NATIONAL ADVISORY COUNCIL FOR HUMAN GENOME RESEARCH
SUMMARY OF MEETING
May 20-21, 2013

The Open Session of the 68th meeting of the National Advisory Council for Human Genome Research was convened at 10:00 AM on May 20, 2013 at the Fishers Lane Terrace Level Conference Center in Rockville, MD. Dr. Eric Green, Director of the National Human Genome Research Institute, called the meeting to order.

The meeting was open to the public from 10:00 AM until 4:30 PM on May 20, 2013. 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 May 20, 2013, and from 8:00 AM until adjournment at 3:00 PM on May 21, 2013 for the review, discussion, and evaluation of grant applications.

Council members present:
Carlos Bustamante
Lon R. Cardon, ad hoc
Joseph Ecker, ad hoc
James P. Evans
Ross C. Hardison
David M. Kingsley
Amy L. McGuire
Howard L. McLeod
Deirdre R. Meldrum
Jill P. Mesirov
Anthony P. Monaco
Robert Nussbaum
Lucila Ohno-Machado
Pamela L. Sankar
Richard K. Wilson

Council members absent:
Howard Jacob
Arti Rai
David Williams

Staff from the National Human Genome Research Institute:

Alexi Archambault, ERP
Alice Bailey, DPCE
Jessica Barry, ERP
Maggie Bartlett, DPCE
Steve Benowitz, DPCE
Shannon Biello, ERP
Leslie Biesecker, DIR
Vivien Bonazzi, ERP
Vence Bonham, DPCE
Joy Boyer, ERP
Comfort Browne, ERP
Shaila Chhibba, ERP
Cheryl Chick, ERP
Monika Christman, ERP
Debra Colantuoni, ERP
Priscilla Crocket, DM
Christina Daulton, DPCE
Camilla Day, ERP
Carla Easter, DPCE
Elise Feingold, ERP
Adam Felsenfeld, ERP
Kim Ferguson, ERP
Ann Fitzpatrick, DM
Colin Fletcher, ERP
Tina Gatlin, ERP
Jonathan Gitlin, DPCE
Zivile Goldner, ERP
Peter Good, ERP
Bettie Graham, ERP
Mark Guyer, ERP
Linda Hall, ERP
Lucia Hindorff, ERP
Heather Junkins, ERP
Rongling Li, ERP
Nicole Lockhart, ERP
Carson Loomis, ERP
Lindsey Lund, ERP
Terryn Marette, ERP
Ian Marpuri, ERP
Jean McEwen, ERP
Keith McKenney, ERP
Vivian Ota Wang, ERP
Brad Ozenberger, ERP
Betsy Parker, DM
Michael Pazin, ERP
Ajay Pillai, ERP
Erin Ramos, ERP
Laura Rodriguez, DPCE
Ellen Rolfes, DM
Tamar Roomian, ERP
Leonard Ross, DM
Jeffery Schloss, ERP
Michael Smith, ERP
Heidi Sofia, ERP
Larry Thompson, DPCE
Michelle Travers, DM
Yekaterina Vaydylevich, ERP
Simona Volpi, ERP
Lu Wang, ERP
Chris Wellington, ERP
Kris Wetterstrand, IOD
Anastasia Wise, ERP
Rosann Wise, DPCE

Others present for all or a portion of the meeting:
Adam Berger, IOM
Joseph McInerney, ASHG
Richard Nakamura, CSR
Kate Saylor, NINDS
Rhonda Schonberg, NSGC
Michael S. Watson, ACMG

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

DIRECTOR'S REPORT

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

Council suggested approaching the Patient-Centered Outcomes Research Institute (PCORI) regarding potential collaborations for genomic medicine initiatives. Dr. Green commented that there have been many meetings between PCORI and the NIH Director to explore potential collaborations. This effort is mainly driven at the NIH level rather than the individual Institute level.

PRESENTATION BY THE DIRECTOR FOR THE CENTER FOR SCIENTIFIC REVIEW

Dr. Richard Nakamura, Director for the Center for Scientific Review (CSR), gave a presentation updating Council on the activities of CSR.

Dr. Green inquired if the Early Career Reviewer (ECR) Program includes a curriculum and mock study sections to train new reviewers. Dr. Nakamura commented that the ECR Program does not include mock study sections; each ECR receives training from the Scientific Review Officer (SRO). Each ECR attends no more than two full peer review sessions per year. The SROs and the review committee chairs feel that this is sufficient and they noted that the ECRs have not compromised the peer review process based on their early stage of career development and their lack of prior review experience.

Council asked for comments regarding the distribution of scores assigned by a review panel to a given set of applications and how CSR prevents false assumptions about scoring compression when in fact a very strong set of applications may have been submitted in a particular round. Council members noted their previous experiences in which the overall quality of the proposals submitted in response to an RFA was poor in absolute terms, but the SRO commented that the mean score for the set of applications was skewed to an impact score that was too low (too poor); the implication being that study sections should strive to produce a particular distribution of scores for all sets of applications reviewed by CSR study sections. Dr. Nakamura commented that CSR does not plan to take a predetermined approach to the problem of scoring distribution in study sections. It was recognized that the distribution and potential compression of scores are long-standing problems. Previous multiple efforts by CSR to address these problems have been systematically unsuccessful. As a result, CSR plans to meet with experts in decision theory to discuss possible solutions. CSR will continue to use strong, excellent scientists as the best judges for peer review. Going forward, they hope to develop theoretically better approaches for peer review and to test them in some study sections. Any lasting changes to the peer review process will be discussed with members of the scientific community in advance of widespread implementation.

Council noted research has shown that gender and racial biases exist in peer review, and they wondered why this has not been addressed directly with the NIH study sections. Dr. Nakamura commented that it is the intent of CSR to address any bias that is discovered in the peer review process. CSR is completing follow-up studies to determine if there are any differences in the quality of the applications that may account for what currently is perceived to be bias. More information is needed in order to design the most appropriate intervention(s). When bias is discovered, the intent of CSR is to retrain reviewers.

Council inquired what causes may underlie the phenomenon of clustering of scores around specific impact score numbers, and what CSR is doing to discourage this habit. Dr. Nakamura suggested that group dynamics may tempt or encourage reviewers to agree on scores for applications that initially score very well. It is only the few reviewers who choose to vote outside of the range after a group consensus is reached that cause differentiation among the scores. CSR recognizes that this is a significant problem that presently lacks a solution.

Council asked why applications to ELSI study sections score poorly compared to applications in other study sections. In this particular case, ELSI applications are reviewed in a study section that was formed by merging two previous review panels. Dr. Nakamura was asked if CSR traces how different sets of applications have been scored before and after the merging of study sections. He noted that tracking scoring histories of applications is based on concerns or complaints that come from a subgroup of the review committee or the scientific community served by the merged study section. However, he cautioned the Council that due to a large drop in the number of awards being made because of budget reductions, many groups assume incorrectly that their area of research is being selectively disadvantaged. CSR rarely finds statistically significant evidence for meaningful scoring shifts after study sections have been merged.

Council supported the data-based approach taken by CSR to identify and resolve issues related to peer review. Council noted that preliminary scoring of applications prior to the live meeting of the study section puts applications in priority order. They wondered to what extent the preliminary scores align with the final scores voted by the entire panel, and if the data gave an indication of: (1) how scoring is affected by the group dynamic, and (2) will we get to the point where in-person meetings are no longer necessary. CSR is systematically exploring the impact and contribution of socialization on score shifting and the review process. It is difficult to definitively determine how in-person meetings affect the outcome of peer review. Dr. Nakamura noted that the CSR hopes to determine if electronic review of applications is equivalent to or better than in-person review sessions.

Council asked for additional comments regarding funding to conduct controlled experiments of peer review. Dr. Nakamura noted that money saved through electronic review is being combined with supplemental funding to support experiments on gender and racial bias. CSR expects these results to clarify the quality of the peer review process. Dr. Nakamura plans to request more money from the NIH to conduct additional experiments.

Council asked if CSR has considered reviewing a subset of applications twice to determine reliability and consistency of scoring of individual applications. Dr. Nakamura replied that this idea is under consideration, but they have not yet carried out such a study. Council speculated that there would be high concordance among two review panels for the top 10% of applications and the lower 50% of applications, but more variability in outcomes would be found among the remaining applications.

Dr. Nakamura noted that a majority of science funding agencies in the United States are experiencing difficulties with regard to funding and have similar challenges to address in their review processes. He noted that America's success is built on federal funding for science and technology.

Council urged CSR to ensure that the best scientists are reviewing grant applications. To encourage scientists to participate as reviewers, Council suggested that incentives be provided

to reviewers to decrease the pressure that principal investigators may face when they are trying to submit their own grant applications while serving on a review committee; e.g., allowing for late submission of all applications, including those that are submitted to RFAs with set-aside funding.

Council suggested collecting mean, median, mode, and standard deviation scoring data for each review meeting; suggesting that a histogram of summary statistics would be beneficial to CSR, reviewers, and the applicants. Dr. Nakamura noted that the collection of data must be anonymous for individual reviewers to respect the confidentiality of the process.

Dr. Nakamura commented that the CSR has two forms of observation and assessment for quality assurance of their SROs. The reviewers and program staff provide feedback on the SROs and there is a supervisory hierarchy at CSR for SROs. The CSR Director, Division Directors and IRG Chiefs attend many review meetings.

PRESENTATION BY ROBERT NUSSBAUM

Dr. Robert Nussbaum gave a presentation entitled, "ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing."

Council supported the recommendations from ACMG regarding reporting of incidental findings in clinical exome and genome sequencing. Council noted that it is critical to acknowledge the nature of the incidental findings. In medicine, incidental findings are arrived at after a methodical analysis of the data has taken place. When genome-scale sequencing is completed and the data have been generated, the data are parsed through a series of informatics filters. The ACMG recommendations include additional filters through which the data should be parsed. Council noted that ordering whole-genome or whole-exome sequence for a patient represents a very broad test, and there should be some hesitation to do this in most cases.

Council acknowledged that there is controversy from physicians regarding the recommendations and questioned (retrospectively) whether there should have been more consultation with stakeholders before publishing the recommendations. Dr. Nussbaum replied that public fora were held for comments on the recommendations, but they may have targeted medical professionals too much, and perhaps more involvement of consumer groups would have been beneficial.

Council commented that many of the controversies regarding the recommendations stem from confusion and misinterpretation, and they wondered if attempts to clarify the recommendations have rectified many of the misinterpretations. Dr. Nussbaum noted that the ACMG has attempted to clarify that these recommendations are for laboratories, not physicians, and the ACMG recognizes that these recommendations will place a burden on the clinician-patient relationship. But it is also clear that some people still hold the view that it was simply a bad idea to release these recommendations.

Dr. Les Biesecker noted that negative reactions to the recommendations may reflect the differing views people have of the field and the role of medical genetics, and whether it differs in some fundamental way from other areas of medicine. Dr. Biesecker stated that he can find no coherent reasons why situations involving the return of genomic test results to patients are any different than results returned to patients following imaging, physical examination, or routine

laboratory chemistry tests. He stated that it will be a challenge to find ways to change the perceptions (held by some) that will allow genomics to move into mainstream medicine.

Dr. McGuire (a co-author on the ACMG report) noted there is a long-standing ethical debate surrounding the nature of genetic test results and issues such as the patient's right not to know, the role of patient preferences, and access to pre-testing genetic counseling. These issues are most prominent for late onset genetic diseases that cannot be treated or prevented, and we know there is very little uptake for genetic testing for these types of traits. The ACMG recommendations are supposed to address results that are actionable and have significant potential clinical benefit. There will always be debate whether there is enough evidence to support the level of clinical benefit to justify what genetic findings are put on the list to report to the physician (or the patient). The question of how much patients should be asked about their preferences of what should be looked for when the analysis of their sequence data is performed should not be lost. There is a reasonable presumption that anytime a patient participates in a comprehensive evaluation, a reasonable person would expect to be informed about any results that are clinically relevant and actionable. But patients will still maintain the right to refuse information. Dr. McGuire agreed that the ACMG report is a set of recommendations for laboratories, but she noted the discussions among the authors did include patient – doctor interactions and what types of information could be communicated to the patients. Dr. Nussbaum concurred noting that the report places a *greater* emphasis on the importance of the physician-patient relationship.

Council asked for comments regarding concerns about false-negative interpretation. Dr. Biesecker acknowledged that false-negative interpretations are a major concern. He noted that Robert Green of Brigham and Women's Hospital has developed the term "opportunistic screening" to mean the data present an opportunity to detect a subset of highly actionable results, but they are not necessarily the complete set of highly actionable results, nor do they include all of the variants in the 57 genes recommended by the ACMG in this report. The ACMG committee was concerned to keep the positive predictive value high because the probability of having the disorder is low. They focused on raising the threshold very high so that if a secondary or incidental finding was returned, it was highly likely that it would be correct. Dr. Nussbaum noted that the ACMG report does not include specific language for reporting sensitivity and specificity of tests, but testing laboratories routinely do report their levels of sensitivity and specificity.

While Council concurred with the perspective of the importance of a very strong relationship between the physician and patient, they also noted this type of interaction requires special knowledge on the part of the physician and the patient, and this does not exist in most cases. Therefore, placing the burden on the interaction between the patient and physician entails a risk that the process may fail quite frequently. This may have contributed to the sentiment expressed by many that there was some prematurity to the release of this report.

Dr. Biesecker noted that the ACMG had a difficult time deciding when to release these recommendations. Despite feelings within the community that the release of these recommendations was premature due to a lack of standardized language, the group decided to push forward because physicians are already ordering these tests and the results are being returned.

Council commented that the ACMG should consider educating physicians about the impact of these recommendations on the physician-patient relationship. Council noted that it is a seductive notion to say that a patient should have the choice to decide what is and is not

reported. But it is difficult for physicians to hold patients to a decision that they made in a hypothetical situation without full understanding of the consequences of their decisions. This is especially true in the case of false-positive results.

Dr. Michael Watson commented that another group within ACMG is working on releasing a report on the technical standards and guidelines for laboratories that include sample reports. Dr. Watson recognized that many system changes will be necessary to implement these recommendations. The ACMG board approved the release of these recommendations at this time with the hope that they would be able to set minimum standards and parameters for the community.

RECENT NHGRI MEETINGS

Genomics and Society Working Group

Dr. Pamela Sankar updated Council on the activities of the Genomics and Society Working Group. She noted that the goal of the group is to serve as a long-standing advisory group for NHGRI. Going forward, the Working Group welcomes comments and questions from Council, including suggestions of topics or areas of research that should be more closely examined. Dr. Sankar noted that the group expects to take on additional roles after a new director is appointed to the Division of Genomics and Society at NHGRI.

Research Training and Career Development Workshop

Dr. Bettie Graham briefed Council on the NHGRI Research Training and Career Development Workshop that was held in April. Dr. Gail Jarvik (co-chair of the Workshop) commented that NHGRI expects to have different mechanisms to fund research training and career development activities in the genomic sciences and genomic medicine. Council commented that training in genomic medicine would be most beneficial at the post-doctoral level where a strong foundation in genomics can be blended with clinical expertise.

Council questioned whether NHGRI should be expanding its training activities at a time when budget limitations and reduced support for research are limiting the number of research positions available. Council asked if NIH-wide market analyses are routinely conducted that might guide the scope of NHGRI's training decisions. Dr. Graham noted that the NHGRI training budget is relatively small and the workshop participants did not believe the training funds allocated will exceed the demand for genomics and medical genomics expertise in the community now, or in the coming years. Dr. Green noted that NHGRI often receives requests from clinical trainees with an interest to be trained in genomic medicine, but there is no vehicle in place to allow them to pursue this type of training. The Advisory Committee to the NIH Director generated a report on the biomedical workforce. The report indicated that there is a demand for physician-scientists trained in genomic medicine. In addition to the discussion about starting training for medical genomics, Council also advocated for training in informatics to continue, as there continues to be an expanding need for this expertise.

Council recommended that NHGRI pursue collaborations and interactions with the categorical ICs at NIH to develop training programs that would integrate the application of genomic technologies to their disease-specific training programs. The workshop participants recommended NHGRI's focus should be on training programs that impart more fundamental knowledge of advances in genomic medicine.

PROJECT UPDATES

Genome Sequencing Program Update: Disease 2020

Dr. Adam Felsenfeld presented a project update on the Genome Sequencing Program: Disease 2020 (D2020).

Members of the Council who also serve on the Sequencing Advisory Panel endorsed the proposed idea of demonstration projects in the short term, and commented that it also would be beneficial to design a long-term project to demonstrate that a large-scale sequencing approach can be successfully implemented to discover the genetic basis of one or more diseases. They also enthusiastically supported the leveraging of existing investments in disease studies across the NIH into other cohorts.

Council expressed some concerns about the proposed D2020 project. First, there is the possible perception that the Large-Scale Sequencing and Analysis Centers program has come to represent an infrastructure that is now searching for a mission. Second, there is concern that readily available existing samples might be used out of convenience, but these samples may lack the detailed and accurate phenotyping that will be needed to understand the biology of the diseases under study, and to establish accurate correlations between the variants that are discovered and the disease parameters being studied. Furthermore, to fully understand the pathogenesis of some diseases it may be necessary to characterize changes in the microbiome over time and correlate that data with genetic variants discovered in the disease cohorts, but the existing disease cohorts may not have this complete array of samples available. In response to these concerns, Dr. Felsenfeld noted that the sequencing centers are already engaged in multiple sequencing projects that can be considered to be early stages of some of the domains of the D2020 framework, and this plan is much more than a simple “self-preservation” project. He did acknowledge that it is difficult at times to separate the current structure of the centers from the D2020 research goals. He also noted the D2020 document should not be interpreted as drawing rigid boundaries between the five proposed project domains. A research project that combined whole-genome sequencing with microbiome data would be very appropriate for this framework, but if those samples are not currently available, NHGRI would have to consider the development of such samples immediately. At this time, NHGRI must concentrate on whether the goals described in the D2020 framework are possible to achieve, determine if there are suitable sample collections available that have good phenotype information, and decide whether the current structure of the Large-Scale Sequencing and Analysis Centers is appropriate to pursue the research goals described in the D2020 framework.

Council asked if the criteria to evaluate the demonstration projects in 2015 have been developed. Staff indicated those criteria will be developed with the advice and assistance of the Sequencing Advisory Panel in the future.

Council asked if NHGRI has had discussions with UK investigators associated with the UK BioBank project since this could be a possible source of samples. Dr. Teri Manolio commented that NHGRI will continue to be in contact with the UK BioBank regarding sample and data availability, but the sequencing centers expressed limited enthusiasm to supply sequencing capacity if there is no perceived disease-focus to the work. Council was supportive of the idea to use the UK BioBank as a resource. It was suggested that the portfolio include several different populations and a multiethnic design, and that the data be posted in dbGaP or have a direct link to the Wellcome Trust. Dr. Manolio noted that the UK Biobank is considering using an exome genotyping array in a large portion of these samples and possibly complete exome sequencing. It would be great if NHGRI could participate in that activity in some way. However,

there are concerns that sequence data obtained from individuals with a variety of disease outcomes may not be as informative as a larger number of aggregated disease cases. It was suggested that with sufficient numbers of specific diseases there would be more enthusiasm to pursue this endeavor.

Dr. Felsenfeld noted that there is substantial overlap between Disease 2020 and the efforts in the Large-Scale Sequencing and Analysis Centers and the Centers for Mendelian diseases. Program Staff frequently discuss opportunities and boundaries between the programs. Due to the short timeline of 18 months, the Disease 2020 project will focus on using existing samples and data. Council endorsed the plan to complete a thorough program assessment in 2015.

CONCEPT CLEARANCE

Dr. Lisa Brooks presented a concept for clearance entitled, "Interpreting Variants in Non-Coding Genomic Regions Using Computational Approaches with Experimental Validation."

Council asked for comments regarding the plan to call for experimental validation as an approach to demonstrate that a variant causes a phenotype of interest, noting that association of variants with specific phenotypes is the more appropriate goal. Dr. Brooks acknowledged that the intention is to focus on computational approaches and predictions accompanied by experimental validation that would increase the likelihood that detected variants are associated with the development of a specific phenotype. There is a range of possible validation approaches that could be developed, some of which would be extremely expensive to implement. Dr. Brooks further noted there are examples where pathway information has been used to narrow the field of possible variants, and model organisms could be employed to establish a link between a specific variant and phenotype causation. Dr. David Kingsley suggested that the phrase "experimental validation" could be left open to interpretation in the hopes of stimulating good ideas in this area.

Council noted that experimental validation efforts held great potential to improve our understanding of the biology of disease. But they may also serve to stimulate new discoveries in Domains 1 and 2 of the NHGRI Strategic Plan. Therefore, high-throughput validation methods may be very cost-effective, but there may be instances where more detailed (so-called gold-plated or gold-standard) validation approaches would be warranted. Council questioned whether staff has considered a plan for how resources in the RFA should be apportioned to computational versus experimental work. Dr. Brooks commented that Program Staff initially suggested a ratio of funds for these two activities, but had been advised by a sub-group of Council not to set specific dollar amounts for these research activities.

In response to a Council query, Dr. Brooks commented that the applications submitted to this RFA should focus on non-coding variants, but it would be acceptable if some targeting of coding regions is included. Methods that are designed to evaluate non-coding as well as coding regions variants would be considered to be responsive to this RFA. The RFA is not looking for applications addressing potential improvements of ways to infer non-synonymous change.

Council suggested including a Coordinating Center in the RFA to provide a set of variants to the grantees who have developed methods in response to the proposed RFA in order to evaluate how effective their approaches prove to be. This would require the development of a gold standard validation method (presumably by the Coordinating Center) that would not be made accessible to the public.

Council approved the Concept unanimously (14 – 0) with the amendment of a title change to, "Interpreting Variants in Non-Coding Genomic Regions Using Computational Approaches with Experimental Support."

COUNCIL INITIATED DISCUSSION

Dr. Eric Green led the Council initiated discussion. Council asked for clarification about information presented in the budget portfolio discussion regarding an apparent decrease in the funds allocated for informatics support, and whether this was related to an NHGRI staffing problem in the area of informatics. Dr. Green indicated it is likely that the reduction is more apparent than real, and the budget for informatics-related research has been more or less the same over the preceding two years. But there is also a staffing problem that has caused some initiatives to be delayed into future fiscal years. Council asked that the staff present an analysis of the NHGRI informatics portfolio at the September 2013 Council meeting.

ANNOUNCEMENTS AND ITEMS OF INTEREST

Dr. Pozzatti drew Council's attention to three documents that were sent to NHGRI:

1) The American College of Medical Genetics and Genomics Report to Council.
2) The American College of Medical Genetics and Genomics Report – Incidental Findings in Clinical Genomics: A Clarification to Council.
3) The National Society of Genetic Counselors Quarterly Report to 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 114 applications, requesting $56,682,221 (total cost). The applications included: 53 research project grants, 3 ELSI applications, 25 RFA applications, 15 research center applications, 2 conference applications, 5 career transition award applications, 1 research scientist development award application, 1 institutional training award application, 3 SBIR Phase I applications, 2 SBIR Phase II applications, 1 individual training applications, and 3 education project award applications. A total of 114 applications totaling $56,682,221 were recommended.

[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.

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

9/10/2013
Date

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

910/2013
Date

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