

NATIONAL ADVISORY COUNCIL FOR HUMAN GENOME RESEARCH
SUMMARY OF MEETING¹
May 21, 2012

The Open Session of the National Advisory Council for Human Genome Research was convened for its sixty-fifth meeting at 10:15 AM on May 21, 2012 at the Fishers Lane Conference Center, Rockville, MD. Dr. Eric Green, Director of the National Human Genome Research Institute, called the meeting to order.

The meeting was open to the public from 10:15 AM until 2:30 PM on May 21, 2012. In accordance with the provisions of Public law 92-463, the meeting was closed to the public from 8:30 A.M. until 10:00 AM, and from 3:00 PM until adjournment at 5:30 PM on May 21, 2012. The Closed Session was continued on May 22, 2012 from 8:00 AM until 3:00 PM for the review, discussion, and evaluation of grant applications.

Council members present:

1. Amy McGuire
2. Richard Wilson
3. Jill Mesirov
4. Pearl O'Rourke
5. Rex Chisholm
6. David Williams
7. David Kingsley
8. Anthony Monaco
9. Carlos Bustamante
10. Pamela Sankar
11. Howard McLeod
12. Richard Myers
13. Michael Boehnke
14. James Evans
15. Deirdre Meldrum
16. Mark Chee
17. Ross Hardison

Ad hoc Council members:

Richard Gibbs (via Teleconference)

Council members absent:

None

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	Carson Loomis, DER
Mela Asefa, DER	Lindsey Lund, DER
Maggie Bartlett, OD	Chengetai Mahomva, DER
Victoria Bishton, DER	Allison Mandich, OD
Vivien Bonazzi, DER	Ian Marpuri, DER
Vence Bonham, OD	Jean McEwen, DER
Ebony Bookman, OD	Keith McKenney, DER
Joy Boyer, DER	Ray Messick, DER
Lisa Brooks, DER	Ebony Mitchell, DER
Kara Brown, OD	Jeannine Mjoseth, OD
Patricia Brown, DER	Marcia Morris, DER
Comfort Browne, DER	Janis Mullaney, OD
Shaila Chhibba, DER	Ken Nakamura, DER
Cheryl Chick, DER	Vivian Ota-Wang, DER
Monika Christman, DER	Brad Ozenberger, DER
Christine Conyers, OD	Diane Patterson, DER
Christine Cutillo, DER	Michael Pazin, DER
Chris Darby, DER	Jane Peterson, DER
Camilla Day, DER	Ajay Pillai, DER
Karen Deleon, OD	Rudy Pozzatti, DER
Carla Easter, OD	Erin Ramos, OD
Elise Feingold, DER	Laura Rodriguez, OD
Adam Felsenfeld, DER	Ellen Rolfes, OD
Tina Gatlin, DER	Tamar Roomian, DER
Zivile Goldner, DER	Karen Rothenberg, OD
Peter Good, DER	Jeff Schloss, DER
Bettie Graham, DER	Derek Scholes, OD
Eric Green, OD	Heidi Sofia, DER
Mark Guyer, DER	Jeff Struewing, DER
Linda Hall, DER	Kathie Sun, DER
Lucia Hindorff, OD	Larry Thompson, OD
Belen Hurle, DIR	Simona Volpi, DER
Heather Junkins, OD	Lu Wang, DER
Caroline Kelly, DER	Kris Wetterstrand, OD
William Kibby, OD	Ed Whitley, OD
Rongling Li, OD	Anastasia Wise, OD
Nicole Lockhart, DER	Rosann Wise, OD

Others present for all or a portion of the meeting:

Michael Watson, American College of Medical Genetics
Kimberly O'Sullivan, FNIH
Andrea Baruchin, FNIH
Frances Correa, International Medical News Group
Lommie Welch, Ohio University
Cate Gilmore, FNIH
Kate Saylor, NIH
Melissa Parisi, NICHD
Tiina Urv, NICHD
James O'Leary, Genetic Alliance
Joann Boughman, American Society of Human Genetics
Elizabeth Duggal, Smithsonian National Museum of Natural History
Jonathan Coddington, Smithsonian National Museum of Natural History
Loretta Cooper, Smithsonian National Museum of Natural History
Kara Blond, Smithsonian National Museum of Natural History
Randall Kremer, Smithsonian National Museum of Natural History
Heather Virdo, Life Technologies Corporation and Life Technologies Foundation
Jamie Rupert, Life Technologies Corporation
Melvin Limson, Association for Molecular Pathology
Mary Williams, Association for Molecular Pathology

INTRODUCTION OF NEW MEMBERS AND STAFF, LIASONS AND GUESTS

Dr. Guyer introduced new Council member Anthony Monaco.

Dr. Guyer introduced new staff members: Zivile Goldner (Senior Program Analyst) and Eugene Passamani (Advisor in Genomic Medicine).

Dr. Guyer introduced Council liaisons: Joann Boughman (American Society for Human Genetics), Ellen Giarelli (International Society of Nurses in Genetics), James O'Leary (Genetic Alliance), Rhonda Schoenberg (National Society of Genetics Counselors) and Michael Watson (American College of Medical Genetic and Genomics).

Dr. Guyer introduced guests: Mary Williams (Association for Molecular Pathology), Melvin Limson, Jamie Rupert (Life Technologies Corporation), Heather Virdo (Life Technologies Corporation) and Frances Correa (International Medical News Group).

APPROVAL OF MINUTES

The minutes from the February 2012 Council meeting were approved.

FUTURE MEETING DATES

The following dates were proposed for future meetings: September 10-11, 2012; February 11-12, 2013; May 20-21, 2013; September 9-10, 2013; February 10-11, 2014; and May 19-20, 2014.

NEW NHGRI INITIATIVE – SMITHSONIAN EXHIBITION

Eric Green announced a historic new partnership between the Smithsonian National Museum of Natural History (NMNH) and NHGRI for an exhibition on the human genome. In addition to celebrating the tenth anniversary of the completion of the Human Genome Project, the exhibition will also commemorate the 60th anniversary of Drs. James D. Watson's and Francis Crick's discovery of the double helix structure of DNA in 1953. The exhibition is anticipated to open in June 2013. The NMNH exhibition, now in

development, will be organized around several themes, including the Genome and You, and The Natural World, Health, and Humanity. The exhibition will present key insights about the human genome to the museum's approximately 7 million annual visitors. The 2,500-square-foot exhibition will occupy NMNH's Hall 23, the exhibition hall that typically houses temporary exhibitions, and which is a particularly appropriate venue since the human genome is comprised of 23 pairs of chromosomes. After at least a year at the museum, the exhibition will travel to other venues around the nation and the world. The exhibition will be accompanied by free educational resources and programs on genetics and genomics.

Generous donors have made this exhibition a possibility. The Life Technologies Foundation, the philanthropic arm of Life Technologies Corporation, has pledged \$3 million to fund the exhibition. Additionally, more than \$500,000 has been raised by the Foundation for the National Institutes of Health (FNIH) from the Brin Wojcicki Foundation, Celgene Corporation, Pacific Biosciences, New England Biolabs, Genentech and Michael and Beth Hunkapiller, the President and Chief Executive Officer of Pac Bio and his wife.

Elizabeth Duggal, Associate Director for External Affairs and Public Programs at NMNH, expressed NMNH's excitement about its partnership with NHGRI on this critical project. Ms. Duggal stressed the synergies between the missions and strategic plans of NMNH and NHGRI. These synergies have enabled the two organizations to collaborate on educating the public about the science of genomics. She thanked Life Technologies Foundation for their generous donation, which has made this exhibition a reality.

Jonathan Coddington, Associate Director for Research and Collections and Senior Curator at NMNH, spoke about the importance of the exhibition to NMNH's scientific programs. The NMNH is a large research institution that focuses on three areas: the earth and planetary systems, any aspect of the natural world, and human and cultural diversity. The NMNH hosts over 300 resident scientists each year and collaborates with about 500 additional scientists around the world. The NMNH believes that genomics and bioinformatics are going to drive research on the biological world in the 21st Century. Therefore, the NMNH, which houses the largest Natural History Biorepository in the world, needs to move towards becoming a museum of genomics by offering DNA and tissue samples from specimens from around the world to biodiversity researchers. The NMNH has also built a 15,000 square foot Genomics Laboratory on the National Mall. Life Technologies has will be providing technological support to this new laboratory.

Heather Virdo, Head of Corporate Giving for Life Technologies Corporation and the Life Technologies Foundation, a non-profit arm of Life Technologies Corporation, conveyed a message on behalf of her organization. Life Technologies is honored to have the opportunity to work with NMNH and NHGRI on this exhibition. The advances that the field of genomics will make in the next several years will be the key to solving critical problems in medicine and global issues such as bioterrorism and fossil fuel dependence. Life Technologies hopes that this exhibition will not only educate visitors on the powerful information we can now unlock from our DNA, but also serve as the catalyst to inspire people about the critical work scientists are doing to improve our lives.

In discussion, Council was extremely enthusiastic and supportive of this new partnership. Representatives from NMNH informed Council that, in addition to publicizing the exhibit via digital and social media, NMNH is exploring the possibility of a documentary with Smithsonian Networks and PBS. There will be many hands-on activities in the exhibition, as well as in the new Education Center that is opening at the same time as the exhibition. The travel plans for the exhibition are being developed with Science North, an organization in Canada. The plan is for the exhibition to travel for four years, with two to three locations per year. This will include international locations. It was noted that scientists would be enthusiastic about donating to the exhibition. Cate Gilmore from the FNIH informed Council that donations for the exhibition can be made through the FNIH and that fundraising from the community will begin soon. A suggestion was made to include a booth in the exhibition where people can ask questions about their genetics and get answers from a natural language user interface similar to Apple's Siri software.

Council inquired about the way in which the exhibition is being planned and built. Kara Blond, the lead exhibition developer, explained that NHGRI has been working closely with the exhibition team at NMNH to develop themes and stories that need to be shared with the public. The process is iterative, with a focus on the visual look and activities that visitors will do. Focus groups are also used to gain insight on everything from the name of the exhibition to the actual content. The exhibition team seeks buy-in from the larger community during the conceptual design phase. Fabrication and installation are the last steps. More plans will be shared with Council in September.

DIRECTOR'S REPORT

NHGRI has created an electronic resource for the Director's Report and associated supplemental material available at <http://www.genome.gov/directorsreport/>. Dr. Green reminded participants that the Open Session of the Council meeting is Webcast live. A permanent video archive of the Open Session of all meetings of the National Advisory Council for Human Genome Research is being created and will be available on the web with associated documents.

I. GENERAL NHGRI UPDATES

Proposed NHGRI Reorganization

NHGRI has moved forward with the proposed changes to its organizational structure. The changes mostly affect the Extramural Research Program and, to a lesser extent, the Office of the Director. The multi-step process is anticipated to be completed this summer and the required approvals are currently being sought at the Department of Health and Human Services. The new organizational structure will be implemented as soon as the approval process is complete. Details about the proposed changes and the reorganization process can be found at <http://www.genome.gov/reorg/>.

Departure of Greg Feero, M.D., Ph.D.

Greg Feero, founding Chief of NHGRI's Genomic Healthcare Branch, has been splitting his time for the last two and a half years between working at NHGRI on topics related to genomic medicine and as a practicing family physician. He has also been working in the family medicine residency program at Maine Dartmouth. Beginning in August, Dr. Feero, who has been at NHGRI since 2006, will turn his attention full-time to his practice and residency activities. He will also soon become a Contributing Editor for *Journal of the American Medical Association* in the area of genomics. Dr. Green thanked Dr. Feero for his tireless work and his deep commitment to the mission of the Institute and to the work needed to make genomic medicine a reality.

NHGRI Staff Member Honored: Teri Manolio, M.D., Ph.D.

Dr. Manolio, Director of the Office of Population Genomics at NHGRI and Senior Advisor to the NHGRI Director for Population Genomics, was awarded the DHHS Secretary's Award for Meritorious Service 2011 on February 21, 2012. She received the award in recognition of her exceptional leadership and coordination of the Department's research response on the health effects of the Gulf of Mexico oil spill. Dr. Manolio was also elected to the Johns Hopkins Society of Scholars. This honor is given to former Johns Hopkins University students or trainees who have made outstanding contributions to science and new knowledge.

II. GENERAL NIH UPDATES

Appointment of Director of the National Heart, Lung and Blood Institute: Gary H. Gibbons, M.D.

Gary Gibbons has been named the director of the National Heart, Lung and Blood Institute (NHLBI). Dr. Gibbons is the Founder and current Director of the Cardiovascular Research Institute at Morehouse School of Medicine, where he also serves as Chairman of the Department of Physiology. Until recently, he served on NHGRI's Board of Scientific Counselors for the Intramural Research Program. He will start his new position in the summer of 2012.

NIGMS Leadership Changes

For personal reasons, Dr. Chris Kaiser of MIT withdrew from becoming the new Director of the National Institute of General Medical Sciences (NIGMS), a position he had originally planned to begin in mid-April. As a result, Dr. Judith Greenberg will continue to serve as Acting Director of NIGMS. The search to identify an NIGMS Director will begin again. Dr. Green has been asked to co-chair the search committee along with Dr. Story Landis, the director of the National Institute of Neurodegenerative Disease (NINDS). Dr. Green invited Council members to send him ideas for potential candidates that the search committee should contact.

Launch of the NIH Genetic Testing Registry

The NIH launched the Genetic Testing Registry (GTR) on February 29, 2012. The GTR is a public database developed by the National Center for Biotechnology Information (NCBI) that aims to catalog and disseminate information about the availability, validity, and usefulness of genetic tests. It operates by voluntary submissions from test providers, capturing information about intended use, target populations, assay limitations, clinical validity, and clinical utility.

'Big Data' Initiative

In March, the Obama Administration launched the 'Big Data' Research and Development Initiative, which aims to improve the nation's ability to extract knowledge and insights from large, complex collections of digital data. Six U.S. government departments and agencies, including NIH, have committed more than \$200 million to fund new initiatives. The National Science Foundation and NIH are participating in a joint solicitation issued in March entitled "Core Techniques and Technologies for Advancing Big Data Science & Engineering." Through this, NIH is particularly interested in imaging, molecular, cellular, electrophysiological, chemical, behavioral, epidemiological, clinical, and other large data sets related to health and disease. There are seven NIH Institutes and Centers participating, with the anticipated total annual funding from NIH being approximately \$3 million. NHGRI anticipates contributing up to \$400,000 annually to this initiative.

'Big Data' Planning at NIH

At the 2012 February Council meeting, Dr. Green reported that a Working Group of the Advisory Committee to the NIH Director had been established to investigate the management, integration, and analysis of large biomedical datasets. This Data and Informatics Working Group is chaired by Larry Tabak (NIH Deputy Director) and David DeMets (University of Wisconsin). The Working Group will provide its report to the NIH Director in June 2012. In preparation for acting on that report, three trans-NIH subgroups have been established in the areas of molecular, phenotype, and imaging data. NHGRI and NIGMS are co-leading the first group focused on molecular data. The ultimate goal is to produce a series of ideas that could be proposed as a new Common Fund initiative in FY2014.

Advisory Committee to the Director NCBI Working Group

Dr. Francis Collins asked for a 'Needs Assessment' to be performed last summer by an ad hoc committee chaired by David Ginsburg from the University of Michigan. That committee recommended that NCBI be given special dispensation with respect to its annual budget because of its ever-growing responsibilities to assimilate and make available biological data, especially genome sequence data. As a result, NCBI has now been guaranteed a budgetary increase each year, regardless of the state of the overall NIH budget.

To ensure appropriate stewardship of this unusual budgetary and programmatic situation, Dr. Collins has established a new working group (WG) of the Advisory Committee to the Director, called the NCBI Working Group. This WG will provide advice about NCBI services, especially with respect to their relative priorities in the face of conflicting demands. Dr. Ginsburg will also serve as the chair of the NCBI WG, which includes Council member Jill Mesirov. Michael Gottesman and Eric Green will serve in an *ex officio* capacity. It is anticipated that this group will meet a few times a year to assess priorities, but will also be able to give input more rapidly if any acute issues or problems arise.

Basic Behavioral and Social Science Opportunity Network (OppNet)

Francis Collins established the Basic Behavioral and Social Science Opportunity Network (OppNet) in November 2009. The mission of OppNet is to pursue opportunities for strengthening basic behavioral and

social science research at the NIH, while innovating beyond the existing investments. All NIH Institutes and Centers collectively fund and manage OppNet. However, OppNet is separate from the Common Fund. In FY2012, NHGRI contributed \$349,000 to OppNet. Grants from the OppNet RFA “Mechanistic Pathways Linking Psychosocial Stress and Behavior” may come to the September Council meeting.

FY2013 NIH Appropriation: Overview

The President delivered his proposed FY2013 budget to Congress this February, essentially calling for a flat NIH budget relative to the current fiscal year. Congress is now holding various hearings, including those about the NIH. On March 20, Dr. Francis Collins and Dr. Tom Insel, Acting Director of the National Center for Advancing Translational Sciences (NCATS), testified before the House appropriations subcommittee responsible for drafting NIH’s budget each year. There was a strong focus on NCATS and the role of the NIH in translational science. On March 28, the corresponding committee on the Senate side held a hearing on the NIH, with Dr. Collins and several institute directors testifying.

Those two hearings took place in the face of some highly unusual circumstances related to the FY2013 NIH budget. There will almost certainly be no agreement about the budget until after the November election. Until then, it will not be known whether the NIH will get the President’s flat budget. It is highly likely that the new fiscal year will start on October 1 under a continuing resolution. This means that the NIH will be asked to temporarily operate assuming the same budget as the previous year.

As a result of last fall’s failed debt reduction negotiations, and the inaction of the deficit-reduction Supercommittee, an automatic 8% – 9% budget cut will occur in early January 2013 unless a new debt deal or other compromise is reached. Such a cut will have extremely negative consequences for the NIH since the budget reduction would be retroactive to October 1, 2012.

Advocates Warn of Sequestration Impact on the NIH

Advocates are expressing concerns about the potential cut to the NIH budget. For example, a United for Medical Research report released the day of the Senate hearing on the NIH budget estimates that such a budgetary cut would lead to the loss of 33,000 jobs in biomedical research across the United States, which is described as a massive step backwards for the field in this country. A Federation of American Societies for Experimental Biology (FASEB) report released last month estimates that such a sequestration will lead to a \$2.8 billion cut to the extramural budget, which would have a devastating effect on medical research. While various proposed solutions are being debated in Congress to avoid the sequestration, including a recently passed House bill, it is hard to predict if any of them will be implemented.

New Report: Leadership in Decline – Assessing U.S. International Competitiveness in Biomedical Research

Late last week, The Information Technology and Innovation Foundation and United for Medical Research released a new report entitled *Leadership in Decline – Assessing U.S. International Competitiveness in Biomedical Research*. This report is highly critical of the U.S.’s commitment to the life sciences, providing evidence of our declining global leadership. The budgetary problems of the NIH are cited as one of the core reasons for this. Dr. Green strongly encouraged Council members and others to read this report.

III. GENOMICS UPDATES

Mourning the loss of Renato Dulbecco

Renato Dulbecco won the Nobel Prize in Medicine in 1975 for his role in drawing a link between genetic mutations and cancer. In 1986, he wrote a heavily cited commentary in *Science* entitled “A turning point in cancer research: sequencing the human genome”. This article was key to the development of support for launching of the Human Genome Project in 1990.

Awards, Recognitions and Prizes to NHGRI-associated Scientists

- **Janet Rowley** was awarded the **2012 Japan Prize** from the **Japan Prize Foundation** in the field of Healthcare and Medical Technology. She will share the award with Brian Druker and Nicholas Lydon

for their respective roles in the development of the first genomically-targeted anti-cancer drug, Gleevec.

- **David Botstein, Eric Lander and Craig Venter** received the **2012 Dan David Prize** from the **Dan David Foundation**. The prizes are awarded annually for achievements having an outstanding scientific, technological, cultural or social impact on our world. Each year, fields are chosen within three time dimensions: past, present, and future. Drs. Botstein, Lander, and Venter were given their award for the future and for genomics research.
- **Tim Ley, Elaine Mardis and Rick Wilson** were awarded the **George Engelmann Interdisciplinary Award** as part of the **2012 Outstanding St. Louis Scientists Awards**. This new award recognizes outstanding achievement in science, engineering, or technology that results from collaboration among two or more individuals across disciplinary or institutional boundaries. In 2008, these three researchers led the team that published a description of the first cancer genome of patient with acute myeloid leukemia.
- **Andy Clark, Ron DePinho, Evan Eichler, Greg Hannon, Harris Lewin, Rick Young and Subra Suresh** were recently elected to the **National Academy of Sciences**.
- **Bruce Korf** has been elected **President** of the **American College of Medical Genetics and Genomics (ACMG) Foundation for Genetic and Genomic Medicine**. He takes over from **Rodney Howell** who has served as President for nine years. Dr. Korf is currently a member of NHGRI's Board of Scientific Counselors in the Intramural Research Program.

Presidential Commission for the Study of Bioethical Issues

The Commission has been considering bioethics issues raised by advances in human genome sequencing. Specifically, the Commission is focusing on issues related to access to and individual privacy protection for genetic information, with a focus on large-scale human genome sequence data.

The Commission published a Request for Comments on Issues of Privacy and Access with Regard to Human Genome Sequence Data. Comments are being received until May 25, 2012 and should be sent to the following email address: info@bioethics.gov. NHGRI staff is in close contact with the Commission to serve as a resource and to provide input on the possible ways in which the Commission could be particularly helpful.

DeciBio Report on Molecular Diagnostics

The life sciences market research firm DeciBio published a report in April that forecasted the next few years of the life science research tools market. Although they looked at many different research tool areas, they found that genomics is expected to be the fastest-growing segment. According to their projections, the genomics sector is poised to grow at 6% annually over the next five years – from \$6.8 billion in 2011 to \$8.9 billion in 2016.

National Bioeconomy Blueprint

The White House Office of Science and Technology Policy recently published a *National Bioeconomy Blueprint*. The document points to various ongoing developments in the biological sciences that will likely have important economic impacts for the nation. The report describes how genomics and bioinformatics are “foundational technologies,” both today and for the future. The report featured, without direct input from NHGRI, NHGRI's graph highlighting the plummeting costs of genome sequencing.

Biotechnology Patents and the Courts

In March 2012, the US Supreme Court ended a long-running patent case between Prometheus Laboratories and Mayo Medical Laboratories over a patent for determining the correct dose of a drug by looking at a patient's blood metabolite levels. Mayo was sued by Prometheus in 2004 for offering its own test with slightly different thresholds for changing dose. The Supreme Court ruled in favor of Mayo, finding that Prometheus was trying to patent a natural phenomenon. The ruling will have implications for the pending case between the American Civil Liberties Union (ACLU) and Myriad Genetics.

Recent Genomics Meeting

- The **2012 Advances in Genome Biology and Technology (AGBT) Meeting** took place in February. Life Technologies and Illumina announced the availability of new DNA sequencing

machines later this year. Oxford Nanopore announced that their USB-sized DNA sequencer, the MinION, will be available later this year.

- The 24th annual **Biology of Genomes Meeting** was held at Cold Spring Harbor Laboratories. Notable highlights from this meeting included several talks on single-cell genomics, impressive updates on cancer sequencing projects, an ELSI panel discussion on genomic literacy, and keynote presentations by Debbie Nickerson and Susan Wessler.

NOVA: “Cracking your Genetic Code”

A NOVA special entitled “Cracking Your Genetic Code” debuted on PBS stations in March. The development of this show was, in part, funded by NHGRI, and numerous familiar faces were featured throughout the one-hour program. The show examines the evolving genomic technologies and research surrounding genetics and genomics-based medicine.

NHGRI Genome Advance of the Month

NHGRI continues to feature a ‘Genome Advance of the Month’ on our website. Two recent publications that were featured since the last Council meeting reported population-level characteristics of loss-of-function variants in the human genome and a personal ‘-omics’ profile approach to personalized medicine.

Genomics in the News

- Council member David Kingsley and his colleagues at Stanford University and the Broad Institute have analyzed the whole-genome sequences of 21 three-spine sticklebacks from around the world. The findings appear in *Nature* and are helping to identify the regions of the stickleback genome responsible for notable phenotypic adaptations.
- *Nature* recently published a paper reporting the genome sequence of the gorilla, an effort involving a consortium of investigators including researchers at the Sanger Institute and Council member Rick Wilson. While confirming that our closest relative is the chimpanzee, the team found some interesting results pointing to many regions of the human genome that more closely resembles the gorilla than the chimpanzee genome.
- Three papers reporting new findings about the genetics of autism were published in *Nature* last month, representing the work led by Evan Eichler, Mark Daly, and Matthew State. Whole-exome sequencing was performed by all three groups, unveiling interesting patterns of gene mutations in autism. Their results suggest modest roles for hundreds of genes in the development of autism and pinpoint a few specific genes as genuine risk factors.
- David Page was recently a guest on The Colbert Report. He discussed the evolution of sex chromosomes on the show. Francis Collins also recently appeared on the show to talk about obesity and the new multi-part HBO series “Weight of the Nation.”
- In early April, NPR ran a story about a preschool academy in New York City that will now require submission of a DNA sample of each child as part of their application. DNA testing will then be performed as part of the evaluation process. As one might imagine, this story had the potential to bring significant distress and debate in the genomics community. However, NPR then admitted this story, issued on April 1st, was just an April Fools’ Day joke.

IV. NHGRI EXTRAMURAL PROGRAM

NHGRI Sequencing Network

The NHGRI Genome Sequencing Program has four components: 1) Large-Scale Genome Sequencing Centers; 2) Mendelian Disorders Genome Centers; 3) Clinical Sequencing Exploratory Research (CSER) Projects; and 4) Informatics Tools for High-Throughput Sequence Data Analysis. Investigators from all four initiatives will meet in October 2012 for the first time.

Large-Scale Sequencing Centers

The Large-Scale Genome Sequencing Centers are undertaking numerous projects, mostly related to complex disease and cancer. In February, the Obama administration announced new efforts to fight Alzheimer’s disease, including earmarking \$50 million of existing funds to cutting-edge Alzheimer’s research. Accounting for half of those funds, the Large-Scale Sequencing Centers are in the late planning

stages for a significant Alzheimer's disease genome-sequencing project in collaboration with the National Institute on Aging and its grantees. The Sequencing Centers produced a number of publications since the last Council meeting on autism, schizophrenia, cancer, comparative genomics, and population genomics among other topics.

The Cancer Genome Atlas

The Cancer Genome Atlas (TCGA) program involves NHGRI's Large-Scale Genome Sequencing Centers. TCGA has been hard at work on about 20 different tumor types, and has papers in press or under review that report analyses for three major diseases: colorectal carcinoma, breast carcinoma, and lung squamous cell carcinoma. Several additional manuscripts are also anticipated this year.

CGHub, the new TCGA sequence data repository developed at the University of California, Santa Cruz, recently opened. Investigators will be able to find all TCGA primary sequence files at CGHub. Throughout this year, CGHub anticipates adding new features to make these data more useful. In an important advance on the policy front, CGHub is the first 'NIH Trusted Partner' for archiving and distributing genome sequence data outside of NCBI or EBI. Several more Trusted Partners for NIH projects are being developed. These will add value to this type of data and make them more useful and accessible to investigators.

TCGA continues to be on target for its ambitious goal of completing comprehensive analyses of more than 20 tumor types by 2014. Genomic data on more than 6,000 cancer cases are available now, with approximately 200 being added to the data portal each month.

Mendelian Disorders Genome Centers

The three Centers for Mendelian Genomics are co-funded by NHGRI and NHLBI. They aim to discover the genetic basis of as many Mendelian disorders as possible. The program's single sample solicitation web portal is now live and a pipeline from sample solicitation to sample assignment to the Centers has been implemented. An educational program focused on Mendelian Genomics is planned for the ASHG annual meeting in 2012. Disease gene discovery is ongoing at the Centers at various stages from sequencing to the identification of disease genes.

Clinical Sequencing Exploratory Research (CSER) Projects

CSER investigators are tackling important regulatory, technical, and psychosocial challenges in bringing genomic medicine to patients. The CSER Steering Committee and the ELSI Return of Results Consortium held their first meeting recently. Topics discussed at the meeting included informed consent, refining definitions of actionability, distinctions between patients and research participants, and success stories from early implementation of clinical sequencing. The CSER Program RFA has been reissued along with an RFA for a CSER Coordination Center that will support both the CSER program and the Return of Results Consortium. Both RFAs have application receipt dates of July 26, 2012.

Informatics Tools for High-Throughput Sequence Data Analysis

The network of grantees funded as part of this fourth component of NHGRI's new Genome Sequencing Program has chosen a name to reflect its mission: "iSeqTools". The aim of this network is to develop robust and reliable analysis tools for use by researchers without specialized computational skills. An effort is being made to leverage NHGRI's considerable investment in sequencing centers as well as initiatives such as 1000 Genomes, Galaxy, and others. A catalog of tools and strategies is being assembled on the iSeqTools wiki to create a knowledge base and to identify synergies.

DNA Sequencing Technology Development

The DNA Sequencing Technology Development Program held its 8th annual grantee meeting in early April. The last day of the meeting included 40 non-grantee individuals who are interested in developing technologies for faster, less expensive, and more accurate DNA sequence generation. The highlight of the grantee meeting were presentations of two papers from the laboratories of Jens Gundlach and Mark Akeson featured on the cover of the April issue of *Nature Biotechnology*. These papers demonstrated reproducible electronic signals corresponding to the sequence of DNA molecules translocating through a nanopore. This progress represents the end of a 20-year odyssey since the idea was first proposed in

1992. The first commercial device that uses nanopores for sequencing DNA is expected to be available commercially later this year.

ENCODE and modENCODE

Ten ENCODE Technology Development awards were funded in April and an eleventh award is expected to be funded in May. These projects aim to develop improved methods for identifying functional elements and for validating their biological function. Three ENCODE RFAs were released in October 2011 and applications were received in December 2011. These RFAs aimed to support research projects that apply high-throughput, cost-efficient approaches in order to extend the ENCODE resources to become as complete catalogs as possible. NHGRI is organizing a modENCODE Symposium, which will be held in the Natcher Conference Center on the NIH campus on June 20-21, 2012. The symposium will be open to the public. There are various integrative analysis papers being planned. The ENCODE Consortium has a main integrative paper and many companion papers currently under review, with publication expected to occur in the early fall. The modENCODE and ENCODE Consortia are currently working to integrate worm, fly, and human ENCODE data. The mouse ENCODE Consortium is currently planning a comparison of human and mouse data.

Ethical, Legal and Social Implications Program

The ELSI Program issued two RFAs in connection with its Centers of Excellence in ELSI Research (CEER) Program – a P20 RFA to fund up to two exploratory Centers and a P50 RFA to fund up to two additional full Centers. These applications are due in July for review in the fall, with funding after the February, 2013 Council meeting. The ELSI Program formally launched its Return of Results Consortium, which consists of investigators on R01 and R21 projects focused on this topic, as well as the investigators involved in the ethical and psychosocial research components of the Clinical Sequencing Exploratory Research (CSER) program and several others with investigator-initiated projects studying issues related to this topic. This Consortium recently held its first face-to-face meeting in conjunction with the CSER Steering Committee. Working Groups have been established dealing with instruments and measures, informed consent, actionability, and special issues relating to returning results in the pediatric context. The April 2012 issue of *Genetics in Medicine* focused on issues relating to return of results and incidental findings. A large number of the papers in that issue are the result of research funded by the ELSI Program, and many of the authors are members of the new Consortium.

Upcoming Planning Meetings

An NHGRI workshop on “Integrating Functional Data for Connecting Genotype to Phenotype” will be held July 30–31. This meeting seeks to explore more deeply some ideas that came out of the planning efforts in the area of ‘basic genomics.’ Specifically, the workshop will address whether there is a practical, systematic way to comprehensively bridge the gap between sequence and phenotype by producing a catalog of multi-level functional annotations of all genomic elements. The workshop will also discuss the utility of potential data types, organization of the information, and integration relative to both translation and the understanding of basic biology.

V. NIH COMMON FUND PROGRAMS

Human Microbiome Project

Funding for the Human Microbiome Project ends in FY2012. Two major publications of the HMP Consortium have been accepted by *Nature* and will be published in June. These two publications will be accompanied by the release of more than 20 companion papers in a *PLoS* virtual ‘HMP Collection.’ Over the last four months, a working group of program staff representing 12 NIH Institutes and Centers developed a proposal for a follow-on program to HMP. The proposal for HMP2 was submitted to the Common Fund in April and is currently being evaluated. A full report about HMP and a possible HMP2 will be given at the September Council meeting.

Knockout Mouse Phenotyping Project

The Knockout Mouse Phenotyping Project (KOMP²) is the second phase of an initiative that aims to create a public resource comprised of mice containing a null mutation in every gene in the mouse genome. In 5 years, KOMP² aims to make 2,500 live mouse strains from knockout ES cells and to

characterize them with a set of systematic phenotyping protocols. KOMP² awards were made in FY2011, with overall funding for the program being \$111 million over 5 years. Three centers proposing to pair mouse production and mouse phenotyping have been funded. In order to make the data and mice available to researchers, an application was funded for a Data Coordination Center and Database at the EBI. This Center is now hosting a website that is being actively updated to show the current status of the project; it will eventually display the phenotype data. KOMP² has committed to collaborate with other international projects in the International Mouse Phenotyping Consortium (the IMPC) to achieve a total of 5,000 phenotyped strains. The IMPC now includes 9 active programs, and KOMP² will be [participating](#) in joint coordination meetings with this Consortium.

Genotype-Tissue Expression

The pilot phase of the Genotype-Tissue Expression (GTEx) Project has been very successful, meeting the projected goals for enrollment and RNA quality. The first dbGaP data release, which will reflect a March 'data freeze,' is expected later this month. The Common Fund is now considering a scale-up proposal to enroll and study a total of 900 donors; a decision is expected soon.

Library of Integrated Network-based Cellular Signatures

The Library of Integrated Network-based Cellular Signatures (LINCS) program will hold its annual Consortium Meeting in November 2012. A request has been submitted to the Common Fund for a one-year extension of the pilot phase of the program through provision of FY2013 bridge funds. If approved, this would allow for the more robust development of a plan for LINCS Phase 2 starting in FY2014. Acting on a recommendation of its External Scientific Panel, LINCS has established a schedule for the quarterly release of data, beginning March, 2012. NIH staff is currently finalizing language for a LINCS data release policy.

Protein Capture Reagents Program

The Protein Capture Reagents Program is maintaining communication through several newly developed working groups focused on data dissemination, validation, and target list prioritization. As part of the Target List Prioritization Working Group, members are seeking community input on priorities for producing human transcription factor reagents. Input will be taken starting June 1 and ending July 31. The Program will then evaluate responses based on rationale and significance. This Working Group has already collected input from the ENCODE Consortium and various other external groups.

Human Heredity and Health in Africa (H3Africa)

The H3Africa project received 51 applications from across the African continent in response to the program's first set of RFAs. These applications were reviewed in March and April. A small group of NIH staff will make site visits to potential grantees later this month. The inaugural H3Africa Research Network Meeting will be held in Ethiopia in October 2012, jointly hosted by the Wellcome Trust, NIH's partner in H3Africa.

Single Cell Analysis

Single Cell Analysis is a new Common Fund program, with the goals of: (1) analyzing general principles of cellular heterogeneity via transcriptional profiling; (2) establishing a 'quantum leap' in spatiotemporal resolution within tissues; and (3) pursuing extensions and applications in the clinic. Applications received in response to three RFAs in each of these areas were reviewed earlier this month. In addition, a workshop for this initiative was recently held that focused on identifying gaps and opportunities in single cell analysis.

NHGRI has a particular interest in this program for several reasons. First, NHGRI is interested in new technologies that might emerge since the institute has historically supported awards that aim to perform DNA sequencing at the single cell level. Second, NHGRI has an interest in understanding networks and pathways generated from genomic data, and understanding the role of cellular heterogeneity at the single-cell level will be crucial for this. Finally, there is potential for advancing clinical applications of genomic technologies that focus on single cells. Programmatically, NHGRI will be involved in making funding recommendations and will participate in managing the grants for this Common Fund project.

VI. NHGRI OFFICE OF THE DIRECTOR

The Electronic Medical Records and Genomics (eMERGE) Network

In March, the eMERGE Network released its online phenotype library and tool called PheKB. PheKB is a knowledgebase for discovering phenotypes from electronic medical records. The purpose of PheKB is to provide a collaborative environment for building and validating electronic phenotype algorithms. There are now 17 phenotype algorithms in PheKB.

On behalf of the eMERGE Consortium, in April, Bradley Malin presented testimony to the National Committee on Vital and Health Statistics (NCVHS) Subcommittee on Privacy, Confidentiality, and Security. NCVHS is a major advisory committee to the Secretary of the Department of Health and Human Services. Dr. Malin presented the eMERGE experience in developing, applying, and evaluating policies and technologies for the governance of electronic medical record systems and biobanks through a lifecycle of data management. This included insights about data collection, data utilization and data dissemination.

GENEVA Initiative

The Gene-Environment Association Studies (GENEVA) Initiative reaches its conclusion at the end of May. Twenty datasets have been posted to dbGaP for a wide variety of phenotypes, all of which have also been imputed to a standard 1000 Genomes reference. Overall, GENEVA investigators have produced more than 50 publications since 2009. Further, they developed a Bioconductor software package called GWASTools for cleaning and analyzing GWAS data.

PhenX Program

Progress continues in the growth of the PhenX Toolkit. Most recently, the National Institute of Drug Abuse (NIDA) provided funds to expand the Toolkit to include additional substance use measures. In February, 43 new measures related to substance use and addiction were added to the PhenX Toolkit. The inclusion of these measures resulted from an eighteen-month collaboration between NHGRI, NIDA, and the PhenX project team and was overseen by a Substance Abuse and Addiction Scientific Panel and expert Working Groups. NIDA is encouraging all grant applicants proposing human-subjects research to use the PhenX Toolkit to increase researchers' ability to combine studies and gain the much-needed statistical power to identify genes related to substance use and addiction.

NEJM Genomic Medicine Series

The complete collection of articles on genomic medicine has now been published as part of the *New England Journal of Medicine* series edited by Greg Feero and Alan Guttmacher.

2012 DNA Day Chat Room

The NHGRI DNA Day Chat Room has been an annual event since 2005. This year's Chat Room was held on April 20 for 9 hours, and was staffed by more than 70 experts from around the country. In total, we received more than 900 questions, of which 764 were answered.

U.S. Science and Engineering Festival

The 2nd USA Science and Engineering Festival took place in April at the Washington Convention Center in Washington, D.C. As with the last festival held in October 2010, NIH was there in force, and NHGRI was among the most involved Institutes. This year NHGRI partnered with the American Society of Human Genetics (ASHG) on joint activities. In total, more than 25 volunteers from the NHGRI participated.

Genomics in Medicine Lecture Series

NHGRI is collaborating with Suburban Hospital in Bethesda and the Johns Hopkins University School of Medicine to hold a monthly grand rounds-style seminar covering topics in genomic medicine. Greg Feero is leading the planning committee for this series. Talks are being held on the first Friday of each month. All of the talks are being videotaped and made available on NHGRI's GenomeTV channel of YouTube.

VII. NHGRI INTRAMURAL RESEARCH PROGRAM

NHGRI Intramural Research Highlights

- Dr. Charles Rotimi and colleagues in the Center for Research on Genomics and Global Health published a study in the *New England Journal of Medicine* identifying a genetic association between the HLA class II locus and the tropical disorder podoconiosis. The condition affects 4 million people in 10 poor countries.
- Dr. KJ Myung reported in *Proceedings of the National Academy of Sciences* the development of a molecular screen that detected 22 DNA-damaging antioxidants. These compounds were shown to be lethal to dividing cells, such as those in tumors.

Current Topics in Genome Analysis

NHGRI recently completed the 10th iteration of its very popular lecture series called *Current Topics in Genome Analysis*. The series was started by Andy Baxevanis and Eric Green as an educational outreach effort of NHGRI's Intramural Research Program in the mid-1990's. In recent years, videos and Powerpoint presentations from these lectures have been posted to our GenomeTV channel of YouTube. Viewership has been remarkable, with over 20,000 views of the lectures from the 2012 series.

Blue Ribbon Panel Review of NHGRI Intramural Research Program

As mentioned at previous Council meetings, the NHGRI Intramural Research Program is currently undergoing a Blue Ribbon Panel review. Members of the Panel include Drs. David Page, Rick Myers (the NACHGR representative), Bruce Korf, Wylie Burke, Nancy Cox, Bob Waterston and Huda Zoghbi. The review will be completed this summer. At the September 2012 Council meeting, there will be a formal presentation about the Blue Ribbon Panel's review and report by Rick Myers and a general presentation about the NHGRI Intramural Research Program by Dan Kastner, the Scientific Director of NHGRI's Division of Intramural Research.

CONCEPT CLEARANCES

Genomic Sequencing and Newborn Screening Disorders by Dr. Anastasia Wise

The Genomic Sequencing and Newborn Screening Disorders concept clearance was first presented to Council in February 2012. The proposed initiative is comprised of two Requests for Applications (RFAs). Council approved the R43/44 Small Business Innovation Research (SBIR) and R41/41 Small Business Technology Transfer (STTR) RFA in February. A decision on the U19 Cooperative Research Program Project RFA was deferred to this Council meeting. The U19 RFA aims to stimulate research in three coordinated areas specifically applicable to newborn screening:

1. Acquisition and analysis of genomic datasets
2. Clinical research advancing understanding of disorders identified via newborn screening
3. Research related to ELSI implications of the possible implementation of broad DNA-based screening of newborns

NHGRI and NICHD each plan to commit approximately \$2.5 million per year for 5 years to this initiative for a total of \$25 million. Five awards are anticipated. Council had the following concerns with the concept clearance in February:

1. A clear scientific rationale is needed for what is expected to be learned from this initiative
2. Population selection – consider the added scientific value of broadening the study population beyond those individuals that are confirmed positive by newborn screening
3. 500 gene targeted sequencing is not enough of an advance
4. ELSI concerns over population selection and study design
5. Concern over public perception, public relations, and consent

In order to address these concerns, a Council Subgroup (Carlos Bustamante, Rex Chisholm, James Evans, Amy McGuire and Pearl O'Rourke) was convened. As a result of a series of discussions with this Subgroup, a revised concept clearance has been developed that addresses each of these concerns:

1. Three research questions that applicants can choose to focus on have been developed:

- i. For disorders currently screened for in newborns, how can genomic sequencing replicate or augment (e.g., make more accurate, comprehensive or inexpensive) known newborn screening results?
- ii. What knowledge about conditions not currently screened for in newborns could genomic sequencing of newborns provide?
- iii. What additional clinical information could be learned from genomic sequencing relevant to the clinical care of newborns?
2. Broaden the initiative to newborns with known newborn screening results (positive or negative)
3. Remove 500 gene targeted sequencing and require whole genome or whole exome sequencing
4. Tailor research to the context of sequencing performed and research questions
5. Require description of informed consent for sequencing and return of results in application

During discussion, Council recommended highlighting the important role ELSI research will play in this program in the RFA. Dr. Wise confirmed that ELSI research will be a required component of any funded project and that the language in the RFA will make this clear. Council encouraged a partnership between the Newborn Screening Program and the Return of Results Consortium to enable the discussion of common ELSI issues. Council expressed concern about the potential stigmatization associated with findings of increased disease risks. For example, the outcome for child with an increased risk of a learning disability would not be known for several years and could lead to the child being stigmatized. Dr. Wise noted that applicants would have to describe what results they plan to return to participants and how these results will be shared.

The motion to approve this concept clearance was passed.

Clinically Relevant Variants Resource by Dr. Erin Ramos

This concept clearance had been presented during the February 2012 Council meeting and deferred to this meeting. Council had several concerns about the proposed initiative in February. Council members felt that NHGRI must clearly be viewed as a leader in this area rather than just funding another group to produce a gene list. There was concern about a single awardee for the program as this could potentially lead to a less optimal product being produced. Additionally, Council thought that the focus of the program should be on genes rather than on variants. Council felt that the consensus process must include a clear hand-off to professional societies for development of clinical practice guidelines. Finally, Council felt it would be best if other NIH ICs collaborated with NHGRI on this program or clearly supported it.

A Council Subgroup was formed to discuss the concerns raised with this concept clearance. Members included Mike Boehnke, Jim Evans, David Kingsley, Howard McLeod, Pearl O'Rourke and Pamela Sankar. The Subgroup held a conference call in March with ASHG, AMP and ACMG participation. Based on this phone call and additional discussions at NHGRI, several revisions to this initiative have been made. The initiative has been re-named as the Clinically Relevant Variants Resource. The purpose of the program is to support a process for identification and dissemination of consensus information on genetic variants relevant to clinical care. The revised goals are to:

1. Identify genetic variants with likely implications for clinical care and incorporate these variants and evidence into a resource that can serve as the substrate for development of practice guidelines
2. Establish a process for transferring this information to appropriate clinical organizations for development of these guidelines
3. Build upon existing programs, unify them, and reduce duplicative efforts across research/clinical organizations

A multi-institutional approach that engages similar efforts and includes diverse perspectives is being sought. Along with NHGRI, other organizations including the ACMG, AMP, ASHG and CAP will be closely involved with the initiative and will jointly appoint a Steering Committee. This will facilitate consultation with relevant constituencies such as other professional societies, regulatory agencies, payers, clinicians, researchers and patients. Applicants will be expected to survey ethical, legal, social, and policy issues regarding results reporting and to propose strategies to integrate and build upon these efforts. Applicants will be expected to describe their plans for engagement and integration with ongoing efforts, data

synthesis, curation, and development of consensus findings, hand-off to the appropriate organizations and professional societies for development of practice guidelines, and dissemination. Applicants will have to provide detailed plans for grouping genes or variants into categories of clinical relevance. Plans for dealing with a profusion of variants of unknown significance and for focusing on particular types of variants or genes will have to be described.

In discussion, Council stressed the importance of support from other ICs for this initiative. Dr. Ramos noted that other ICs have looked at NHGRI's plans and are very interested in the initiative, with some potentially considering co-funding. Collaboration with the Mendelian Disorders Sequencing Centers was encouraged, as was a five-year period of funding. Council highlighted the importance of encouraging participation in the initiative by non-geneticists for their expertise on diseases. The International Standards for Cytogenomic Arrays (ISCA) Consortium has a database containing whole genome array data from a subset of the ISCA Consortium clinical diagnostic laboratories. Council suggested integrating the information in the ISCA database into the database created for this new initiative. Additionally, the new database can be designed keeping the strengths and weaknesses of the ISCA database in mind. In the event that the Clinically Relevant Variants Resource is not well received, Council felt that NHGRI should have a plan in place to ensure that the effort is not wasted. Additionally, Council recommended that NHGRI should have a plan for how professional societies will develop guidelines to move beyond a database. Joann Boughman from ASHG, Mary Williams from AMP and Michael Watson from ACMG noted that NHGRI's level of engagement with professional societies has been high, and that NHGRI is filling an important need for clinicians in the rapidly changing field of genomics through this initiative. Michael Watson pointed out that developing consensus and evidence-based guidelines is an expensive process. He emphasized the importance of designing the evidence collection process with the aim of the lowest guideline development costs in mind. Dr. Watson also stated that the rate of compliance with medical guidelines is only 50%. To be utilized successfully, clinical decision-making support tools need to be integrated into electronic medical systems that clinicians actually use. Dr. Ramos clarified that NHGRI will seek input on how to transition to guidelines in the smoothest way possible.

The motion to approve this concept clearance was passed.

NHGRI TRAINING PORTFOLIO by Dr. Bettie Graham

A few members of Council had met with NHGRI staff in February to discuss the NHGRI training portfolio. The group included: Michael Boehnke, Carlos Bustamante, Rex Chisholm, Ross Hardison, Amy McGuire, Howard McLeod and Deirdre Meldrum. The purpose of the discussion was to respond to the need for more training programs in light of budget constraints and to review NHGRI's current training programs and assess how they align with the Strategic Plan. Additionally, the group discussed the gaps in NHGRI's training programs, the work other NIH ICs are undertaking in these areas, and how to shape the future of NHGRI's training programs.

The group of Council members concluded that there are several areas of continuous need in training. All students must be trained in bioinformatics and statistics. There will be a need to train basic scientists to who can conduct research in clinical settings. Individuals need to be trained to develop methods for analyzing and interpreting large datasets.

Dr. Graham presented the goals of each of NHGRI's 12 T32 training grants and the grantee's plans for alignment with NHGRI's strategic plan. She also presented comments from trainees on their program's strengths and suggested improvements. Dr. Graham provided Council with information about the educational impact of NIH's 54 Clinical and Translational Science Awards (CTSAs) that support training in gap areas including informatics, bioinformatics, biostatistics, computational and molecular medicine. Dr. Graham suggested several options for the path forward. These included establishing a sub-committee of Council to focus on training, holding workshops to address needs in training and career development, a recommendation from Council on the level of funding that NHGRI should invest in training, aligning current training programs with the strategic plan and publishing RFA(s) in identified gap areas.

During discussion, Council members emphasized the critical need for truly interdisciplinary scientists who can work alongside clinicians. A multidisciplinary training environment is necessary for scientists to begin translating research into the clinic. At the same time, Council acknowledged that NHGRI must be cautious about being overly ambitious. It is important to train students with core expertise and give them the ability to talk across disciplines, but this cannot mean being in training for an excessive period of time.

Council felt that there is a great need for biologists who are trained to work with large datasets and who can utilize quantitative approaches in their biological research. It was noted that NHGRI training program graduates do gain experience in handling large datasets. It was suggested that it would be helpful to know how many trainees enter programs with a strong quantitative background and build on their biological expertise as compared to those with a strong biological background who build on their quantitative skills. Programs could be better designed to meet the goal of training scientists to use quantitative approaches in solving biological problems if this information were known. Council also thought that increasing awareness about employment opportunities in biology would be an effective way to draw undergraduates with quantitative skills to fill this need.

Members of Council wanted to know about the number underrepresented minorities that are part of NHGRI's training programs. Dr. Graham reported that approximately 10% of the trainees are underrepresented minorities. She also reported that NHGRI's Diversity Action Plan (DAP) has been providing training for underrepresented minorities for several years. Council inquired about the DAP program and its success. Dr. Graham pointed to the number of trainees who have graduated from the program and joined graduate programs and medical schools as a sign of the success of the program. However, she also noted that while the program has been successful, it will take a long time to meet all its goals.

Council was asked for guidance on the amount of training NHGRI should be funding. Currently, approximately two percent of NHGRI's budget is spent on training while the NIH as a whole spends approximately three percent of its budget on training. The NIH level might be inflated due to NIGMS's efforts in training. Council members felt that this was an important conversation not just for NHGRI, but NIH as a whole. There are many reports of underemployed people with PhDs. If this is true, then the amount of training might either need to remain the same or be cut. Some Council members recommended examining the jobs that NHGRI trainees are performing three to five years after completing the program. If these jobs are focused on genomics, then the level of training could either stay the same or increase. There was also a suggestion to increase the scope of the training program beyond just training PhDs. Instead of completely repurposing the job outlook of a person with such a degree, thought could be given to adding skills to someone who is already employed through certifications. Council members also noted that it is difficult to predict what the status of biomedical research funding will be five years from now, which is when graduates of today's programs will be applying for grants. This makes it hard to gauge the appropriate level of training for NHGRI to invest in.

Currently none of the training programs make their educational materials available online. It was noted that it very complicated and expensive to do this, but that it might be beneficial to post best practices across programs online. Council also highlighted the importance of the training program in maintaining internationally competitiveness in genomics.

A Working Group needs to be created to determine how to meet training needs to cover all of the five domains of genomics research highlighted in NHGRI's strategic plan. Council can expect to hear more from NHGRI staff about training in the future.

PROJECT UPDATE

1000 Genomes by Dr. Lisa Brooks

All samples for the 1000 Genomes project have been collected. These 2,500 samples are either already available or will be available from the repository at the Coriell Institute. They do not have any identifying or phenotypic data associated with them. A paper on Phase 1 data set will be submitted for publication

this June. The Phase 1 data set contains low-coverage (4X – 6X) whole-genome sequence data, exome data with deep coverage in exons and genotype data with 2.5 million SNPs from 1,092 samples collected from 14 populations. More than 35 Mb of additional sequence has been found as insertions across the many genomes. The phase 1 data set contains 38 million SNPs (70% novel), 2 million indels (62% novel) and 14,000 deletions (54% novel). Haplotypes integrating SNPs, indels and deletions have been found. The project produced haplotypes integrating all the variant types. Several discoveries have already been made from these data. New tools to analyze the datasets and information on function have also been developed. In what is a major advance for big data at the NIH, the data are available in the cloud through Amazon Web Services.

The Phase 2 data set comes from 1663 samples from 19 populations. The Broad Institute is calling variants in this data set using current methods. There are no plans to publish on the data; instead time will be invested to improve methods to map reads and call variants. By December 2012, Phase 3 data production will be complete. All remaining samples will be sequenced for a total of 2,500 unrelated samples. Variant calling will take place in spring 2013 and a final integrated data paper will be prepared in the summer of that year.

After the 1000 Genomes project is complete, investigators will work with the Genome Reference Consortium to fix assembly and sequence errors, provide alternative assemblies in structurally variant regions and provide entire haplotypes. Consideration will also be given to public data sets that would be valuable for supporting human genetic studies. These data sets might include more populations and genomic data related to function.

In discussion, Council members were extremely enthusiastic about the usefulness and impact of the 1000 Genomes project. The importance of moving beyond identification of variants to large-scale efforts that involve testing variants and their function was emphasized. Dr. Brooks noted that each sample collected for the project has a cell line and that consents are in place for functional studies. However, IPS cells cannot be created under the current consent document. Adding additional populations to future studies was seen as something that should be considered. However, Council felt that any future studies should leverage the existing investment by undertaking functional studies on samples that have already been collected. A question was raised about the value of investing in the study of the function of variants that are not associated with disease. It was noted that while the variants might not be associated with disease, information about them can be used and leveraged in studies of disease. Additionally, they contribute to the understanding of the biology of genomes and regulation. Council discussed the importance of phenotypic data in addition to sequence data. However, having phenotypic data would make it difficult for data to be available openly at the scale of the 1000 Genomes data, due to dbGaP policies. A suggestion was made to consider next steps after the completion of 1000 Genomes through a meeting or a Council Subgroup.

NIH POLICY ON APPLICANTS WITH MORE THAN \$1.5 MILLION IN GRANT SUPPORT by Dr. Bettie Graham

The language in the 2013 Department of Health and Human Services, National Institutes of Health, Overall Appropriations, states: “NIH will also establish a process for additional scrutiny and review by an Institute or Center’s Advisory Council of awards to any principal investigator with existing grants of \$1.5 million or more in total costs.” In response to the appropriations language, NIH has developed a policy for applications for research grants from an investigator whose funding from NIH exceeds the \$1.5 million threshold. The policy calls for a Special Council Review (SCR) to determine whether there is good justification for making an additional award to that investigator.

All competitive revisions and competing applications in the RPG line will be subject to SCR. The RPG line includes mostly, but not exclusively, the following activity codes: R00, R01; R03; R15; R21; P01; UH2/UH3; DP1 and DP2. The following will be included in the >\$1.5 million total annual cost threshold:

- P01s and multiple-component and multiple-PI/PD RPGs in which all PI/PDs meet the threshold
- Funded grants and applications that have been designated for funding from all NIH institutes and centers

- Multi-year supplements included in out-year budget
- Active RPG awards (exclusive of no-cost extensions)

The following will be excluded in the >\$1.5 million total annual cost threshold:

- Applications in response to RFAs
- P01s, multiple-component RPGs, and multiple-PI/PD RPGs in which at least one PI/PD does not exceed the \$1.5 million threshold
- Project Leader's funds and core costs on P01 applications
- Diversity and re-entry supplements

NHGRI has developed a plan to comply with this policy. For each Council meeting, a report will be generated that lists all eligible applications from PIs/PDs that exceed the \$1.5 million threshold. NHGRI staff will review the list for accuracy. If necessary, the report will be modified to include multiple-year administrative supplements. The grants management and program staffs will work together to finalize the list, including only applications that are likely to be considered for funding. NHGRI has an established process for bringing special actions to Council. This same process will be used for SCR of applications that exceed the \$1.5 million threshold. Specifically, a Batch Staff Analysis will be prepared that will include all applications that are subjected to SCR. For each application on the Batch Staff Analysis, the program director will describe the research and justify how it fulfills the criteria "consider for funding" or "not consider for funding." The staff will include a recommendation. At least two Council members will be assigned to lead the Council discussion, but all Council members will be expected to participate in the discussion. Following the discussion, a vote to "consider for funding" or "not consider for funding" will be taken. The decision will be documented in the Council Summary Statement. For SCR applications that will not be considered for funding because of the threshold, staff will notify the institutions and the PIs/PDs. NIH will implement this policy beginning with the October 2012 Council for applications that will be paid in FY13.

In discussion, Dr. Graham clarified that this is an NIH-wide policy. The policy does not affect the process by which review panels are run. Council will be the only body that will be reviewing applications to ensure that this policy is enforced. Due to the exclusion criteria, the policy should only affect approximately two to three applications at a given Council meeting.

UPDATE ON X CHROMOSOME PROGRAM NOTICE by Dr. Anastasia Wise

The Whole Chip concept clearance was presented to Council in May 2011. The proposal was to support broader utilization of genome-wide association (GWA) data in GWA studies of human disease. Goals included facilitating more comprehensive analysis of existing GWA data and developing and validating new quality control and genotype-calling procedures as well as statistical methods, analytical strategies, and study designs for under-utilized information (primarily X, also Y, MT, and copy number variation data). At that time, Council had made the following recommendations:

1. Publish a Notice to encourage applications
2. Present findings at meetings
3. Write a paper on findings for a prominent journal
4. Return to Council in approximately one year with an update on X chromosome analysis numbers in the GWAS Catalog
5. Remove CNV data

Since the concept clearance was first presented, NHGRI has taken several steps to address Council's recommendations. NHGRI issued a Notice (NOT-HG-11-021) to encourage analysis and methods development for X chromosome GWAS data. The objectives of the Notice were to obtain and analyze existing GWAS data for phenotype associations with X chromosome variants, as well as Y, and MT variants, focusing on datasets where these data have not been analyzed. Additionally, the Notice aimed to develop, validate, and disseminate new user-friendly QC and analytic methods with open-access and include diverse populations. The first applications in response to the Notice have undergone peer review. Presentations on the X chromosome have also been made at several venues. Overall, only 33% of GWAS papers include X chromosome analyses.

Council felt that their initial concerns had been addressed and had no further concerns.

COUNCIL-INITIATED DISCUSSION

Council did not have any proposed topics for future meetings. Council was reminded that at the September Council meeting, there will be a formal presentation about the Blue Ribbon Panel's review of NHGRI's Intramural Program and a general presentation about the NHGRI Intramural Research Program by Daniel Kastner, the Director of NHGRI's Division of Intramural Research.

ANNOUNCEMENTS AND ITEMS OF INTEREST

The American College of Medical Genetics and Genomics Quarterly Report might be of interest to Council and can be accessed through the Council agenda: <http://www.genome.gov/27548774>.

CONFLICT OF INTEREST

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

REVIEW OF APPLICATIONS

In closed session, the Council reviewed 237 applications, requesting \$195,194,095 (total cost). The applications included 105 research project applications, 20 ELSI applications, 65 RFA applications, 21 research center applications, 3 conference grant applications, 3 career transition awards, 1 institutional training grant application, 10 SBIR Phase I, 4 SBIR Phase II, 1 STTR Phase I, and 1 STTR Phase II applications and 3 individual training applications. The Council concurred with the recommendations made by the Initial Review Groups on a total of 148 applications totaling \$123,022,789.

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