NATIONAL ADVISORY COUNCIL FOR HUMAN GENOME RESEARCH
MEETING SUMMARY
February 8-9, 2016

The Open Session of the 76th meeting of the National Advisory Council for Human Genome Research (NACHGR) was convened at 10:00 AM on Monday, February 8, 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 February 8, 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 February 8, 2016, and from 8:30 AM until adjournment on February 9, 2016, for the review, discussion, and evaluation of grant applications.

Council members present:
Eric Boerwinkle
Lon Cardon
Joseph Ecker
James Evans
Chanita Hughes-Halbert
Howard Jacob
Robert Nussbaum
Lucila Ohno-Machado
Arti Rai
Carol Bult, ad hoc
Brenton Graveley, ad hoc
Gail Henderson, ad hoc
Mark Johnston, ad hoc
Jonathan K. Pritchard, ad hoc
Dan Roden, ad hoc
Val Sheffield, ad hoc
Jay Shendure, ad hoc
David Walt, ad hoc

Staff from the National Human Genome Research Institute:
Ronit Abramson, DPCE
Yasmeen Beckett, DM
Steven Benowitz, DPCE
Vence Bonham, IOD and DIR
Joy Boyer, ERP
Larry Brody, ERP
Comfort Browne, ERP
Christine Chang, ERP
Monika Christman, ERP
Julie Coursen, ERP
Priscilla Crockett, DM
Valentina Di Francesco, ERP
Cecilia Dupecher, ERP
Brenda Iglesias, ERP
Alex Lee, ERP
Kevin Lee, ERP
Jon LoTempio, Jr., ERP
Elise Feingold, ERP
Adam Felsenfeld, ERP
Ann Fitzpatrick, DM
Colette Fletcher-Hoppe, ERP
Tina Gatlin, ERP
Jyoti Gupta, ERP
Bettie Graham, ERP
Linda Hall, ERP
Tarnzetta Hampton, DM
Rebecca Hong, DPCE
Carolyn Hutter, ERP
Sonya Jooma, ERP
Heather Junkins, ERP

Rongling Li, ERP
Nicole Lockhart, ERP
Ebony Madden, ERP
Casey Martin, ERP
Jean McEwen, ERP
Donna Messersmith, DPCE
Ray Messick, DM
Hannah Naughton, ERP
Annie Niehaus, ERP
John Ohab, DPCE
Teri Manolio, ERP
Mike Pazin, ERP
Ajay Pillai, ERP
Lita Proctor, ERP
Erin Ramos, ERP
Sylvie Richards, DM
Laura Rodriguez, DPCE
Jessica Rosarda, DIR
Jeffery Schloss, ERP
Elle Silverman, ERP
Laura Skow, ERP
Michael Smith, ERP
Heidi Sofia, ERP
Jeffery Struewing, ERP
Adrienne Tracy, DM
Susan Vasquez, DPCE
Simona Volpi, ERP
Vivian Ota Wang, ERP
Chris Wellington, ERP
Kris Wetterstrand, IOD
Bob Wildin, DPCE
Ken Wiley, ERP
Rosann Wise, DPCE
Kira Wong, ERP

Others present for all or a portion of the meeting:
Charlisse Caga-Anan, NCI
Adam Fagan, Genetics Society of America
Regina James, NIMHD
Elisabeth Kato, AHRQ
Michael S. Watson, American College of Medical Genetics and Genomics
Min Zhang, Purdue University

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

APPROVAL OF MINUTES FOR THE SEPTEMBER 2015 MEETING

FUTURE MEETING DATES
May 16 - 17, 2016 May 8 - 9, 2017
Sept. 12 - 13, 2016 Sept. 11 - 12, 2017
Feb. 6 - 7, 2017

DIRECTOR'S REPORT
Dr. Eric Green presented the Director's Report to Council. Council had no comments or questions regarding the report.

REPORT ON THE NHGRI INTRAMURAL RESEARCH PROGRAM
Dr. Dan Kastner, NHGRI's Scientific Director, gave a report on the NHGRI Intramural Research Program, presenting various scientific accomplishments and its role catalyzing genomics research.

Council inquired about the Intramural Research Program's budget of $105 million and whether that figure included the costs of the Clinical Center and the NIH Intramural Sequencing Center (NISC). Dr. Kastner clarified that the NIH Clinical Center charges a "flat tax" of 14% to all of the Institutes/Centers for the ability to make use of the Clinical Center facilities. For NHGRI's ~$100 million intramural budget, this comes out to approximately $14 million a year. Given NHGRI

pays by percentage, rather than number of patients evaluated, Dr. Kastner acknowledged that the Institute would benefit from making more extensive use of the Clinical Center.

NISC accounts for approximately $7 million of the intramural budget, with most of this money used to maintain its sequencing platforms and bioinformatics analysis work. Dr. Kastner noted that NISC is relatively competitive with commercial sequencing companies, as NISC's costs are approximately $500 per whole-exome sequence. There are also value-added features of using NISC, because in addition to sequencing DNA on a fee-for-service basis, NISC staff will perform a basic level of variant analysis for NIH investigators.

Council asked for elaboration on the 10,000 Recall Cohort and NHGRI's recruitment efforts and goals for diversity. Dr. Kastner commented that this program is in its infancy, and that it will take up to two years to accrue all of the participants for this study. The goal is to establish a large cohort of individuals with deep genomic information so that investigators at the NIH and elsewhere can then go back to select individuals and conduct more detailed clinical phenotyping. This level of deep phenotyping would be completed at the NIH Clinical Center and would allow for the rich characterization of many genotype-phenotype relationships. The participants in this Recall Cohort will be ascertained by an investigator studying a specific condition, and then are "rolled up" into the NIH Recall Cohort Program. Thus, in contrast to ClinSeq, whose participants are volunteers (and thus have an inherent self-selection bias), the Recall Cohort is selective for individuals with rare conditions. In an effort to include individuals with more common conditions or as normal controls, the Intramural Research Program is working to establish a relationship with INOVA Fairfax, a hospital in Northern Virginia. INOVA Fairfax has approximately 8,000 fully genotyped individuals, most of whom are women who recently gave birth to a child.

In response to a question, Dr. Kastner clarified that, within the Intramural Research Program, "tenure" implies a long-term commitment on behalf of NHGRI to the investigator, provided that he or she maintains productivity as judged by the NHGRI Board of Scientific Counselors.

Council asked for additional examples in which the Intramural Research Program either performed "high risk, high reward" research or quickly responded to the needs of the community. Dr. Kastner responded that NIAID recently started an initiative to study the Zika virus, and the NIH was instrumental in responding to the Ebola virus outbreak (in 2015) and the HIV/AIDS epidemic (in the 1980s). Additionally, Dr. Kastner commented that the NIH's ability to conduct large longitudinal patient cohort studies through the Clinical Center is unique. Lastly, Dr. Kastner added that the most important cornerstone of the Intramural Research Program is establishing excellence in the research it conducts.

PRESENTATION – Update on the Human Heredity and Health in Africa (H3Africa) Initiative

Dr. Jennifer Troyer gave an update on the Human Heredity and Health in Africa (H3Africa) Initiative, an NIH Common Fund program that aims to enhance capacity for using contemporary research approaches – in Africa by African scientists – to understand the genetic and environmental factors that determine disease susceptibility and drug responses in African populations.

Council asked for additional information on how H3Africa is collaborating with African organizations and what H3Africa is doing to enhance these internal collaborations. Dr. Troyer commented that the group Accelerating Excellence in Science in Africa (AESA) has been a

helpful catalyst for these collaborations. Based in Nairobi and created by the African Academy of Sciences (AAS) and the New Partnership for Africa's Development (NEPAD) Agency, AESA aims to move the center of gravity for decision making and grants management to the African continent. To encourage collaborations, the Director of AESA has attended H3Africa meetings. Additionally, the Wellcome Trust, which also funds H3Africa projects, has decided to partner with AESA and may decide to have AESA manage their awards/programs going forward. Lastly, AESA has been helpful in encouraging African governments to honor their commitment to devote 1% of their GDP to support scientific research.

Council applauded H3Africa's work forming research relationships in Africa, building capacity, and engaging young African scientists in the research process. As a testament to H3Africa's success, Council noted that GlaxoSmithKline (GSK) has been following their engagement models and building on H3Africa's existing infrastructure to create new medicines ***in*** Africa (rather than repurposing existing Western medicines). GSK is making their resources publicly available to H3Africa investigators and relinquishing many intellectual property rights.

Council noted that some of the training programs that have served African countries [e.g., the Medical Education Partnership Initiative (MEPI) sponsored by the Fogarty International Center] have ended. NHGRI staff responded that in the next round of H3Africa, they plan to increase their engagement with Fogarty. Staff also noted that Fogarty will be managing the training portion of H3Africa going forward, and will integrate this training program with some of the other programs they run.

One of H3Africa's great successes has been creating a culture of collaboration, which is particularly challenging to achieve given the diversity of investigators and countries involved in the initiative. For example, many culture-specific challenges arise in creating consent forms and in developing protocols for using and sharing biological samples. It has also been challenging to create an African SNP array, the development of which keeps falling behind schedule. While there were recruitment lags at the beginning of the program, these have been largely overcome within the last year.

Council encouraged H3Africa to think creatively about how to incorporate ELSI research into the H3Africa Initiative (e.g., they could investigate the barriers and facilitators of genomic research that are rooted in economic or political factors). Council was pleased to hear that the Ethics Working Group of H3Africa includes individuals across all of the H3Africa sites. This cross-site collaboration has been instrumental in developing broad consent models and establishing biobanking practices.

In moving towards implementation, Council voiced the importance of establishing shared phenotypes. Dr. Troyer commented that the Phenotype Harmonization Working Group has identified eight core phenotypes that all sites are studying, and has also set standards for additional phenotypes to be explored. Additionally, there are six H3Africa grants that are specifically looking at hypertension and cardiovascular disease.

Council inquired about NHGRI's strategy for increasing the amount of funding devoted to ELSI research within H3Africa. Dr. Troyer responded that, although they have asked to double or triple these funds for next year, the Common Fund will not decide on the budget until April 2016.

REPORT – Roundtable on Inclusion and Engagement of Underrepresented Populations in Genomic Research

Vence Bonham reported on the Roundtable on Inclusion and Engagement of Underrepresented Populations in Genomic Research, a meeting held by NHGRI on September 16, 2016.

Council was pleased to hear of the productive discussions at the Roundtable and commented that NHGRI should welcome this opportunity to refine how its programs approach diversity, inclusion, and engagement. The meeting was particularly successful at discussing the scientific need to promote diversity and the importance of studying gene-environment interactions. In addition, there was a fruitful discussion on the need to focus on the full spectrum of diversity (e.g., socioeconomic, geographic, etc.) rather than just ancestral-based diversity.

Council commented that developing specialized interdisciplinary centers for genomics and disparities was a high priority. It was recommended that these centers focus on developing the infrastructure to analyze issues related to health disparities in an empirical, scientific, and substantive manner.

Council discussed the need to retrospectively mine data already collected, as well as the need to engage with populations going forward to collect richer data. For instance, with the advent of the Precision Medicine Initiative (PMI) cohort population, there could be a significant amount of data available that NHGRI could use to broaden participation in research. In addition, Council recommended leveraging the data generated by H3Africa, provided the relationship was established in a collaborative, rather than exploitive, manner.

Council commented that there is a significant amount of existing data and research on the influence of social and environmental factors on health disparities, and it will be important for the aforementioned centers to build on this research, rather than simply repeating it. The epidemiology research community and social science investigators have substantial experience related to the causes of health disparities and the challenges associated with recruitment and retention of individuals from diverse populations. NHGRI should harness this existing research, and then apply it to its unique research agenda and initiatives. It was strongly recommended that the proposed centers should not conflate the discussion of health disparities with a discussion on the contribution of ancestral background to health outcomes and disease risk.

Council noted that it is critical for NHGRI to focus not just on increasing minority participation, but on increasing retention and improving long-term engagement (i.e., issues that arise during the whole lifetime of the study). One specific way that NHGRI could encourage this is by requiring grantees to submit detailed plans and reports on their minority participation and retention. These reports should be supplemented with information on which methods the grantees found particularly successful to increase retention (e.g., providing travel reimbursement, outreach to clinics, collecting back-up contact information, etc.). Additionally, grantees should be expected to engage with the community and build trust. These detailed annual reports could be very helpful for evaluating success for determining which factors are most useful for improving participation, retention, engagement, and trust. Lastly, it was noted that, in order to improve trust and engagement, it is vital to build diversity within the genomics research community.

REPORT – Integrating Genomic Sequencing into Clinical Care: CSER and Beyond Workshop

Dan Roden presented a workshop report from the CSER and Beyond Workshop held on September 28, 2015. Council did not have any comments or questions about the report.

CONCEPT CLEARANCE - Clinical Sequencing Evidence-generating Research (CSER2)
Dr. Lucia Hindorff presented the concept clearance for the Clinical Sequencing Evidence-generating Research (CSER2) project.

Council was supportive of the CSER2 concept and believed the CSER project has been a successful program worth expanding. Council noted that a commitment to interoperability, standards, and data exchange across CSER sites is essential to long-term success of the project, and genomic medicine more broadly.

Council discussed the extent to which CSER2 should integrate with existing NHGRI Division of Genomic Medicine (DGM) research projects. They acknowledged that some redundancy is necessary to have synergy between projects. It was noted that CSER2 is unique in comparison to other DGM research projects in that it focuses on clinical sequencing and clinical utility at the individual level, whereas other current research projects, such as eMERGE, have a greater focus on populations.

Council was supportive of a broad and inclusive definition of diversity as it applies to the CSER2 concepts. In addition to individuals with racial/ethnic diversity (referred to as "ancestral diversity" in these discussions), CSER2 should include participants who are underserved due to socioeconomic factors, education factors, and/or geographic location within the US. Beyond laying out a clear mandate for diversity in the CSER2 FOAs, Council encouraged NHGRI to develop standards by which diversity can be monitored so that diversity goals at each site can be objectively measured and determined. Furthermore, Council emphasized that it is important to move past just recruitment, and to focus on long-term retention and engagement of all participants recruited to the clinical sites.

Council noted that, even with the passage of the Genetic Information Nondiscriminatory Act (GINA), many people still hold concerns about insurability issues due to the possibility of genetic discrimination. Council believes this fear may influence people's participation in genomics research and uptake of DNA sequencing for clinical use, and encouraged NHGRI to include this research topic in the RFA. Additionally, it was recommended that the CSER2 Coordinating Center reach out to BlueCross BlueShield Technology Evaluation Center and the Palmetto Molecular Diagnostics (MolDx) Program. The Coordinating Center should play a key role in disseminating CSER2's research advances to the broader community and to professional societies.

Some Council members were worried about the precedent of establishing a separate FOA for the clinical sites with enhanced diversity. However, Council was also pleased to hear that NHGRI expects the clinical sites and the diversity-focused clinical sites to interact on a regular basis and to have very similar research activities and goals.

Council approved the Clinical Sequencing Evidence-generating Research (CSER2) concept (clinical sites) by a vote of 15 in favor, none opposed, and no abstentions.
Council approved the Clinical Sequencing Evidence-generating Research (CSER2) concept (clinical sites with enhanced diversity) by a vote of 15 in favor, none opposed, and no abstentions.
Council approved the Clinical Sequencing Evidence-generating Research (CSER2) concept (coordinating center) by a vote of 15 in favor, none opposed, and no abstentions.

CONCEPT CLEARANCE – Investigator-initiated Clinical Sequencing Research (iCSR)
Dr. Lucia Hindorff presented the concept clearance for the Investigator-initiated Clinical Sequencing Research (iCSR) program.

Council was very supportive of the iCSR concept, and discussed the importance of opening up these research opportunities to the larger community (i.e., not just for the current CSER investigators). Some Council members encouraged NHGRI to consider increasing the allotment for the iCSR program, even if that meant funding one less CSER2 clinical site. Council also emphasized that the proposed award size ($300,000 per year) seemed small, and that NHGRI should consider altering the budget cap to allow requests up to $500,000 per year. Additionally, NHGRI should consider the option to apply for a planning grant, which would be a helpful mechanism for institutions not previously involved in CSER to develop the institutional infrastructure and plan future research studies.

Council discussed the extent to which the iCSR FOA should lay out specific research topics related to CSER, or leave it open to all of genomic medicine so that investigators could propose their own research topics. NHGRI staff noted that these two options are not necessarily mutually exclusive. The NHGRI DGM research portfolio has historically been more consortium-based, so staff views the proposed iCSR FOA as a 'first-step' in moving towards more investigator-initiated awards. If many strong applications come in related to genomic medicine (but not necessarily related to CSER topics), then NHGRI could still fund these applications and cite programmatic balance as justification. Council believed it will be important to invite and include iCSR awardees to CSER2 consortium meetings.

Council recommended that the third aim of the iCSR RFA ("investigation of the function of putative pathogenic genomic variants identified in CSER and CSER2") be broadened to include the functional characterization and study of any variants of unknown significance (VUSs) (i.e., not just those identified through CSER).

Council discussed whether the same institution should be eligible to receive a CSER2 clinical site award, and an iCSR award. Council agreed that individual researchers should not be eligible to receive awards for both, but that different researchers at the same institution could apply for either award. It was noted that ENCODE program staff had a similar discussion with Council last year, and that DGM staff should look at the language that ENCODE decided to use.

Council approved the Investigator-initiated Clinical Sequencing Research (iCSR) concept by a vote of 15 in favor, none opposed, and no abstentions.

COUNCIL-INITIATED DISCUSSION
Council was interested in hearing a presentation from the National Library of Medicine and Precision Medicine Initiative Directors, once these positions are filled. Similarly, when the nominated FDA Director has been approved, Council would like an update on the interactions between NHGRI and the FDA. NHGRI staff noted that the Director of the National Institute for Minority Health and Health Disparities (NIMHD) has been invited to give a presentation at the May, 2016 NHGRI Council meeting.

Council asked for a presentation at the next Council meeting on the length awards made to investigator-initiated grants. NHGRI staff commented that unsolicited R01 awards are generally limited to three years of funding to reflect the fact that the field of genomics research evolves at a very rapid pace. For many years, past Councils have consistently advised that NHGRI limit

awards to three years for unsolicited grants to ensure that adequate funding is available to support newly emerging important areas of genomics research. Staff noted that R01 awards made to new investigators are frequently for longer than three years to provide stability to young investigators. There are also budgetary advantages to keeping major programs or large R01s to a four-year cycle.

REVIEW OF THE STATEMENT OF UNDERSTANDING

Dr. Pozzatti reviewed the Statement of Understanding between the National Advisory Council for Human Genome Research and the Staff of the National Human Genome Research Institute, which is reviewed at every February Council meeting. Council approved the Statement of Understanding by a vote of 15 in favor, none opposed, and no abstentions.

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 185 applications, requesting $111,623,798 (total cost). The applications included: 87 research project applications, 18 cooperative agreement (U01 or U24) applications, 23 ELSI research program (R-series) applications, 1 research center application, 26 institutional training applications, 1 conference application, 6 career transition award applications, 2 clinical investigator award (K08) applications, 13 SBIR Phase I applications, 3 SBIR Phase II applications, 2 STTR Phase 1 applications, 1 STTR Phase 2 application and 2 Research Education (R25) applications. A total of 128 applications totaling $63,593,714 were recommended by the Council.

05/16/2016
Date

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

05/16/2016
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.