NATIONAL ADVISORY COUNCIL FOR HUMAN GENOME RESEARCH
MEETING SUMMARY
September 21-22, 2015

The Open Session of the 74th meeting of the National Advisory Council for Human Genome Research (NACHGR) was convened at 10:00 AM on September 21, 2015, 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 September 21, 2015. 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 6:30 PM on September 21, 2015, and from 8:30 AM until adjournment on September 22, 2015, for the review, discussion, and evaluation of grant applications.

Council members present:
Eric Boerwinkle
Lon Cardon
Joseph Ecker
Chanita Hughes Halbert
Howard Jacob
Amy McGuire
Anthony Monaco
Robert Nussbaum
Lucila Ohno-Machado
Arti Rai
Carol Bult, ad hoc
Mark Chee, ad hoc
Brenton Graveley, ad hoc
Gail Henderson, ad hoc
Len Pennacchio, ad hoc
Dan Roden, ad hoc
Val Sheffield, ad hoc
Jay Shendure, ad hoc
David Walt, ad hoc

Council members absent:
James Evans
David Page

Staff from the National Human Genome Research Institute:
Ronit Abramson, DPCE
Ernesto del Aguila, DPCE
Alice Bailey, DPCE
Vence Bonham, IOD
Gerry Bouffard, IRP
Joy Boyer, ERP
Larry Brody, ERP
Monika Christman, ERP
Julie Coursen, ERP
Priscilla Crockett, DM
Chris Darby, ERP
Jyoti Dayal, ERP
Camilla Day, ERP
Valentina di Francesco, ERP
Carla Easter, DPCE
Alvaro Encinas, DPCE
Jon Lotempio, Jr., ERP
Elise Feingold, ERP
Adam Felsenfeld, ERP
Ann Fitzpatrick, DM

Colin Fletcher, ERP
Tina Gatlin, ERP
Bettie Graham, ERP
Linda Hall, ERP
Rebecca Hong, DPCE
Carolyn Hutter, ERP
Sonya Jooma, ERP
Heather Junkins, ERP
Rupindei Kahi, ERP
Cristina Kapostis, DPCE
Estae Lawrence, DPCE
Rongling Li, ERP
Nicole Lockhart, ERP
Ebony Madden, ERP
Allison Mandich, IOD
Casey Martin, ERP
Jean McEwen, ERP
Jeannine Mjoseth, DPCE
Jim Mullikin, IRP
Hannah Naughton, ERP
Annie Niehaus, ERP
Kiara Palmer, DPCE
Teri Manolio, ERP
Mike Pazin, ERP
Ajay Pillai, ERP
Lita Proctor, ERP
Erin Ramos, ERP
Laura Rodriguez, DPCE
Jeffery Schloss, ERP
Michael Smith, ERP
Heidi Sofia, ERP
Kelsey Stafstrom, DPCE
Jeffery Struewing, ERP
Simona Volpi, ERP
Vivian Ota Wang, ERP
Chris Wellington, ERP
Kris Wetterstrand, IOD
Bob Wildin, DPCE
Caroline Young, PPAB

Others present for all or a portion of the meeting:
Sarah Beachy, Institute of Medicine
Judith Benkendorf, American College of Medical Genetics and Genomics
Adam Fagan, Genetics Society of America
James O'Leary, Genetic Alliance
Joseph McInerney, American Society of Human Genetics
Chloe Poston, Genetics Society of America
Rhonda Schonberg, National Society of Genetic Counselors
Joe Selby, Patient-Centered Outcomes Research Institute

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

APPROVAL OF MINUTES FOR THE MAY, 2015 MEETING

DIRECTOR'S REPORT

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

Council took a few minutes to honor the memories of Dr. William Gelbart and Dr. Elizabeth Thomson.

REPORTS

"Genomics and Society Working Group" by Lisa Parker

Dr. Lisa Parker is the current Chair of the Genomics and Society Working Group (GSWG), and Associate Professor in the Graduate School of Public Health at the University of Pittsburgh. Dr. Parker gave a presentation on activities of the GSWG, and a report from their recent meeting that took place on April 26-27, 2015, on the NIH main campus.

Council desired clarification on the GSWG's thought process on the Precision Medicine Initiative (PMI). One aspect that was discussed by the GSWG at the April meeting was how they would support the infrastructure for examining ELSI issues that might arise from the PMI. As the PMI develops, the GSEG will try to respond to the various documents and reports generated as a means of supporting the aforementioned infrastructure. Council also wanted to make note of a manuscript from the GSWG about the PMI that is currently under review with the journal *Genetics in Medicine*.

Council inquired how the GSWG delineates the different areas of ELSI research in the health services domain. Council specifically asked how issues related to health services, healthcare costs, and the social and behavioral responses to genomic data will be incorporated into the larger body of ELSI research. Though there are differing opinions among the GSWG members as to how these areas of research can be supported, there is consensus that research absolutely needs to be done in these areas going forward. The GSWG has concerns whether the current ELSI research budget can sustain the amount of research needed in all of these research domains. The GSWG also cited a need to identify projects that can be funded within the next year whose research can contribute foundationally to health services research, analysis of cost, and analysis of the relevance of the behavioral response to the rollout of genomic medicine. This may be the most effective way that the ELSI research program could make meaningful contributions as genomic medicine expands in scope.

Workshop Report, "Workshop on Research Directions in Stevens Johnson Syndrome – Toxic Epidermal Necrolysis" by Teri Manolio

Dr. Manolio gave a presentation on the NHGRI-sponsored workshop on research directions in Stevens Johnson Syndrome – Toxic Epidermal Necrolysis (SJS-TEN). This workshop was held on March 3-4, 2015, on the NIH main campus. Slides and webcast recordings from this meeting are available on the NHGRI website: http://www.genome.gov/27560487 Council discussed the challenges facing the drug discovery field, noting that many adverse drug reactions (ADR) seem to be a function of the HLA haplotype of individuals. Genetic testing of the HLA locus is now routinely done on nearly every drug trial as part of monitoring for possible ADR. But the biology of ADR is not as simple as an interaction between a drug and a particular HLA haplotype since adverse responses occur in much lower frequency than the allelic frequency of the affected HLA haplotype. Council noted that the fundamental mechanism behind this HLA haplotype risk is not at all understood, and there is a great need for basic research to be done on this topic, which could shed light on the basic molecular underpinnings of ADR. The knowledge gained from such studies could have much broader implications for other clinical domains including: transplantation research, cancer susceptibility testing and management of chronic viral infections such as HIV.

Council was interested to know the current state of DNA sequencing methods (and the cost) to interrogate the HLA region of the genome. The HLA-B locus remains a difficult region to sequence. The key challenge is to get long sequencing reads to be able to determine haplotype information with speed and great accuracy. Council noted there are many NIH institutes that would welcome inexpensive and accurate HLA haplotype technology, but none of them are in a position to lead such as effort. If the cost can be reduced sufficiently, it would be useful to include HLA typing as part of newborn screening programs. Improving HLA typing was viewed as something NHGRI could provide leadership on, and it would address many areas of the 2011 NHGRI Strategic Plan.

"Genomic Medicine Working Group & Genomic Medicine 8 Meeting" by Teri Manolio

Dr. Manolio gave a presentation on the current state of the Genomic Medicine Working Group as well as on the NHGRI-sponsored workshop on an overview of the NHGRI's genomic medicine programs and future opportunities in genomic medicine research. This workshop was held on June 8–9, 2015, at the Hilton Washington D.C./Rockville Hotel in Rockville, MD. Slides and webcast recordings from this meeting are available on the NHGRI website: http://www.genome.gov/27561558.

Council noted that the recommendations for future opportunities in genomic research are very broad and that further refinement on these opportunities will need to be made.

For the future Genomic Medicine 9 (GM9) meeting, Council acknowledged the importance of incorporating basic science knowledge into genomic medicine. The major challenge at this time is acquiring functional information about newly discovered variants that are thought to be associated with disease development in patients. The functional characterization of variants will have to be done with a very rapid turnaround in order to provide biological insights that might be useful to guiding the clinical care delivered to patients.

Dr. Manolio noted that the GM9 Meeting is scheduled for April 19-20, 2016; the meeting location has not yet been determined.

PRESENTATIONS

"The Complementarity of Comparative Effectiveness Research and Precision Medicine" by Joe Selby

Dr. Selby gave a presentation on the Patient-Centered Outcomes Research Institute (PICORI), PMI, and comparative effectiveness research.

Council was interested to know if PCORI monitors cost. Dr. Selby responded that PCORI does not directly monitor costs, due to the inconsistent manners with which cost data are collected and analyzed, and that costs are known to vary in different regions of the nation. Instead, PCORI analyzes overall resource utilization. From resource utilization metrics, theoretically, one could determine costs, but PCORI does not attempt to determine or monitor cost data.

Dr. Selby addressed a few questions about data sharing. PCORI wants to position itself near the front of the "open science" movement (provide ready access to data collected in their sponsored research). Since PCORI does not fund as many grants as other funding agencies, it is easier for them to gain approval from the individual principal investigators to share the data from their research funded by PCORI. There are efforts within PCORI to draft an open science policy in order to help their awardees to be prepared to share their data and protocols upon request. Dr. Selby acknowledged that PCORI does not have the infrastructure in place to store all the data generated by PCORI-funded grants, but by alerting the grantees of the open data initiative, the grantees can be ready to share their data and protocols upon request.

Dr. Selby expanded upon a targeted genome sequencing effectiveness trial being run at the University of California, San Francisco. This trial is using targeted genome sequencing as one piece of evidence to guide clinicians as to how often women should have mammograms performed. The trial is randomized where one set of patients gets a mammogram every year from 40 – 75 years of age, and the other set of patients is counseled about their risk based on targeted genome sequencing data. Researchers then gather an assessment of the preferences

from those patients who received targeted genome sequencing, at which point the patients then make a decision about their healthcare going forward. Council asked whether or not this trial was screening solely BRCA 1/2, and Dr. Selby clarified that a broad panel of genes is being sequenced. Council wanted to know what research activities in this trial PCORI was funding, and Dr. Selby clarified that outside providers, not PCORI, are covering the targeted genome sequencing costs.

Since PCORI typically focuses on clinical questions that tend to be disease-specific, Council asked what a single-disease and single-disease research means to PCORI in the context of genomics. Council also noted that NHGRI struggles with defining single-disease in the clinical setting. Dr. Selby believes there can be collaborations between NHGRI and PCORI as he can envision ways that genomics research can help shed light on possible treatment options for individual diseases.

Council asked if PCORI would consider providing funding for phenotyping of patients as part of a disease study. Dr. Selby responded that though PCORI does not typically pay for diagnostic tests, it does not mean that PCORI would never fund this type of research.

Council asked about the biorepository work being done by PCORI. Dr. Selby noted that PCORnet has a biorepository taskforce that is in the process of ramping up their activity. These samples, though, are currently not going to be available to outside researchers. Dr. Selby did say that PCORI intends to make all these samples available at some point, as one of the main goals of PCORnet is to have outside researchers engage with and use these data.

COUNCIL-INITIATED DISCUSSION

Council expressed a desire to learn more about the PMI, and Dr. Green noted that it will become a regular update during future council meetings. Council also wanted to know what the role of NHGRI and the broader genomics community should be in promoting or engaging with the PMI.

Council would like to hear from the Large Scale Genome Sequencing Centers at a future Council meeting; specifically, what the initial plans and goal(s) of the Centers for Common Disease will be.

Council would like to maintain close contact with the FDA especially in light of the PMI, as there is a feeling that the process for approving devices needs to be more streamlined. NHGRI may invite Dr. Robert Califf to present on the current state of the FDA at a future Council meeting, depending on the status of Dr. Califf's confirmation proceedings. Council suggested that the FDA's CIO could also present if Dr. Califf is not available.

Council would like to hear from the next Director of NLM at a future Council meeting, once the new Director is in place.

Council would like to hear from the recently appointed director of NIMHD (Elisio Perez-Stable) at a future Council meeting.

Some Council members noted they have detected a push-back against the PMI in the social, behavioral, and public health fields, and the suggestion was made to have a dialog involving public health and behavioral scientists to help alleviate this tension. Some of the main arguments leveled against the PMI are that it is much too focused on genetics and genomics as

the major determinant of health and disease, and the benefits of this initiative could be shared with many more people if more traditional public health research methods were employed, rather than generating and analyzing genomic information on a smaller number of people as currently envisioned for the PMI. Another concern is that many behavioral health and social science researchers believe that PMI may reinforce pre-existing health disparities due to the involvement of expensive data generating and data analysis technologies. The PMI Working Group acknowledged that this initiative could broadly increase health disparities, but they have been working to ensure this does not happen. Council expressed a desire to hear presentations from researchers about steps that could be taken to reduce health disparities in the context of the PMI.

Council noted that some critics of PMI have expressed disappointment that more funding is being directed to genetic and genomic research, while behavioral and public health research has been left out of the discussions and design of PMI. Council offered a suggestion that in the same way that ELSI research was designed to be an integral part of the Human Genome Project, it needs to be emphasized that behavioral health and public health issues are embedded in the PMI. One Council member who has served on the PMI Working Group confirmed that behavioral and public health issues and research questions were often discussed at Working Group meetings, and if the PMI is successfully implemented it should enable a myriad of public health research questions to be explored using the resources and data that will be generated along the way.

Finally, Council would like to hear more presentations by genomics investigators working in the basic sciences.

ANNOUNCEMENTS AND ITEMS OF INTEREST

There are a number of documents in the ECB under the open session tab and also linked to the agenda on the Council webpage: http://www.genome.gov/27562458.

There are updates from the society liaisons from the American Society of Human Genetics, National Society of Genetic Counselors, and the American College of Medical Genetics and Genomics. The American College of Medical Genetics and Genomics also released a policy statement that defines the scope of practice for the specialty of medical genetics.

Dr. Amy McGuire, Dr. Tony Monaco, and Dr. Carlos Bustamante will be rotating off Council after the September 21-22, 2015 Council meeting. Dr. Jim Evans will be rotating off Council after the February 8-9, 2016 council meeting.

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 to them.

REVIEW OF APPLICATIONS[1,2]

In the Closed Session, the Council reviewed 180 applications, requesting $294,419,064 (total cost). The applications included: 62 research project applications, 26 cooperative agreement (U24, U41 & UM1) applications, 17 ELSI Research Program applications, 8 research center applications, 3 institutional training grant application, 3 conference applications, 1 career transition award application, 32 research scientist development award applications, 10 SBIR Phase I applications, 3 SBIR Phase II applications, 3 STTR Phase 1 applications, and 20 Research Education applications. A total of 105 applications totaling $223,433,925 were recommended.

02/09/2016
Date

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

02/09/2016
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.

[2] A subset of the K01 and R25 applications were submitted in response to BD2K initiatives and were temporarily assigned to NHGRI.