user-customized display. PheGenI also allows users to filter on p-values of association and functional class. The PheGenI interface was designed to be simple and user-friendly. The NHGRI-NCBI staff are continuing to meet regularly to discuss potential improvements. A draft manuscript is currently in progress. Future improvements to the resource already planned include a YouTube demonstration of PheGenI, incorporation of additional data types and databases, a downloadable ideogram, and improved documentation. Council members were encouraged to submit questions about the resource through the "Write to the Help Desk" link feature at the bottom of the PheGenI page, or by contacting Dr. Hindorff directly.

Council members expressed enthusiasm and interest for the innovative resource.

PROGRAM UPDATES

ENCYCLOPEDIA OF DNA ELEMENTS (ENCODE). Dr. Elise Feingold presented an update of the ENCODE project. She began by reviewing the program objective of ENCODE, which is to compile a comprehensive resource of all the functional sequences in the human genome, and the companion modENCODE project to do the same for the genomes of selected model organisms, including *C. elegans* and *D. melanogaster.* A small mouse ENCODE project began in 2009 with ARRA support. Technology development for ENCODE has also been an integral component of the program from the beginning. A mid-course review was held in the Spring of 2010, which resulted in the extension of the production projects for a fifth year in order to take advantage of established production capabilities and to give NHGRI additional time to plan future activities.

There are multiple ways to access ENCODE data, including the UCSC Genome Browser, Ensembl, FlyBase, and WormBase, among others. Each database has various resources, including raw and derived data. There have been approximately 2000 data submissions. modENCODE investigators recently produced two significant papers in *Science* that were followed shortly by 19 companion papers in *Nature*, *Genome Research*, *Genome Biology and Database.* Data integration will be the focus of the modENCODE consortium in the fifth year, both within and between the two species. There will be a modENCODE Analysis Working Group meeting on May 21-22, 2011. Plans for ENCODE include increased coordination of data generation, integrated data analysis across data types, integrated analysis of mouse and human data, and integrated analysis of all species. There will be a joint Analysis Working Group session on May 23 during the joint Consortia meeting.

Recent findings from ENCODE indicate that GWAS disease and trait-associated variants are concentrated in regulatory DNA. These discoveries, among others, imply that correlations between the functional elements identified by ENCODE and disease-and trait-associated genetic variants can lead to testable hypothesis as to how disease-associated genotypes relate to disease phenotypes. This is one example of how ENCODE is poised to have a significant near-term impact on interpreting genomic information associated with human disease.

Dr. Feingold also discussed a related effort, the Common Fund Epigenomics Project, which was initiated in 2008. The project includes the support of reference epigenome mapping centers, technology development, discovery of novel epigenetic marks in mammalian cells, and epigenomics of human health and disease. Several of the investigators in the Epigenomics Project are also ENCODE investigators. There will be a joint meeting between ENCODE and the Epigenomics Roadmap project on May 25 to discuss ways to achieve further synergies.

MICROBIOME RESEARCH. Dr. Lita Proctor presented an update on microbiome research. The Human Microbiome Project (HMP) consists of two clinical centers, four sequencing centers that aim to produce data relevant to the "normal" microbiome, computational tool and technology development projects, ELSI research grants, and a number of demonstration projects studying the link between microbiome and disease. The normal cohort study aims to study 300 people, and analyze the microbiome from five body sites: nasal, oral, skin, gastrointestinal and urogenital. So far, the HMP Consortium has reported that distinct microbiomes exist, that some body sites have more stable microbiomes than others, and that the function of microbiomes has been characterized on several levels. An example of the analyses that have been performed with whole genome data is a metabolic reconstruction of the oral and gut microbiomes. Another finding is that across microbiomes, microbial species are diverse, but metabolic pathways are less so.

There have been 93 publications to date that have cited HMP support. Data that will be released in May 2011 include processed reads and assemblies from microbiome metagenomes, an annotated gene index for all proteins predicted from these assemblies, and processed 16S rRNA sequences. The American Society for Microbiology (ASM) meeting in May 2011 will feature the HMP. Invited speakers during the late-breaking session on May 24, 2011 include HMP investigators, Dirk Gevers and Curtis Huttenhower. Furthermore, two publications are in preparation for *Nature.* Lastly, a Microbiome Brainstorming Session was held on April 26, 2011 with participation by 22 external experts, and approximately 30 NIH representatives representing eight ICs. The agenda focused on potential future initiatives in microbiome research and challenges for such efforts.

Council members asked whether there has been an HMP study on monozygotic or dizygotic twins. Dr. Proctor responded that twins have not been a part of the normal HMP cohorts, and that Dr. Jeff Gordon's group has published some work on this approach.

MEETING REPORTS

NGS DATA MANAGEMENT WORKSHOP. Dr. Peter Good presented a summary of the Next Generation Sequence (NGS) Data Management Workshop that was held on May 4-5, 2011. The workshop was held primarily in response to NCBI's announcement in February 2011 on the closure Sequence Read Archive (SRA), a repository of primary NGS data. NIH has provided additional funds to NCBI to prevent the immediate closure of the SRA and to allow it to ramp down SRA activities. It should be noted that other archives are still available to accept data (i.e., the European Nucleotide Archive (ENA) and the DNA Data Bank of Japan (DDBJ)).

Several NIH ICs participated in organizing the two-day workshop, which was co-chaired by Owen White and Gabor Marth. The immediate goal of the workshop was to explore potential approaches to providing NGS data to the community. The proximate and long-term goals were to develop recommendations on business models for the future of NGS data management and to highlight areas for research to solve the fdifficult problems.

Action items from the workshop were designed to address the urgency of providing near-term solutions for the wide range of genome projects and included the need, to develop working groups on metadata; and to continue to look at compression methods including efficient compression of quality scores. Other potential actions include a pilot project to use Cloud computing, a workshop on human subjects and security issues in sharing large genomic datasets, exploration of data aggregation centers or data brokers to facilitated data submission to repositories and further consideration of data structures, tools, and databases beyond the two to three-year horizon.

Council members agreed that the workshop has helped force people to think more carefully about the large volumes of data that are currently being generated and archived. Council members discussed the possibility of a pilot project to store data using cloud computing; BioNimbus was mentioned as an example of a non-commercial, academic cloud. At the same time, the Council recognized that there are security concerns associated with cloud computing. Finally, the workshop reinforced the idea that any solution developed for the next two to three years may not work for the long term.

GENOMICS AND ELECTRONIC HEALTH RECORDS (EHR) WORKSHOP.
Dr. Jeff Struewing presented a summary of the Genomics and EHR Workshop that was held on April 27-28, 2011. Organizers included Greg Feero, Joy Boyer, Larry Brody, Lucia Hindorff, and Susan Vasquez. There were representatives at the workshop from academia, government, EHR vendors, insurers and professional societies. The HHS Office of the National Coordinator anticipates that 80% of the country will adopt EHRs by 2019, and that both the health IT and genomics communities are making progress on largely independent tracks. The goal of the workshop was to clarify the issues surrounding the intersection of health IT systems in the US in the era of genomic medicine, and to understand the opportunities and challenges to fully realizing the potential benefits of genomic integration. Workshop participants debated the need to adopt and extend existing standards, and the role of the EHR as a medico-legal document. The workshop highlighted efforts in the eMERGE Network as well as within PhenX as a resource for phenotype standards.

Council member Rex Chisholm noted that the relevance of this workshop to the efforts from the eMERGE Network. Other Council members noted that there was a lot of discussion concerning ELSI issues at the workshop. Council was also interested in using PheGenI to develop a standard clinical annotation. Pearl O'Rourke highlighted the need to address informed consent as a form of public health reporting mechanism. Overall, Council agreed that the workshop was timely in light of the widespread adoption of EHRs.

CONCEPT CLEARANCES

Future of ENCODE. Drs. Elise Feingold and Peter Good presented a concept clearance for three RFAs, one for ENCODE projects to continue using current technology to pursue the goal of generating comprehensive catalogs of the functional elements in important genomes (U54), one to support a single centralized database to serve as a data coordination and analysis center (U41), and one to enhance data analysis activities beyond ENCODE participants (U01). As background, they noted that the major long-term goal for ENCODE-type projects is to identify functional elements of the genome and that the mid-course review of 2010 concluded that the long-term goals of completing the catalog of functional elements should still be priority for NHGRI, and that current technology and reagents are not sufficiently robust. In February 2011, Council unanimously cleared an ENCODE Technology Development RFA to solicit applications for R01 and R21 projects to improve the sensitivity and cost of ENCODE analysis, and for high-throughput biological validation.

In discussion, Council asked about the division of effort between human and model organisms in the first RFA. Drs. Good and Feingold explained that the primary emphasis would be human studies, the secondary emphasis would be on mouse, but that continued work on fly and roundworm would be considered; the final decision will, of course, depend on the applications and the reviews. Council expressed concern that the proposed budget would not be enough to support data analysis and the ENCODE Coordinating Center. Dr. Good clarified that the 40% reduction in funding partially accounts for increased efficiency, but would seek Council's advice if members find the budget requests in the proposals were inadequate. Council recommended that more support be given to the Data Analysis and Coordination Center RFA for ENCODE. Council members also suggested discussion with other ICs about collaboration and contributing support to these proposed efforts.

The motion to approve the concept clearance passed unanimously.

GENOMICS OF GENE REGULATION. Drs. Peter Good and Elise Feingold presented a concept clearance for demonstration projects on the genomics of gene regulation. NHGRI has obtained considerable community input about the need for more detailed information about the structure and dynamics of chromatin, its relationship to the regulation of expression, and gene regulatory networks. Better technologies are needed to reduce the cost of experimental analysis, to reduce sample size, and for high-throughput functional tests for the functioning of both DNA and RNA in the control of gene expression. The goal of the proposed RFA is to solicit applications for research projects that will use genomic data and genomic technologies to advance the understanding of genetic regulatory systems. The proposed mechanism of support is a U01 Cooperative Agreement, and all sites would participate in the Genomics of Gene Regulation (GGR) network.

In discussion, Council expressed concern that the GGR data analysis centers would be over-worked and inadequately supported. Council recommended that the budget be increased as the proposed experiments are likely to be very expensive. Council members were overall very enthusiastic. The motion to approve the concept passed unanimously.

ANALYZING THE WHOLE CHIP FOR GWAS. Dr. Teri Manolio presented a concept for a project on "Analyzing the Whole Chip for GWAS." The scope of the proposal is to support broader utilization of genome-wide association (GWA) data in GWAS of human disease. Goals include facilitating more comprehensive analysis of existing GWA data, developing and validating new quality control and genotype calling procedures, and developing and validating new statistical methods, analytical strategies, and study designs. Only 32% of GWAS papers from January 2010 to March 2011 included analysis of the X chromosome. The lower genotyping accuracy on the X chromosome could be due to difficulties with clustering algorithms, the pseudo-autosomal region that is shared with the Y chromosome, missing data, and higher levels of chromosome anomalies. Interpretive challenges regarding X chromosome analysis are associated with the issue of X-inactivation. Analytical challenges include lack of imputation software until recently, difficulty in assigning haplotypes, and a need to accommodate different expectations for Hardy-Weinberg equilibrium (HWE) and minor allele frequency (MAF) estimation.

Community opinion about the readiness for analyzing the X chromosome varies. Some think that X chromosome analysis will occur naturally now that imputation programs regularly include the sex chromosomes. Others think that the initiative is premature and will first require sequence data from X, Y, and mitrochondria (MT). The objectives of the whole chip initiative are to obtain and analyze existing GWA data for phenotype associations with X, Y and MT variants; to focus on datasets where these data have not been analyzed; to develop, validate and disseminate new user-friendly quality control and analytic methods; and to include diverse populations. The proposed mechanism of support would be the R01 Research Project Grant. Other NIH institutes will be encouraged to participate and to fund applications with a wider range of phenotypes.

In discussion, Council agreed that this concept should be revisited in 8 months at the earliest. Council was concerned about the potential issue of stimulating analysis methods, when there are currently no methods available to analyze X, Y or MT SNPs. Also, Council did not think there were enough SNPs on the Y chromosome to analyze in the first place, and the concept lacks a strong incentive to find strong associations in these regions. Council also noted that there are ongoing analyses within existing consortia that will address X chromosome analysis. Council encouraged NHGRI staff to develop a publication about the data that are available, and to issue a program announcement (PA) that would not carry a funding commitment.

The motion to *not* approve this concept as an RFA passed unanimously.

COUNCIL-INITIATED DISCUSSION. Council requested an update on the next-generation sequencing data storage issue at its September meeting. Dr. Green noted that it will take some time to develop an NIH-wide plan to address the broad issue of computational biology. Council agreed that any discussion about large-scale informatics at the next meeting should have a narrow NHGRI-focus.

The Council meeting in September will be heavily devoted to reviewing grant applications. The Open Session might only feature the Director's Report, while the rest of day one and day two will be allotted to the Closed Session.

ANNOUNCEMENTS AND ITEMS OF INTEREST

Mark Guyer commended the American College of Medical Genetics Report and National Society of Genetic Counselors (NSGC) Quarterly Report to Council.

CONFLICT OF INTEREST

Mark Guyer read the Conflict of Interest policy to Council and reminded the members to sign the forms provided.

REVIEW OF APPLICATIONS

In closed session, the Council reviewed 185 applications, requesting $178,234,553 (total cost). The applications included 75 research project grants, 17 ELSI grants, 44 RFAs, 24 research center grants, 4 conference grants, 2 career transition awards, 1 institutional training award, 11 SBIR Phase I grants, 1 SBIR Phase II grant, 1 STTR Phase I grant, 1 individual training grant, 3 education project awards, and 1 mentored quantitative research center award. A total of 114 applications totaling $97,735,359 were recommended.

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

_____ _____

Date

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

_____ _____

Date

Eric Green, M.D, Ph.D.
Chairman
National Advisory Council for Human Genome Research