NATIONAL ADVISORY COUNCIL FOR HUMAN GENOME RESEARCH
SUMMARY OF MEETING[1]
September 10, 2012

The Open Session of the National Advisory Council for Human Genome Research was convened for its sixty-sixth meeting at 10:00 A.M. on September 10, 2012 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 10 A.M. until 6:00 P.M. on September 10, 2012. In accordance with the provisions of Public law 92-463, the meeting was closed to the public from 8:00 AM to 10:00 AM on September 10, 2012 and from 8:00 AM until adjournment at 2:00 PM for the review, discussion, and evaluation of grant applications.

Council members present:
Michael Boehnke
Carlos Bustamante
Lon Cardon, *ad hoc*
Mark Chee
Rex Chisholm
Joseph Ecker, *ad hoc*
James Evans
Ross Hardison
Howard Jacob, *ad hoc*
David Kingsley
Amy McGuire
Howard McLeod
Deirdre Meldrum
Jill Mesirov
Anthony Monaco
Richard Myers
Robert Nussbaum, *ad hoc*
Lucila Ohno-Machado, *ad hoc*
Arti Rai, *ad hoc*
Pamela Sankar
David Williams
Richard Wilson

Council members absent:

Pearl O'Rourke

[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:

Alexi Archambault, DER
Mela Asefa, DER
Alice Bailey, OD
Jessica Barry, DER
Maggie Bartlett, OD
Vivien Bonazzi, DER
Vence Bonham, OD
Joy Boyer, DER
Lisa Brooks, DER
Comfort Browne, DER
Shaila Chhibba, DER
Cheryl Chick, DER
Monika Christman, DER
Colleen Clark, DIR
Deborah Colantuoni, DER
Christine Conyers, OD
Camilla Day, DER
Karen DeLeon, OD
Carla Easter, OD
Jerrell Edelen, DER
Alvaro Encinas, OD
Elise Feingold, DER
Adam Felsenfeld, DER
Ann Fitzpatrick, OD
Tina Gatlin, DER
Bettie Graham, DER
Eric Green, OD
Mark Guyer, DER
Zephaun Harvey, DER
Lucia Hindorff, OD
Jean Jenkins, OD
Heather Junkins, OD
Daniel Kastner, DIR
Bill Kibby, DER
Laura Koontz, OD
Rongling Li, OD
Paul Liu, DIR
Nicole Lockhart, DER
Carson Loomis, DER
Lindsey Lund, DER
Terryn Marette, DER
Ian Marpuri, OD
Jean McEwen, DER
Glenn McFadden, DER
Keith McKenney, DER
Jeannine Mjoseth, OD
Janis Mullaney, OD
Ken Nakamura, DER
Vivian Ota Wang, DER
Brad Ozenberger, DER
Betsy Parker, OD
Eugene Passamani, OD
Michael Pazin, DER
Jane Peterson, DER
Ajay Pillai, DER
Rudy Pozzatti, DER
Lita Proctor, DER
Erin Ramos, OD
Laura Rodriguez, OD
Tamar Roomian, DER
Karen Rothenberg, OD
Jeff Schloss, DER
Derek Scholes, OD
Heidi Sofia, DER
Jeff Struewing, DER
Kathie Sun, OD
Larry Thompson, OD
Katya Vaydylevich, DER
Simona Volpi, DER
Lu Wang, DER
Chris Wellington, DER
Kris Wetterstrand, OD
Anastasia Wise, OD
Jeff Witherly, OD
Sherry Zhou, DER

Others present for all or a portion of the meeting:
Adam Berger, Institute of Medicine
Joann Boughman, American Society of Human Genetics
Greg Feero, Maine General Health
Kenton Hasson, Canon US Life Sciences Inc.
Milianne Ly, Deloitte Consulting
David Page, Massachusetts Institute of Technology and Whitehead Institute
Rhonda Schonberg, National Society of Genetics Counselors
Joan Scott, National Coalition for Health Professional Education in Genetics
Michael Watson, American College of Medical Genetics

INTRODUCTION OF NEW MEMBERS AND STAFF, LIAISONS, AND GUESTS

DIRECTOR'S REPORT

Dr. Green presented the Director's Report to Council.

Council wanted to know if the ENCODE and Common Fund Epigenomics Program Joint Tutorial at ASHG would be similar to the previous ENCODE-GENEVA joint meeting. Dr. Michael Pazin replied that the ASHG tutorial is more of a classroom-type discussion with practicals on how to use the ENCODE and Epigenomics data. ENCODE currently has no plans for future meetings, but it is always looking for opportunities for more people to utilize its data.

PRESENTATION OF THE GENOMIC MEDICINE WORKING GROUP

Dr. Rex Chisholm and Dr. Teri Manolio presented the activities to date of the NHGRI Genomic Medicine Working Group.

Council wanted to know how this working group's activities fit into current NHGRI activities developing a genotype to phenotype database. Dr. Manolio noted that these database activities are ongoing in the Clinically Relevant Variants Resource initiative, while the Genomic Medicine Working Group is more downstream.

Council asked about the involvement of decision support tools and any collaboration with electronic medical record providers. Dr. Chisholm replied that the eMERGE Electronic Health Record Integration working group focuses on integration of genomic information into the electronic health record (EHR). eMERGE will likely produce approaches for developing the logic for decision-support systems and methods for physically integrating the decision-support into the EHR. Current models look similar to radiology records. The three largest EHR providers have attended an eMERGE Steering Committee meeting and said they wanted guidance from eMERGE and other customers in terms of how to add these new functions to the EHR. Dr. Manolio added that a lot of work has been done with Epic and Cerner, as most eMERGE sites utilize these platforms.

Council questioned if the working group had any activity around somatic mutations and oncology. Dr. Chisholm noted that the working group wanted to include germline as well as somatic mutations, with microbiome samples as a future possibility. The Genomic Medicine working group has a subgroup focusing on cancer. The cancer subgroup is looking at best practices as well as specific projects where the group can get new data comparing germline and somatic mutations. Integration of TCGA data would also be useful. The group has not focused on the payer space in oncology.

Council was curious if the Genomic Medicine working group was focusing on elements downstream of DNA based on successes with epigenomics. Dr. Chisholm responded that the current focus is on germline DNA mutations because of the complexities with capturing RNA transcripts at the right times and conditions. The working group is definitely open to expanding its scope in the future.

WORKSHOP PRESENTATIONS

Project Updates and Meeting Reports

Workshop on "Establishing a Central Resource of Data from Genome Sequencing Projects"

Dr. Lisa Brooks presented highlights from the "Establishing a Central Resource of Data from Genome Sequencing Projects" workshop, which was held on June 5-6, 2012.

Council agreed that we need to change a lot of current paradigms to allow for broader patient consents and the availability of summary data from genome sequencing projects. Dr. Green noted that NHGRI will be creating a Data Informatics working group as an advisory body on these issues. We have previously presented an inventory of available sequence data to IC directors, who thought that broad consents would significantly advance the pace of research. Council cautioned that we cannot overlook protections and privacy of patient data.

Workshop on "Sequencing in Cohort Studies and Large Sample Collections"

Dr. Teri Manolio presented highlights from the "Sequencing in Cohort Studies and Large Sample Collections" workshop, which was held on June 28-29, 2012.

Council thought that NIH should work harder to target more diverse cohorts and cohorts that have not traditionally been analyzed. The meeting attendees thought the highest priority criteria for designing cohorts were large size, availability of broad baseline phenotyping, and ongoing patient contact. Council thought additional important criteria for selecting cohorts should include underrepresented ethnic groups, broad consents and contact for data deposition, investigator compliance for data deposition, and past behavior of investigators in terms of data deposition. It would also be of great value to aggregate data of different types and create a repository of samples with phenotypes that can be accessed.

Workshop on "Integrating Functional Data for Connecting Genotype to Phenotype"

Dr. Adam Felsenfeld presented highlights from the "Integrating Functional Data for Connecting Genotype to Phenotype" workshop, which was held on June 30-31, 2012.

Council noted that the meeting helped elucidate how differently people interpret the phrase "genotype to phenotype." Meeting attendees thought the database should be anything from a resource with function data for every gene to a resource that returns results to investigators. NHGRI needs to refine its vision so that this resource aligns better with the strategic plan and can integrate with other NHGRI programs like 1000 Genomes, GTEx, and ENCODE. A focused pilot project would help clarify what is possible.

Council thought the workshop should have a series of very focused follow-up meetings rather than waiting to have one larger follow-up meeting. At one of these meetings, the attendees need to work on a definition of function to determine how we interpret and use all of the data.

NHGRI GWAS Catalog Updates

Dr. Lucia Hindorff presented updates to the NHGRI GWAS Catalog.

Council was impressed with all of EBI's updates to the GWAS Catalog but would like to see some additional features. Council thought the catalog should be able to give the exact locus of any variant listed. Each variant would then have a hover-over box that would take the user to the variant's listing in the catalog. Council also wondered if a user could apply any ontology to the catalog. MESH should work at present, but at a later point EBI will include synonyms that should work for ontologies. Council also

asked if the catalog tracks copy number variant data. Dr. Hindorff noted that the catalog currently uses rs numbers for SNPs, and that PheGenie would be a better tool for tracking CNVs.

Council wondered if data collection would ever become automated to handle the large amount of genetic studies. Dr. Hindorff noted that the GWAS Catalog team is very aware of this issue and is pursuing solutions for the near future.

Council thought it would be useful to capture data on the most frequent users and search terms so that the GWAS Catalog team can tailor future alterations to the user base. At present, we can collect city and state information as well as if the user's email ends in .org or .edu. Dr. Green occasionally receives summary data.

NHGRI and the Common Fund

Dr. Mark Guyer made a presentation describing NHGRI's prominent role managing a relatively large number of the current Common Fund projects.

Council wondered how NHGRI can take on so many Common Fund projects. NHGRI plans for certain staff commitments for each project. We have hired more staff because of additional funding from the Common Fund. Each project proposal includes RMS budget plans to cover travel. This still does not cover other costs like grants management and administrative costs. Common Fund ideas, however, come from a variety of places. Some projects were ideas of Dr. Francis Collins during his tenure as the NHGRI director, while others were developed within NHGRI. During a discussion about the future funding of the Undiagnosed Diseases Program the other IC directors recommended to Dr. Collins that the UDP should be considered as a possible Common Fund program. NHGRI has a lot of prior experience managing top-down, community-oriented resource projects. Because the Institute is not disease-specific and focuses on enabling different types of technologies, NHGRI is frequently viewed as well qualified to manage Common Fund programs.

Council wanted to see a graph of the Common Fund budget over time. Dr. Green noted that legislation initially established the Common Fund budget at $250 million. Over time, that number has increased and has stabilized at its current size of $500 million.

Family History Concept Clearance – Anastasia Wise

Collection of family history data has been a standard part of medical practice and represents the single strongest measure for genetic-based risk of common diseases. Family history data have been shown to be helpful in placing people into proper disease risk classifications. Researchers have combined family history data and genomic data to provide additional evidence for disease risk calculations. Family history data may help with the interpretation of whole-genome sequence data in electronic health records in the future. Among current NHGRI programs, only two of the ten eMERGE sites collect family history data. NHGRI has previously supported family history programs, including the U.S. Surgeon General's My Family Health Portrait tool, demonstration projects around the use of the U.S. Surgeon General's tool, and incentives for including family history in electronic health records. NHGRI also played a key role in hosting the State of the Science conference on Family History and Improving Health in 2009.

The proposed funding opportunity consists of two RFAs for 4-6 study sites and a coordinating center. NHGRI would commit $4 million per year for four years for a total of $16 million overall. The goal of the initiative is to translate current family history approaches to successful use in routine clinical settings. Applications for the initiative would address the following goals: 1) Develop streamlined methods for entry and interpretation of family history data in the EHR; 2) Develop and evaluate risk algorithms using streamlined methods, and 3) Increase the efficiency and inter-operability of family history data collection and use. This proposal has been worked on by the trans-NIH Family History working group, which is composed of 18 ICs, the NIH Clinical Center, and recently the Health Resources and Services

Administration (HRSA). NHGRI has encouraged the participation of other ICs within the working group. Many have shown enthusiasm but are unable to commit funds until they see the actual RFA.

In discussion, Council wanted to know if the initiative would address how to collect family history data more accurately. Dr. Wise said that any study would need to do some measurements to judge the accuracy of the data. Council then asked if the expectation is to get one set of methods that will work across diseases. Staff anticipates that this initiative will not be a one-size-fits-all approach.

Council then questioned how staff developed budget estimates for this concept. Dr. Wise said that estimates were based on anticipated personnel and supplies costs. In this case, the main costs go towards bioinformatics support to develop systems for data collection and integration as well as costs for medical personnel. When asked if the program could operate with reduced funds, Dr. Wise noted that the program seeks to understand family history data collection in different clinical settings, ranging from large tertiary hospitals to small primary care practices, so reduced funds would reduce the number of settings in which development could be tested. NHGRI is hoping to get other ICs to donate money to reduce the NHGRI contribution. Council asked further about why this could not be a Common Fund program. NHGRI noted that it has been involved with family history initiatives for a number of years and has gained expertise. Additionally, since this program is disease-agnostic, it fits under NHGRI's scope. NHGRI hopes to partner with other ICs who would be willing to donate money to fund applications that are relevant to their research goals.

Council brought up the issue of "state of the art" family history collection. Dr. Wise replied that family history tools have been developed in a research context. Some of these methods take more time than is available during a patient visit with a physician to collect data. These methods also need to be able to present collected family history data in a way that is easily understandable and useful for clinicians. The initiative allows investigators to decide at what point of the process data would be entered. Dr. Greg Feero noted that the Stage 2 Meaningful Use Criteria has made vendors focus on the gathering of data rather than the validation side of confirming data accuracy.

Council wondered if this initiative could expand to include the VA or Department of Defense, or possibly use an SBIR mechanism. Dr. Wise responded that we could reach out to these groups, as we recently did with HRSA. Council also noted that the structuring of the initiative as a consortium will allow its tools to be well tested at multiple sites. Furthermore, the large EHR vendors need to collaborate and work with this consortium to develop best practices. The family history tools from this initiative would also allow NHGRI to conduct larger studies with this family history data available.

The initiative was approved with 13 votes yes, 3 votes no, and 1 abstention.

NHGRI INTRAMURAL DISCUSSION

Dr. Daniel Kastner presented a summary of research activities within the NHGRI Division of Intramural Research. Drs. David Page and Richard Myers later presented findings of the Blue Ribbon Review Panel.

Council wanted to know how the Clinical Center is staffed and whether that had an effect on decisions made by the Undiagnosed Diseases Program. Dr. Kastner noted that the Clinical Center is staffed by physicians and faculty members from participating institutes. This means that the Clinical Center sometimes has particular strengths based on the institutes involved. Dr. Green hopes that a broad national replication and dissemination of the UDP might lead to different centers specializing in fields that the Clinical Center does not cover. Council also wanted to know the procedures for CLIA-approved analyses for clinical trials using next generation sequencing. Dr. Kastner noted that each institute pays for its own sequencing, as there is not a central CLIA-approved lab on campus.

Council wanted to know how NHGRI is dealing with the risk of departure of top NHGRI investigators to other institutions based on pressures on the institute. Dr. Kastner responded that he will handle this issue

on a case-by-case basis. The most recent investigators to leave the institute had particular personal reasons for their career decisions, but it is a concern. Certain things are easier to do in the extramural realm than the intramural setting, which may cause investigators to leave. For example, intramural investigators have a hard time finding supplemental funding outside of institutional allocations. Dr. Myers noted that the sequencing facilities and medical staff need to be attractive to keep investigators here. Dr. Page noted that, because of the current economic landscape, more investigators would lean towards the intramural program because of the relative stability in funding for intramural investigators. Council further noted that many young investigators were not developing as hoped as they approached the point of tenure considerations, even after multiple site visits. Dr. Page noted that leadership must attentively support their young investigators to reach excellence. Dr. Kastner noted that the last of the site visits instigated some major changes to NHGRI's review process to make it more rigorous and thorough.

Council wanted to know how NHGRI determines budget allocations between intramural and extramural and how that ratio is adjusted during times of budgetary stress. In the face of a budget reduction, NIH leadership has decision authority how a decrease would be applied to each institute. But for the division of the NHGRI budget, Dr. Green has the decision authority. In general, Congress wants NIH intramural programs to be no more than 10% of an institute's budget. Therefore, for NHGRI, it does not seem feasible to increase the size of the intramural program. Because NHGRI operates within the government's civil service system, changes tend to take place slowly. However, the current ratio of intramural to extramural funding is not fixed, and is subject to review from various advisory groups. Dr. Page emphasized that there should be an explicit explanation and articulation of the rationale for the current intramural allocation of 20% of the NHGRI budget. Dr. Kastner noted that NHGRI investigators are starting to not replace people who leave because of the current state of the budget. These types of reductions may allow NHGRI to make some adjustments to the overall intramural budget over time.

COUNCIL-INITIATED DISCUSSION

There was no Council-initiated discussion.

CONFIDENTIALITY AND CONFLICT OF INTEREST

Mark Guyer read the Confidentiality and Conflict of Interest policies to Council and asked them to sign the forms provided.

REVIEW OF APPLICATIONS

In closed session, the Council reviewed 101 applications, requesting $24,103,907 (total cost). The applications included 63 research project grants, 15 ELSI grants, 4 research center grants, 3 conference grants, 2 career transition awards, 9 SBIR Phase I applications, 1 SBIR Phase II application, 1 STTR Phase I application, 2 individual training applications, and 1 education project award. A total of 59 applications totaling $13,165,609 were recommended.

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

02/12/2013
Date

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

02/12/2013
Date

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