NATIONAL ADVISORY COUNCIL FOR HUMAN GENOME RESEARCH
MEETING SUMMARY
September 12-13, 2016

The Open Session of the 78th meeting of the National Advisory Council for Human Genome Research (NACHGR) was convened at 10:00 AM on Monday, September 12, 2016, at the Fishers Lane Terrace Level Conference Center in Rockville, Maryland. 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 12, 2016. 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 12, 2016, and from 8:30 AM until adjournment on September 13, 2016, for the review, discussion, and evaluation of grant applications.

Council Members Present
Eric Boerwinkle
Jeffrey Botkin
Carol Bult
Joseph Ecker
Brenton Graveley
Jonathan Haines
Gail Henderson
Trey Ideker
Howard Jacob
Mark Johnston
Robert Nussbaum
Sharon Plon
Jonathan Pritchard
Aviv Regev
Dan Roden
David Walt

Staff from the National Human Genome Research Institute:

Omar Al Jammal, ERP
Julia Baker, ERP
Vence Bonham, IOD and IRP
Joy Boyer, ERP
Larry Brody, ERP and IRP
Comfort Browne, ERP
Christine Chang, ERP
Monika Christman, ERP
Ernesto Del Aguila, DPCE
Valentina Di Francesco, ERP
Cecilia Dupecher, ERP
Carla Easter, DPCE
Alvaro Encinas, DPCE
Elise Feingold, ERP
Adam Felsenfeld, ERP
Kim Ferguson, ERP
Ann Fitzpatrick, DM
Colette Fletcher-Hoppe, ERP
Tina Gatlin, ERP
Margaret Ginoza, ERP
Brenda Iglesias, ERP
Kevin Lee, ERP
Jonathan Lotempio, Jr., ERP
Peter Good, ERP
Bettie Graham, ERP
Jyoti Gupta, ERP
Linda Hall, ERP
Lucia Hindorff, ERP
Rebecca Hong, DPCE
Carolyn Hutter, ERP

Sonya Jooma, DPCE
Kevin Lee, ERP
Ashley Lewis, DPCE
Rongling Li, ERP
Nicole Lockhart, ERP
Jonathan Lotempio, ERP
Ebony Madden, ERP
Allison Mandich, IOD
Teri Manolio, ERP
Jean McEwen, ERP
Keith Mckenney, ERP
Donna Messersmith, DPCE
John Ohab, DPCE
Vivian Ota Wang, ERP
Kiara Palmer, DPCE
Mike Pazin, ERP
Ajay Pillai, ERP
Lita Proctor, ERP
Erin Ramos, ERP
Jeffery Schloss, ERP
Michael Smith, ERP
Heidi Sofia, ERP
Jeffery Struewing, ERP
Michelle Tallman, ERP
Elizabeth Tuck, DPCE
Simona Volpi, ERP
Lu Wang, ERP
Chris Wellington, ERP
Kris Wetterstrand, IOD
Bob Wildin, DPCE
Kira Wong, ERP

Others present for all or a portion of the meeting
Siobhan Addie, NAS
Melissa Garcia, NHLBI
Joy Natham, BETAH Associates
Derek Scholes, ASHG
Rhonda Schonberg, NSGC

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

APPROVAL OF MINUTES FOR THE MAY 2016 COUNCIL MEETING

FUTURE MEETING DATES
Feb. 6-7, 2017
May 8-9, 2017
Sept. 11-12, 2017
Feb. 12-13, 2018
May 21-22, 2018
Sept. 24-25, 2018

DIRECTOR'S REPORT

Dr. Eric Green gave his Director's Report.

With regard to the NIH Clinical Center administrative changes presented in the Director's Report, Council inquired whether patients and patient advocates would be included in the hospital's advisory board. Dr. Green responded that patients and advocates were to be included on this board.

Council noted there is an appearance of overlap between two research programs, Clinical Sequencing Exploratory Research (CSER), and Implementing Genomics in Practice (IGNITE). There is also the possibility for synergy with these two programs and Council asked how staff

planned to address these two issues. Dr. Teri Manolio responded that CSER2 applications are currently under review, and she cannot yet comment on the opportunities for collaboration; however, staff intend to leverage overlap if it occurs. Dr. Manolio stated that this matter will be discussed at the February 2017 Council meeting when the CSER2 applications are considered. Council then noted that education for non-geneticist practitioners is a focus of other consortia, and there is hope that the CSER investigators will take advantage of what the other genomic medicine consortia have achieved. Council further encouraged NHGRI Program Staff to look at overlap and opportunities for synergy among the working groups in each of the research programs. Council also asked if the workshop that was held for payers could be shared with the American College of Medical Genetics and Genomics. That meeting was not video recorded, but a summary of the workshop is being prepared by NHGRI staff. Dr. Ebony Madden noted that attendees at the IGNITE workshop stressed the importance of inclusion of payers in the future research goals of the IGNITE program

PRESENTATION – Seizing Unprecedented Opportunities: NHLBI Trans-Omics in Precision Medicine (TOPMed). Dr. Gary Gibbons, Director of the National Heart, Lung, and Blood Institute.

Dr. Gary Gibbons gave a presentation on TOPMed

Council noted the importance of NHGRI's Ethical, Legal and Social Implications (ELSI) Research Program and inquired whether NHLBI had considered a similar program. Dr. Gibbons responded that TOPMed has some ELSI features and sees ELSI as a great opportunity for collaborative synergy.

Council questioned why NHLBI's design for its data sandbox did not include data derived from model organisms that can help investigators to understand the connection between genotype and phenotype, and how that can inform our understanding of the biology of genomic variants in humans. Dr. Gibbons responded that comparative genomics is an important tool for studying the functional significance of genomic variants, and datasets from model organisms should be included in a data commons.

Council noted it will require deliberate and targeted efforts to increase the representation of minorities and underserved population in large-scale genomic studies such as TOPMed. Dr. Gibbons concurred with that statement.

Council was pleased to note the synergies that could be achieved by the close interactions and cooperation between TOPMed and NHGRI's Centers for Common Disease Genomics (CCDG), and the Council asked how these two Institutes could broaden the participation and coordination of other NIH Institutes and Centers (ICs) engaged in large-scale studies of other diseases. Dr. Gibbons noted it only makes sense to conduct these types of studies as partnerships.

Dr. Green asked Dr. Gibbons how NHLBI plans to coordinate with the Precision Medicine Initiative (PMI) and if there will be an organizational framework to answer important research questions. Dr. Gibbons responded that the PMI was initiated to be a "disease-agnostic" program; but as the number of PMI participants increases, it is inevitable that phenotypes highly relevant to NHLBI's research mission will be found in the PMI cohort. Thus, PMI's fullest potential will be realized when it links back to individual ICs and enables them to ask questions that are disease-specific.

Council asked what data from TOPMed are being returned to participants, and whether there are ongoing research activities studying this process and outcomes. Dr. Gibbons responded that TOPMed is generating lots of data from several different studies and multiple cohorts, and it has not been possible to develop a single approach to returning results. This is another area where collaboration between NHLBI and NHGRI could be very beneficial, given NHGRI's domain expertise in returning genetic/genomic data to participants in research settings.

Council asked if NHLBI had a timeline for the dissemination of initial results from TOPMed. Dr. Gibbons responded that 60,000 whole genome sequences (WGS) are expected this year. Council further inquired whether the NHLBI cohorts were broadly phenotyped. Dr. Gibbons replied that the cohorts started out very much focused on cardiovascular disease, but if other ICs participate in TOPMed it could be an opportunity to expand the phenotyping of the current and future cohorts in TOPMed. Council asked whether TOPMed cohort participants could be re-contacted and re-consented. Dr. Gibbons responded that all samples accepted into TOPMed need to be properly consented from the beginning or they were excluded from the project.

PRESENTATION – Opportunities for Synergy between the NHGRI Genome Sequencing Program (GSP) and TOPMed

Dr. Adam Felsenfeld gave a presentation on the NHGRI GSP and areas for collaboration with TOPMed.

Council asked about lessons learned from The Cancer Genome Atlas (TCGA), and whether they were generalizable to this new collaboration. Dr. Felsenfeld responded that many lessons were learned, and that TCGA was very successful. He further stated that NHGRI collaborated with NIDDK on some diabetes work and learned lessons from those interactions. Staff see many common features, even though each program can stand on its own. Dr. Felsenfeld continued that the most overarching lesson from these experiences pertains to data, and that without robust resources and well-characterized data, collaboration becomes less productive. Dr. Green added that each IC has a different culture, and relationships and collaborations with colleagues at each IC have to be managed in individual ways.

Council asked why more ICs have not signed on to the GSP. Dr. Felsenfeld responded that NHGRI is working closely with NIA as well as NIDDK and NEI. He stated that these collaborations take time, and there is hope that more will join and add value to the consortium. New Institute Directors have recently been named at NICHD and NIMH, and there is opportunity and optimism to establish collaborations with those ICs for large-scale genome sequencing studies.

REPORT – Genomic Medicine Working Group

Dr. Teri Manolio gave a report on the activities of the Genomic Medicine Working Group (GMWG) of the NACHGR.

Council asked if the GMWG has considered plans for MOOC-style (massively open online course) training. Dr. Manolio responded that it has not yet been explored. Council further stated that individuals have had success with MOOCs at the postdoctoral and international collaborator levels, but they could be used (for example) for clinicians seeking information about the clinical

relevance of genomic variants. Dr. Green reminded Council that the GMWG represents the Extramural Research Program (ERP) portfolio and that the Division of Policy, Communications, and Education (DPCE) works to disseminate information for both the general public and healthcare providers. Council can anticipate hearing more about these education efforts at future meetings.

REPORT – Genomic Medicine IX Meeting

Dr. Carol Bult gave a report on the 9th Genomic Medicine Meeting (GM9).

The focus of the GM9 meeting was interpreting the clinical significance of a genomic variant of unknown significance (VUS), and how research on the biological function of these variants can be better aligned to be of maximal value and utility to clinicians. Council noted evidence-based medicine is based largely on randomized case-control studies. Thus, many physicians are uncertain how to use information about the function of a genomic variant that is obtained in a model organism or a tissue culture system. This increases the challenge of providing functional information about VUSs that will be useful to clinicians.

Council then held a broader discussion about what has been learned in the CSER consortium about returning VUS results. The ACMG classification scheme does allow information from animal models to be included. Similarly, the Clinical Genome Resource (ClinGen) has created a framework for scoring the weight of functional data derived from model organisms, as part of the gene validity matrix that is used. But the challenge remains to help clinicians understand how to use the results of functional studies in model organisms, and information that is not obtained from patients in a clinical trial setting.

PRESENTATION – U.S. Precision Medicine Initiative

Mr. Eric Dishman gave a presentation on the U.S. Precision Medicine Initiative (PMI).

Council asked if the cross-cutting areas described in the talk represent an exhaustive list or are merely examples of potential fields. Mr. Dishman responded that the list is not exhaustive, but will be fleshed out with the help of NIH staff.

Council asked if PMI had some kind of special authority to work with greater flexibility for matters such as issuing contracts. Mr. Dishman stated that the PMI is authorized to use a funding mechanism called Other Transactional Authority (OTA). The OTA is flexible and will be modulated over time as needed in the PMI. Mr. Dishman further stated that PMI will create software where needed, but the expectation is that in most cases, existing software will be used or modified to support the needs of the PMI.

Council asked what provisions were made for biobanking samples for future analyses. In the near term, only blood and urine will be collected for the PMI. Discussions are underway to determine what additional biological samples should be collected, and how, when, and by whom the samples should be used. There are also discussions exploring what kind of metadata PMI needs to capture. Council suggested collecting stool samples for microbiome research.

Council then asked what thought has been given to manage public expectations about the PMI. Mr. Dishman stated that a large part of managing expectations is to communicate the principles

and long-term goals of the PMI, and not to set overly aggressive goals too early in the program timeline. Mr. Dishman noted there is an expectation that precision medicine means this will be a genomic study; but rather than collecting genomic data on all participants from the outset, the plan is to do some pilot studies in 2017 to examine what can be done with whole-exome and whole-genome datasets, and whether the existing systems are able to manage those data. There are also plans to create communications, branding, and educational materials for multiple audiences.

Council asked whether children and pregnant women would be included in the PMI. Mr. Dishman responded that pregnant women will be included, but children, incarcerated people, and those with cognitive impairment will not be part of the early stages of the PMI. However, there is a roadmap that includes a timeline of when those groups will be brought into the program.

Council noted that in the first 7 months of the initiative, 8 grants have been awarded and more than 30 organizations were involved in those awards. This was viewed as a remarkable achievement and Council asked how this was accomplished so quickly. The OTA has a very short timeline, and has enabled the PMI to move so quickly. The OTA makes use of a modified version of the NIH peer review process.

Council asked Mr. Dishman to explain how the PMI plans to define race and ethnicity. Mr. Dishman responded that the applicants had to define their catchment area(s), and explain the many axes of diversity that would be studied in their research plans. The applicants have set recruitment goals to enroll people from diverse backgrounds over time. This will be done by different investigators working in different geographical regions and involving different populations of participants. The expectation is that much will be learned from the recruitment approaches. One central IRB will be employed for the PMI.

Council noted that government can benefit from industry experience and asked how some of the new approaches being used by the PMI could be translated to other parts of NIH. Mr. Dishman responded that there are many infrastructure and product-development methods that are quite robust and have been shown to work in many industry settings over a number of years. There may be great value to import some of these methods to an organization like NIH.

Council asked for a comment on plans for data release in the PMI. Mr. Dishman responded that the PMI faces the same issues as the rest of NIH and hopes to contribute to the endeavor.

COUNCIL-INITIATED DISCUSSION

Council brought up the issue of the role of model organisms, particularly in light of the discussion earlier in the day of how model organisms can be used to inform functional changes associated with newly discovered genomic variants. The underlying issue is the value and assessment of current models, which may be expensive but very useful. Council went on to note that model organisms may be particularly valuable now that genomic technologies can be applied to single cells, and they are the logical systems to use to study genome-editing tools such as CRISPR-Cas9.

Council enjoyed the morning presentations and stated that the juxtaposition between Dr. Gibbons' and Dr. Felsenfeld's presentations was particularly informative and illustrated the partnership between the Institutes.

Council would like to see a presentation by the new NLM Director. Dr. Green stated that Dr. Patricia Brennan is slated to make a presentation at the February 2017 meeting.

Council suggested it would be interesting and appropriate to invite representatives of payer organizations to a Council meeting in an effort to build a bridge between NHGRI and companies who assess quality and clinical utility of genomic data. Council suggested Palmetto as a possibility. Council noted that representatives from BlueCross–BlueShield have had interactions with NHGRI in the past.

Council would like to see a discussion on the intersection of epidemiology events across large populations, and whole-genome datasets that represent a depth of information about one individual.

Council would also like to address the needs that non-geneticist clinicians have with regard to genomic medicine. Some of the work being done in the Centers of Excellence in ELSI Research (CEER) would be useful for this. Council wants a better understanding of the position of ELSI in the wider research community.

Council praised advancements in electronic health records (EHRs) and the development of patient portals, and would like to know how EHRs are marking data available to patients and if those models could be used in other research settings. A lot of research has been done to determine what data the participants would like to have returned, but Council would like to know more about the methods, technologies and platforms that have been developed to address this challenge.

Council highlighted the lack of information on cost effectiveness of genomic data in the clinical setting and suggested it was time to bring in health economists to help address this key question. Dr. Larry Brody pointed out that NIH can do research, but can't directly study the issue of cost effectiveness.

Council would welcome a presentation from Dr. Tony Beck, the NIH Program Director for the Science Education Partnership Award (SEPA). These are K – 12 science education projects, many of which have a genomics component.

ANNOUNCEMENTS AND ITEMS OF INTEREST

Two reports have been sent to NHGRI, one from the American Society of Human Genetics and the other from the National Society of Genetic Counselors.

PRESENTATION – 23 (Pairs) Plus 1 Lessons Learned

Dr. Jeffery Schloss delivered a presentation on his 24 years of service working at NHGRI. He will retire on December 31, 2016.

Council asked Dr. Schloss for his comments on the future of DNA sequencing. Dr. Schloss replied that there was much yet to be done to advance the technology of DNA sequencing. While DNA sequence quality is generally quite good, there are other aspects of the sequencing process that need to be improved, particularly the way data will flow into pipelines. He predicted that soon DNA sequencing will be performed as a routine characterization of any material one wished to study. He also advocated to expand the definition of sequencing beyond the four nucleotides of DNA to include modified bases, sequencing of RNA molecules, and being able to detect the protein molecules that are in contact with specific regions of genomic DNA. Dr. Schloss speculated that applying some of the principles that have been used in the development of DNA sequencing methods to some of the other characterization challenges we face, such as phenotyping, could facilitate the application of genomics to the clinic.

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]

In the Closed Session, the Council reviewed 203 applications, requesting $159,281,719 (total cost). The applications included: 89 research project applications (R01, R03, R15 or R21) 73 cooperative agreement applications (U01, U24, or UM1), 10 ELSI applications (9 R-series and 1 career development), 2 research center applications (U41), 1 conference application (R13), 2 career transition award applications (K99/R00), 12 SBIR Phase I applications (R43), 8 SBIR Phase II applications (R44), 2 STTR Phase 1 applications (R41), 1 STTR Phase 2 application (R42), 1 Clinical Investigator Award application (K01), and 2 Research Education applications (R25). A total of 120 applications totaling $86,108,956 were recommended by the Council.

2/7/2017 Rudy Pozzatti

Date

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

2/7/2017 Eric Green

Date

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.