NATIONAL ADVISORY COUNCIL FOR HUMAN GENOME RESEARCH
MEETING SUMMARY
February 10-11, 2014

The Open Session of the 70th meeting of the National Advisory Council for Human Genome Research (NACHGR) was convened at 10:00 AM on February 10, 2014, at the Fishers Lane Terrace Level Conference Center in Rockville, MD. Dr. Eric Green, Director of the National Human Genome Research Institute (NHGRI), called the meeting to order.

The meeting was open to the public from 10:00 AM until 4:30 PM on February 10, 2014. 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 and 4:30 PM to 6:00 PM on February 10, 2014, and from 8:00 AM until adjournment on February 11, 2014, for the review, discussion, and evaluation of grant applications.

Council members present:
Eric Boerwinkle, ad hoc
Carlos Bustamante
Lon Cardon, ad hoc
Joseph Ecker, ad hoc
James Evans
Chanita Hughes-Halbert, ad hoc
Howard Jacob
Howard McLeod
Deirdre Meldrum
Jill Mesirov
Anthony Monaco
Martin Kreitman, ad hoc
Robert Nussbaum
Lucila Ohno-Machado
David Page, ad hoc

Council members absent:
Arti Rai
Amy McGuire

Staff from the National Human Genome Research Institute

Ronit Abramson, DPCE
Alexi Archambault, ERP
Alice Bailey, DPCE
Jonathan Bailey, DPCE
Jessica Barry, ERP
Maggie Bartlett, DPCE
Steve Benowitz, DPCE
Shannon Biello, ERP
Vivien Bonazzi, ERP
Vence Bonham, DPCE
Ebony Madden, ERP
Joy Boyer, ERP
Lawrence Brody, ERP
Comfort Browne, ERP
Cheryl Chick, ERP
Monika Christman, ERP
Shane Clark, ERP
Deborah Colantuoni, ERP
Catherine Crawford, ERP
Priscilla Crockett, DM
Christina Daulton, DPCE
Camilla Day, ERP
Rachel Dexter, DM
Nicholas Digiacomo, ERP
Carla Easter, DPCE
Alvaro Encinas, DPCE
Elise Feingold, ERP
Adam Felsenfeld, ERP
Leigh Finnegan, ERP
Ann Fitzpatrick, DM
Colin Fletcher, ERP
Brandon Floyd, ERP
Tina Gatlin, ERP
Jonathan Gitlin, DPCE
Peter Good, ERP
Bettie Graham, ERP
Mark Guyer, IOD
Linda Hall, ERP
Lucia Hindorff, ERP
Carolyn Hutter, ERP
Heather Junkins, ERP
Rongling Li, ERP
Nicole Lockhart, ERP
Mark Lucano, DM
Allison Mandich, IOD
Teri Manolio, ERP
Jean McEwen, ERP
Keith McKenney, ERP
Jeannine Mjoseth, DPCE
Preetha Nandi, ERP
Jacqueline Odgis, ERP
Vivian Ota Wang, ERP
Michael Pazin, ERP
Ajay Pillai, ERP
Erin Ramos, ERP
Laura Rodriguez, DPCE
Leonard Ross, DM
Kate Saylor, DPCE
Jeffery Schloss, ERP
Michael Smith, ERP
Heidi Sofia, ERP
Jeff Struewing, ERP
Kathie Sun, ERP
Larry Thompson, DPCE
Jennifer Troyer, ERP
Yekaterina Vaydylevich, ERP
Simona Volpi, ERP
Lu Wang, ERP
Steven Weiss, DM
Chris Wellington, ERP
Kris Wetterstrand, IOD
Anastasia Wise, ERP
Sherry Zhou, ERP

Others present for all or a portion of the meeting:

Stacey Gabriel, Broad Institute
Ellen Giarelli, ISONG
Richard Gibbs, Baylor College of Medicine
Joanne Goodnight, Jackson Laboratory
Tabitha Hendershot, RTI International
Eric Lander, Broad Institute
Joseph McInerney, ASHG
Leah Miller, NIH/OD
James O'Leary, Genetic Alliance
Rhonda Schonberg, NSGC
Richard Wilson, Washington Univ. St. Louis

INTRODUCTION OF NEW COUNCIL MEMBERS, NHGRI STAFF, LIAISONS, AND GUESTS

APPROVAL OF MINUTES FOR SEPTEMBER 2013 MEETING

DIRECTOR'S REPORT

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

Council asked about the applications for the Big Data to Knowledge (BD2K) Centers of Excellence RFA. While the number of applications received is confidential information, the applications will be coming to the NACHGR in May, 2014.

A Council member praised the ENCODE event with the CHARGE Consortium. It provided a great opportunity for ENCODE both to educate others and to hear about community needs to help plan future research activities.

Council members expressed appreciation for the monthly newsletter from Dr. Green. Dr. Green encouraged Council members, and others, to let NHGRI know if there are specific topics of interest.

REPORT ON NHGRI INTRAMURAL RESEARCH PROGRAM by Dan Kastner

Dr. Dan Kastner gave a presentation on the NHGRI Intramural Research Program (IRP).

Council asked Dr. Kastner how he promotes the implementation of high-risk/high-reward research given that investigators working in the Intramural Research Program (IRP) are also expected to be highly productive and cannot afford to engage in high-risk research that is expected to have a high rate of failure. Dr. Kastner acknowledged that this is a very difficult challenge. As an organization looks more carefully at the level of productivity of investigators, that scrutiny does encourage people to engage in research focused on incremental advances rather than higher-risk, longer-term ones. When talking with NGHRI Intramural investigators, and particularly when discussing investigators' work during reviews, Dr. Kastner encourages them to take on longer-term projects that do involve some level of risk.

Council also wondered about what Dr. Kastner does to maintain morale in the IRP given the current environment. Dr. Kastner said that maintaining morale is very important, and that one advantage he has is the very understanding, flexible administrative staff at NHGRI. NHGRI handles budget difficulties by being transparent and engaging the faculty in decisions so that specific cuts are not simply coming down from above. Dr. Green added that while recent years have brought new stresses to Intramural investigators, maintaining moral is currently very challenging throughout the biomedical research community, whether inside or outside of NIH.

Council inquired about the role that innovation plays in evaluating Intramural investigators, as it is an important evaluation criterion for outside investigators. Dr. Kastner agreed that innovation is important, and said that while he did not list it on the slides, innovation is taken into consideration during investigator reviews.

Council noted that the IRP at NHGRI approaches 21% of the NHGRI budget, compared with an average of about 13% across the other NIH IRPs, and wondered whether that percentage is something that NHGRI will be asked to reduce. Dr. Kastner said that this large percentage

makes it very important to justify the NHGRI IRP by demonstrating excellence. Dr. Kastner recognizes that the funding percentage for the NHGRI IRP cannot go any higher, and that further thought about the right size of IRPs across NIH will be part of the new long-term plans that Francis Collins has requested from each IRP. Dr. Green added that NHGRI has not been given any indication that the IRP budget should decrease, but rather that the NHGRI IRP has been asked to do more and more due to the desire to grow the medical aspects of genomics at NIH. There are not any resources to allow the NHGRI IRP to grow, but there is also no reason to think it should not be the size that it is, so long as NHGRI intramural investigators continue to demonstrate excellence.

Council wondered whether the five NHGRI strategic plan areas are used to assess the portfolio of research done in the IRP laboratories. Dr. Kastner said that they do look at the strategic plan, although the IRP skews more towards the biology of human disease and the science of medicine categories. Dr. Green added that before the strategic plan was developed, the NHGRI Extramural Research Program did very little in the clinical realm, but that the intramural and extramural areas of investigation are beginning to overlap much more.

PRESENTATION FROM NATIONAL CENTER FOR ADVANCING TRANSLATION SCIENCES (NCATS) DIRECTOR by Chris Austin

Dr. Chris Austin gave a presentation about NCATS and its role in catalyzing translational innovation.

Council noted that a number of the problems with therapeutics seem to come down to engineering and delivery, and wondered if NCATS is making a concerted effort to look at new ways for therapeutic targeting. Dr. Austin said that determining and understanding the principle interactions that govern small-molecule interactions with target molecules is the way to achieve predictability and being able to target drug delivery. Given our current limited knowledge of three-dimensional structures and the ways in which molecules interacts, the way we approach the problem is to generate massive amounts of data and then work backwards to identify the principles and patterns that govern interactions; the NCGC (NIH Chemical Genomics Center) will be focusing on this in the future. NCATS is also working with structural biologists and with engineers at DARPA as well as the pharmaceutical industry on novel ways to identify compounds efficiently. Overall, the problem lies in understanding the general principles. Eventually, Dr. Austin would like to eliminate the need for screening.

Council remarked on the flat rate at which new drugs are coming to market, and the fact that the cost of drug development is going up so much because drugs are failing much later in the development process than they did fifteen years ago. NCATS is uniquely positioned to access expertise and knowledge from all of the NIH institutes/centers about drug targets that are highly relevant to particular diseases. Council asked what is being done to draw out that expertise. Dr. Austin noted that NCATS is deeply engaged with other institutes in conversations about targeting for specific diseases (he cited Alzheimer's disease as one example). NCATS is also focused on general enabling validation technologies and how they can be improved.

Council encouraged NCATS to continue focusing on making logarithmic advances. Dr. Austin acknowledged that many of the investigators involved in the Clinical & Translational Science Awards (CTSA) program understand the enormous scale of the opportunities before them, but they have often lacked a clear mission statement from the NIH about what the research NIH wants them to pursue. He noted the vast majority of these investigators have expressed enthusiasm for the programmatic refocusing that is being planned for the CTSA program.

Dr. Green mentioned that he and Dr. Austin have had many conversations about the opportunities for collaboration between NHGRI and NCATS. Dr. Austin added that he is very excited the CTSA program because he believes that the many of the things that are needed in the genomic medicine space are theoretically available through the CTSA program. Harnessing the expertise available in the CTSAs could very powerfully enable some of the collaborative studies they have discussed. The current limitation is not NHGRI but NCATS, and Dr. Austin is working to ensure that NCATS can become a good partner.

RECENT NHGRI MEETINGS

Report on Genomic Medicine VI Meeting by Teri Manolio

Dr. Teri Manolio gave a presentation on the meeting *Genomic Medicine Centers Meeting VI: Global Leaders in Genomic Medicine*, which was held on January 8-9, 2014 in Washington, DC.

A Council member who attended the meeting noted that there was a very clear desire to try to have a United Nations of genomic medicine, but not reinvent things that have already been done. A number of the suggested activities would not require a lot of money. People came to the meeting looking for collegiality and to begin common efforts to solve problems. The number of problems is daunting, but working on something specific, like the concept of eradicating an adverse drug reaction, might make people dedicate themselves to the effort.

Council wondered if there has been any attempt to engage the World Health Organization (WHO). The WHO might be in a unique position to help organize a world-wide consortium that is less western-centric. Dr. Manolio agreed that engaging the WHO could be helpful, although it has not been done yet.

PROJECT/PROGRAM UPDATES

H3Africa Initiative by Jane Peterson

Dr. Jane Peterson gave an update on the Common Fund H3Africa Initiative

Council praised the way H3Africa has been able to get the ethics committee chairs from various countries together, and wondered whether there are similar activities to involve Ministers of Science or Ministers of Health. If these ministers see value in the program, they may be willing to provide some money. Dr. Peterson said that the chair of the Outreach and Communications Working Group is very excited about bringing governments on board. That committee is working on recruiting ambassadors throughout the continent. These ambassadors will then help with outreach to Ministers of Science. In addition, every time H3Africa meets in a different country, they try to invite the Minister of Health or a major government official to attend.

Council asked whether H3Africa has received any pushback from the countries in Africa where H3Africa does not have any presence. Dr. Peterson noted that the places without H3Africa sites often do not have much science going on in general.

In response to a question about where the PIs of the African sites were trained, Dr. Peterson said that a number of them trained in Europe. Several PIs have returned to Africa after retiring from their research careers in European countries. Some of the PIs received their earlier education in Africa, but they generally went abroad to complete their PhDs.

Council noted that given the tribal, ethnic, and other differences across populations in Africa, it is likely that a DNA chip will not be applicable to all populations, and asked about the rational for building a chip rather than doing sequencing. Dr. Peterson said the primary factor was cost and the limited funds available.

Council raised the question about the reliability of communications across the Consortium, and wondered whether all of the PIs have satellite hookups. Dr. Peterson said that while broadband service is present in many countries, the reliability of the service is not consistent. H3ABioNet is doing a survey of the bandwidth in these places. Council suggested that USAID might be helpful in increasing access to broadband. Dr. Peterson stated that the Communications and Outreach Working Group is trying to start an advocacy group to help governments understand that if they want science to grow in their country, then they must increase bandwidth. The Communications and Outreach Working Group is trying to gain more influence with the African Union, and has had some contact with UNESCO.

Council mentioned that several other European countries are investing in African researchers, and wondered how connected H3Africa is to these countries. Dr. Peterson said that H3Africa is interested in working with anyone who wants to be involved in genomics in Africa. Several European countries are already involved.

In response to a question about the role of Wellcome Trust, Dr. Peterson said that NIH and Wellcome Trust do not co-fund H3Africa projects; rather, they fund different projects in the consortium. H3Africa allowed PIs to submit identical proposals to both NIH and Wellcome Trust. Wellcome Trust had their own peer review and made their decisions based on their criteria. Wellcome Trust is also now contributing to a center within H3ABioNet that supports meetings and communication, and is starting to co-fund other infrastructure projects. Mark Guyer added that once grants have been made, NIH has been co-managing the program as a whole with Wellcome Trust.

PRESENTATION FROM LARGE-SCALE SEQUENCING AND ANALYSIS CENTERS INVESTIGATORS by Eric Lander, Richard Gibbs, and Richard Wilson

Dr. Eric Lander, Dr. Richard Gibbs, and Dr. Richard Wilson discussed the scientific goals of genome sequencing over the next five to ten years, and which large-scale activities they believe are most critical for advancing the field.

Council wondered about the role of model organisms in the future of genome sequencing and the study of diseases. Dr. Lander stated that the human is a great system to identify the genes involved in disease development, but is a difficult system in which to identify gene interactions. There is an expectation that a certain percentage of the heritability associated with diseases will result from gene interactions, and model animal systems will be very useful to characterize that component of heritability. Dr. Wilson added that although model organism sequencing was not discussed during their presentations, it continues to be done at the large-scale sequencing centers.

In response to a question about how he imagined the implementation of genome sequencing into the clinical setting might happen, Dr. Gibbs noted that the bottleneck right now is delivering fully annotated information to everyone, but that capacity is increasing rapidly. A growing demand for quick and effective annotation that is digestible both to researchers and clinicians will push this edge and drive further development.

After hearing during the presentation about case/control studies and basic research moving into the clinic, Council asked when economic factors might encourage skipping case-control studies and going straight to the general population, and what genome sequencing would look like in that situation. Dr. Lander said that the economics of genome sequencing in the general population depends on the frequency of the disease. At some point, it makes sense to move into the general population, but it depends on the frequency of the disease and on having good clinical characterization of the patients. Dr. Lander believes that individual diseases will move from case-control studies to the general population at different times, driven by the cost in different settings. For multi-disease studies or GWAS, it would make sense to skip the case-controls if the size and characterization of the disease populations are good enough. Dr. Gibbs added that a big part of the answer to this question is the need to move data into routine clinically accessible medical records, and the degree to which issues of ontology, phenotyping standards, and communication between different aggregators of the data have been solved.

Council asked for examples of where genome sequencing data are being returned to patients. Dr. Gibbs said that his center has just passed 2,500 cases in the Mendelian diseases diagnostic group, and in 25% of cases they have been able to identify a genetic variant that is known to be pathogenic. Each family receives a report, and the center does have the infrastructure to support this effort, which includes genetic counselling. At Dr. Wilson's institution, they are planning within a year, to have all admitted AML patients receive exome and transcriptome sequencing.

Council noted that one of the rationales behind genome sequencing at scale was to identify missing heritability information, and they questioned what would be gained by increasing the scale of studies to 25,000 case and controls. Dr. Lander said that it depends on the genetic architecture of the particular disease being studied. But for every disease where the scale has been increased thus far, one to two interesting results have emerged, even in cases where the power has remained relatively low. That suggests that discovery will continue as the scale of studies is increased. How much those results will account for missing heritability is unknown and difficult to estimate. But Dr. Lander pointed out that each additional genetic discovery offers another potential drug target.

Council mentioned that the community seems hesitant to move from whole-exome to whole-genome sequencing, and wondered what would be needed to push the field, aside from lowering the cost. Dr. Wilson said that cost is certainly an important factor, and it does not help that whole-genome sequencing requires more intense computation. The way to move whole-genome sequencing forward is to commit to more projects that do whole-genome sequencing as a primary activity. Dr. Lander emphasized that the power to detect in a whole-genome study is substantially lower than the power to detect in an exome study, because in exomes, all of the mutations in a gene are aggregated while in a whole-genome, a researcher must make an estimation of the size of the region over which variants will be aggregated, and this can diminish power. Dr. Lander noted that the NHGRI ENCODE project has been very helpful in figuring out how to aggregate over functionally meaningful units of the genome.

Council commented that there is a layer of functional biology activity that the three large-scale sequencing centers are involved in, but this research was not addressed during the presentations. Council would appreciate hearing more about the spectrum of activities the sequencing centers are involved in, particularly with regard to the centers' vision for integration that will help us to better understand the function of the genome. The concern is that the community will transition to whole-genome sequencing in clinical applications, but we will not

have sufficient understanding of the function of non-coding regions of the genome to be able to return meaningful information to patients.

Council asked for more information on which technology development efforts are the most crucial for advancing the field. Dr. Gibbs said that functional assays that can migrate through vast datasets and differentiate which variants are critically involved in disease development from those that are not would be tremendously helpful. There is a real need to accelerate that field of research right away. Dr. Gibbs further mentioned there is still a need for faster, cheaper, and more accurate nucleic acid sequencing. Dr. Lander added that a whole set of functional tools are needed to accelerate the discovery of the genetic basis of disease. For example, single-cell DNA sequencing technologies are becoming available, and we are discovering new cell types in the immune system and achieving better classification of glioblastomas by our ability to characterize the populations of cell types that make up those tumors.

Council returned to the discussion of whole-exome versus whole-genome sequencing. Some Council members expressed surprise that the genome sequencing centers are not doing more whole-genome sequencing, as they are uniquely able to carry out whole-genome sequencing at scale. Dr. Lander noted that if whole-genome sequencing and whole-exome sequencing cost the same amount, his center would absolutely do whole-genome sequencing. However, because the price is so different, whole-exome sequencing provides a lot more power to make discoveries. There is a cost to deciding to look at an entire genome. The long-term goal is whole-genome sequencing on every sample, but there is a need to prove value at every stage of the process towards that goal.

Council asked the presenters what role they believe GWAS and common variants in under-studied populations will play in the coming years. Dr. Lander replied that it is very clear that different populations offer major advantages to the study of specific diseases that we must not overlook in planning genetic studies. Disease-associated variants may be rare in some populations, but much more common in other populations, and it is possible to make discoveries about many genes in populations that have undergone bottlenecks. The right way to expand to non-European populations is to create partnerships that involve the US and countries like Finland, parts of Africa, India, and other places that have had interesting population bottlenecks. In order to discover the whole history of human disease, scientists will need to use all populations, not just those populations that are convenient.

COUNCIL-INITIATED DISCUSSION
Eric Green

Council noted that the Global Alliance for Genomics and Health is having a large meeting in March and asked for a report at the May Council on NHGRI's reaction to the meeting. Dr. Green said that about five people from NIH will be attending and feedback to Council will be provided.

ANNOUNCEMENTS AND ITEMS OF INTEREST
Rudy Pozzatti

Dr. Rudy Pozzatti drew Council's attention to two items of interest:

1) An article in *The Atlantic* titled "When Will Genomics Cure Cancer"
2) National Society of Genetics Counselors Report to February Council

REVIEW OF THE STATEMENT OF UNDERSTANDING BETWEEN NACHGR AND NHGRI

There have been no substantive changes made to the Statement of Understanding between NACHGR and NHGRI since last year. Dr. Pozzatti provided a brief description of the major features of this document.

The Statement of Understanding was accepted by Council.

CONFIDENTIALITY AND CONFLICT OF INTEREST

Dr. Pozzatti read the Confidentiality and Conflict of Interest policy to Council and asked the members to sign the forms provided.

REVIEW OF APPLICATIONS[1]

In closed session, the Council reviewed 198 applications, requesting $61,686,567 (total cost). The applications included: 129 research project grants, 10 ELSI applications, 14 research center applications, 3 conference applications, 3 career transition award applications, 1 research scientist development award, 20 SBIR Phase I applications, 1 SBIR Phase II applications, and 10 education project award applications. A total of 191 applications totaling $61,686,567 were recommended.

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

6/2/2014
Date

Rudy Pozzatti
Rudy Pozzatti, Ph.D.
Executive Secretary
National Advisory Council for Human Genome Research

6/3/2014
Date

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

[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” votes.