NATIONAL ADVISORY COUNCIL FOR HUMAN GENOME RESEARCH
MEETING SUMMARY
September 8-9, 2014

The Open Session of the 72nd meeting of the National Advisory Council for Human Genome Research (NACHGR) was convened at 10:00 AM on September 8, 2014, at the Fishers Lane Terrace Level Conference Center in Rockville, MD. Dr. Eric Green, Director of the National Human Genome Research Institute (NHGRI), called the meeting to order.

The meeting was open to the public from 10:00 AM until 5:45 PM on September 8, 2014. In accordance with the provisions of Public Law 92-463, the meeting was closed to the public from 8:00 AM to 10:00 AM and 6:00 PM to 6:30 PM on September 8, 2014, and from 8:00 AM until adjournment on September 9, 2014, for the review, discussion, and evaluation of grant applications.

Council members present:

Carlos Bustamante (by phone)
Lon Cardon
James Evans
Howard Jacob
Amy McGuire
Howard McLeod
Deidre Meldrum
Jill Mesirov
Anthony Monaco
Robert Nussbaum
Lucila Ohno-Machado
Arti Rai (by phone)
Eric Boerwinkle, ad hoc
Carol Bult, ad hoc
Joseph Ecker, ad hoc
Chanita Hughes-Halbert, ad hoc
David Page, ad hoc
Dan Roden, ad hoc
Val Sheffield, ad hoc
Jay Shendure, ad hoc

Council members absent:

Martin Kreitman, ad hoc

Staff from the National Human Genome Research Institute

Alice Bailey, DPCE
Shannon Biello, ERP
Joy Boyer, ERP
Lawrence Brody, ERP
Comfort Browne, ERP
Christine Chang, ERP
Cheryl Chick, ERP
Monika Christman, ERP
Julie Coursen, ERP
Catherine Crawford, ERP
Camilla Day, ERP
Valentina Di Francesco, ERP
Nicholas Digiacomo, ERP
Jimmy Do, DM
Elise Feingold, ERP
Adam Felsenfeld, ERP
Leigh Finnegan, ERP
Brandon Floyd, ERP
Kimberly Ferguson, ERP
Elise Galloway, DPCE
Daniel Gilchrist, ERP
Peter Good, ERP
Bettie Graham, ERP
Linda Hall, ERP
Lucia Hindorff, ERP
Carolyn Hutter, ERP
Brenda Iglesias, ERP
Heather Junkins, ERP
Destiny Lancaster, ERP
Alexander Lee, ERP
Rongling Li, ERP
Ebony Madden, ERP
Allison Mandich, IOD
Teri Manolio, ERP
Keith McKenney, ERP
Jean McEwen, ERP
Edson Mendonca, DM
Jeannine Mjoseth, DPCE
Hannah Naughton, ERP
Annie Niehaus, ERP
Vivian Ota Wang, ERP
Bianca Patel, ERP
Michael Pazin, ERP
Ajay Pillai, ERP
Lita Proctor, ERP
Erin Ramos, ERP
Laura Rodriguez, DPCE
Ellen Rolfes, DM
Jeffery Schloss, ERP
Michael Smith, ERP
Heidi Sofia, ERP
Jeff Struewing, ERP
David Trantin, ERP
Jennifer Troyer, ERP
Yekaterina Vaydylevich, ERP
Simona Volpi, ERP
Lu Wang, ERP
Chris Wellington, ERP
Kris Wetterstrand, IOD
Ken Wiley, ERP
Anastasia Wise, ERP
Rosann Wise, DPCE

Others present for all or a portion of the meeting:

Adam Berger, IOM
Adam Fagen, Genetics Society of America
James O'Leary, Genetic Alliance
Lonnie Welch, Ohio University
Pamela Sankar, University of Pennsylvania
Robert Wildin, Northwest Genetics
Michael Watson, ACMG
Joseph McInerney, ASHG
Elizabeth Tuck, ASHG
Rhonda Schonberg, NSGC
Vivien Bonazzi, Office of the ADDS/NIH
Phil Bourne, Office of the ADDS/NIH

FAREWELL TO DEPARTING COUNCIL MEMBERS

INTRODUCTION OF NEW NHGRI STAFF, LIAISONS, AND GUESTS

APPROVAL OF MINUTES FOR THE MAY, 2014 MEETING

DIRECTOR'S REPORT

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

Council asked about the rationale for increasing the length of the biographical sketch section of NIH applications in light of the reduction of this section a few years ago. Dr. Graham explained that this is an idea taken from the Howard Hughes Medical Institute process and aims to allow a contextual summary of the PI's accomplishments, instead of a simple list of publications, in order to make the section more informative. New investigators will be brought to the attention of the reviewers by the Scientific Review Officer, and this format will allow early career investigators to highlight their contributions to science, such as work done as part of a large consortium, that otherwise would be not be obvious. It is also more in line with the format used by tenure and promotion committees, as well as online publication databases such as Orchid.

The difference between the biosketch and the personal statement will be clarified as part of the ongoing pilots of the new biosketch, but the personal statement should be a story about the investigator, rather than a summary of scientific accomplishments, linked out to papers, as in the biosketch.

Council noted that three people involved with NHGRI are part of the NIH-wide HeLa Genome Advisory Committee: Robert Nussbaum, Russ Altman, and Rick Myers.

Presentation from the NIH Associate Director for Data Science by Philip Bourne

Dr. Philip Bourne gave a presentation as the new NIH Associate Director for Data Science (ADDS), emphasizing the BD2K (Big Data to Knowledge) Initiative. The ADDS Office now serves as the central contact for activities involving data science, opening communication channels across the NIH Institutes and Centers (ICs) and with extramural groups.

Council expressed concern that while a common, accessible computation resource (e.g., the Cloud) is an attractive idea, having several different ones based on cost effectiveness can lead to the replication and movement of large datasets across the internet. Dr. Bourne's hope is that by having a common space, more researchers will be able to locate and use existing datasets, rather than replicating and moving them. It will be important to test this by tracking data usage from a variety of biological studies during the testing and piloting stages currently being planned.

Another issue raised by Council was who should shoulder the fiscal responsibility for database maintenance and how NIH resources are being used for this task. Dr. Bourne explained that, apart from NHGRI and NIGMS, it is currently unclear how much is being spent on database maintenance by individual NIH ICs. It is also unclear how much *should* be spent by the various ICs. To address this, the ICs are now surveying their grant programs to gather information about their level of investment in database maintenance. One approach to continuing database maintenance is to recognize that while individual databases are currently highly curated, they exist as many separate entities, and this creates impediments to investigators that may wish to

do analyses across several data resources. If there were ways to put highly curated datasets from different databases into a shared environment, this would likely reduce cost and increase utility to the research community.

Council also asked for a clear and consistent policy on the use of the Cloud for data that involve human subjects research, as current policies are extremely confusing to the community. Dr. Bourne's group is working to harmonize the policies across NIH, but as a new entity, there is still concern about the Cloud, and there is a need for some successful implementation examples to further this area.

Dr. Bourne also clarified that the 'compute dollars' he mentioned in his presentation as part of a possible Cloud implementation plan would still be part of the budget of a research grant, but would be represented as hours of compute time, instead of dollars included in the actual award. A harder issue will be who will pay to maintain data generated and hosted on a website that is a viable resource to the research community if the grant is not renewed. Determining the value of the generated data is an essential part of that decision process, but the value of data is extremely hard to assess. Value is not based simply on the number of uses and downloads, but on how the data are used and the other research activities that are enabled by the data.

Patient information was another issue raised by Council, as their experience has indicated that local IRBs have limited familiarity and generally no set policies on the use of the Cloud. Dr. Bourne acknowledged this is a significant problem, and it is compounded by the fact that the range of data types collected on patients is extremely broad. His office is looking to hire someone with appropriate expertise on patient data, informed consent, and human subjects protections to help with this issue.

Council cited the new genomic data sharing policy that has now been released and called for more policy to be developed for the sharing of clinical data that would enable the use of Cloud computing and address the misperception that data on the Cloud cannot be adequately protected. Dr. Bourne acknowledged the difficulty of this challenge, but noted there is increasing pressure from investigators to solve this problem. He also noted the emerging cultural change that healthcare is becoming patient-centric; in particular, patients are increasingly gaining control of (have access to) their own genomic data. There are examples of cohorts of patients putting their health records and data, in an anonymized way, into a shared resource to be used for research purposes. This is happening most frequently in European countries that have socialized medicine. He raised the suggestion that NIH may be able to leverage these activities to create an international cohort with self-consent.

Council inquired how Dr. Bourne planned to gather input from the community on the standards that should be established when collecting clinical data in order to make the data more useful and accessible to the research community. Council noted that information systems currently being developed to manage clinical data would benefit tremendously if standards could be established sooner rather than later. Dr. Bourne noted that engaging organizations (e.g., Global Alliance for Genomics and Health) that are currently involved in developing recommendations and standards for their own purposes is a good way to catalyze a broader discussion on this topic. Dr. Bourne noted that NCBI is collecting information from a number of NIH Institutes for this purpose. The Office of the National Coordinator is another possible source of guidance and recommendations as well. There will also be workshops throughout the coming year to work on standards development.

Council and Dr. Bourne both emphasized that databases and software tool developers need their contributions to be recognized and acknowledged, especially for career development of young investigators. One approach would be to work with journals and ask them to require the citation of any software tool or database that was used to perform an analysis. Another idea is micro-publication of software, for example through PLoS (Public Library of Science), where every code that is written gets attribution, thus building a publication record as software is developed and also building the potential for collaboration and competition.

Future Opportunities for Genome Sequencing and Beyond Workshop Report by Adam Felsenfeld

Dr. Adam Felsenfeld presented a summary of the Future Opportunities for Genome Sequencing and Beyond Workshop held on July 28-29, 2014.

Council noted that the workshop report mentioned defining boundaries along the path from discovery to function and discovery to clinical translation of the genomic variants associated with common diseases. Council questioned whether boundaries *should* be set. They noted that the interface between discovery and function is an intellectually stimulating and challenging environment. Overall, progress might be enhanced by the active linking of discovery and functional work as well as of discovery and clinical translation. Dr. Felsenfeld clarified that the intent is not to set boundaries, rather the boundaries should be blurred, and there is a belief that there will be utility to blurring the boundaries.

Producing more "gold standard" genomes and increasing the amount of work done in comparative genomics also emerged as areas of continuing importance. Understanding structural variation is expected to enhance our understanding of disease causation. Dr. Felsenfeld clarified that careful consideration would be given to the populations that would be chosen for the gold standard genomes.

ELSI (Ethical, Legal, and Social Implications) areas were not included in the workshop by design, and will be discussed separately. Social justice issues did come up during workshop discussions, particularly around population selection and training.

The importance of good design and large sample size was raised in the workshop as important elements, as well as ensuring that more populations are represented.

Adjudication of variants also came up as a central goal, implying that we will also have to grapple with clinical outcomes.

CONCEPT CLEARANCES

"Common Disease Variant Discovery (CDVD)" presented by Adam Felsenfeld

Dr. Felsenfeld gave a presentation on the concept to pursue large-scale genome sequencing to study many aspects of common diseases.

Council asked for clarification about the intent to conduct comprehensive studies of common diseases, and noted that there are three parameters that can be explored – all of which will contribute to a comprehensive investigation of a disease. These include the sample size, the architecture of the disease, and the coverage of the genome (e.g., whole-exome versus whole-

genome sequence data). The most ambitious study would seek to maximize all three of these parameters.

Council noted that the concept is not entirely comprehensive. It proposes to go deep on sample size, semi-broad on diseases, but favors whole-exome sequencing (WES) over whole-genome sequencing (WGS), which can impact the ability to target disease. Dr. Felsenfeld emphasized that the program has to be realistic about the amount of funding available, but will have the ability to adjust to advances in technology and cost reductions as they occur, which the program hopes to push forward. A transition to whole-genome sequencing is expected to happen in the four years covered by this program.

Blurring boundaries (mentioned above) and measuring progress were mentioned as important goals during the workshop, but the concept seems to deviate from that. Council suggested that something more focused and visionary may be needed to leverage the resources for such a large and impactful program. Some of the points in the workshop slides, which are not included in the concept, would help, as well as potentially changing the title to reflect the catalytic nature that the concept seeks to have.

Council also expressed the view that the 25,000 proposed cases and control samples, and any partnerships, should be integrated and leveraged for the most powerful experimental setups. Phenotyping of these samples will be critically important. But the way the concept is written reflects a focus on genotyping and sequencing processes, and the phenotyping costs and challenges are not addressed adequately. Council noted that it will likely not be possible to obtain a cohort of 25,000 samples without combining cohorts from different collections. While each collection may be of high quality, they were not originally designed to be integrated into one set. Thus, it would be advantageous to combine forces with some of the other institutes/centers and start prospective sample gathering, so that the consents and necessary phenotypic information are collected in the various cohorts.

NHGRI aims to hold collaborators to open data sharing policies, while recognizing that unique data access circumstances may exist for a given collection of samples.

While the basic concept for genome sequence of large cohorts to identify variants associated with common disease represents a logical approach, Council noted there is no guarantee of success. Therefore, it would be prudent to design the program in such a way that even if comprehensive sets of variants are not found, the results of the study will still be informative. This may require selecting cohorts with high-quality environmental data and longitudinal information. Developing metrics for measuring success will be important for this program. One metric can be the discovery of rare functional variants in common diseases; however, it will also be important to define success and failure based on whether specific questions about diseases are answered, and not simply rely on achieving production goals.

Council also highlighted the importance of pursuing variants that are protective for disease; for example, variants that influence low blood pressure or low LDL levels. Thought needs to be given to how the phenotype of protection should be defined. If the program emphasizes only the collection and study of disease samples, an important opportunity will be lost.

Council questioned to what extend the centers will be required to work together, and offered some scenarios that could be considered as NHGRI decides how best to use the retained funds proposed in the concept. Dr. Felsenfeld confirmed that the centers will be expected to work together in a highly collaborative manner on multiple projects, and there are encouraging

examples of effective collaborations that the centers have achieved in the current funding phase. But NHGRI is open to various opportunities to leverage funding and resources from other sources, and all options will be considered.

Dr. Pozzatti reminded Council members that they will be voting for the concept, not a funding amount or plan. The amount of funds listed in the concept document represents a realistic estimate on the part of staff of what would be needed to achieve the goals presented in the concept; therefore, Council should expect to see a similar funding amount in the resulting funding opportunity announcement (FOA) when it is published.

Council approved the concept as proposed, with 11 votes for approval, none opposed, and 7 abstentions.

"Centers for Mendelian Genomics (CMG)" presented by Lu Wang

Dr. Wang gave a presentation on the concept to renew the Centers for Mendelian Genomics program.

Council questioned if anyone has surveyed OMIM (Online Mendelian Inheritance in Man) to determine how many traits/diseases may have samples available to be analyzed. Dr. Wang explained that the sample solicitation efforts of the current program have been low scale, whereas the renewal FOA will designate more funds for solicitation and outreach to obtain samples. Working with Ada Hamosh (PI of OMIM), the grantees have gone through the list of diseases in OMIM, and have identified likely Mendelian diseases and the PIs that have published on these diseases in an effort to start soliciting more samples. The consortium of CMG investigators has expressed confidence that a sufficient number of samples can be obtained to support the goal of characterizing 300 new Mendelian disorders over the four years of the renewal phase of this program.

One Council member suggested attracting support from the other institutes by selecting diseases based on their interests. Dr. Wang agreed that this is a possibility. The current collaboration with NHLBI, which provides a contribution of about 16% of the funding, follows another model in which X01 applications have been used to solicit samples. However, NHLBI has not been able to solicit enough samples for 16% of the pipeline, so the CMGs have been asked to focus on heart, lung, and blood phenotypes in their solicitations as well. Other institutes suggested by Council were NEI, NIMH, and NIDDK, as those likely have defined cohorts that would be suitable for the CMG investigators to study.

Council asked for clarification on the difference between cases considered to be "solved" and "completely solved." Dr. Wang clarified that the CMG investigators use the terms "project completed" when a likely causal or associated variant has been found in at least three families, or that a disease can only be partially explained by the variants discovered (genetic heterogeneity and modifiers). "Completely solved" refers to variants where functional data have been obtained (likely with help from a collaborator), and the functional data serve to validate the causality of the variant in the disease phenotype. Council suggested that another term be used to define "solved" cases. They noted examples where modifier genes affect the phenotype, and labeling a phenotype as solved when an underlying variant is discovered could be misleading. Some members of Council mentioned that the function component described in the concept document is very much underplayed. Drs. Pozzatti and Wang explained that the mention of some functional work was included because it has become difficult for the grantees to publish their variant discovery work without some demonstration of validation through functional studies.

Another Council member suggested a different approach to address the challenge of functional studies – a supplement mechanism that would allow the centers to reach out to investigators who have expertise with the gene in which variants have been discovered. This would allow the functional analysis work to be done by those best-suited to the task. Several Council members encouraged developing a process by which functional analysis could be performed.

Council noted that as the CMGs move on to study rarer Mendelian diseases, this will likely mean smaller families sizes, fewer cases, less well-defined phenotypes, and greater heterogeneity – all of which can lead to a higher rate of mistakes and false positives. This means that the program may need to develop stricter criteria for what constitutes a 'solved' disease, and there may be a need to includes functional analyses in that process.

Council noted that commercial laboratories are also doing a lot of Mendelian disease discovery through their whole-exome sequencing work, prompting Council to ask if this information is being captured and made available to the broader scientific community. Dr. Wang stated that the program continues to push for sharing of this information from the commercial labs.

A Council member asked about specifically selecting and reaching out to populations of interest for research, such as populations with consanguineous families, in a way that would make them feel like partners. Dr. Wang reported that one of the centers has done genome sequencing of consanguineous families, and it has been very successful for characterizing extreme phenotypes.

Council approved the concept with 11 votes for approval, none opposed, and 7 abstentions.

"Genome Sequencing Program Coordinating Center (GSPCC)" presented by Adam Felsenfeld

Dr. Felsenfeld gave a presentation on the concept to create a coordinating center that would perform administrative and data analysis activities for components of the Genome Sequencing Program.

Council noted the important need for overall program management, and there is an expectation that the need for coordination will increase both among the centers as well as across the different sequencing components. But a major concern was raised by Council that the concept proposes to merge two types of activities: project coordination and data analysis plus study design. Furthermore, as more DNA sequencing platforms emerge, study design and analysis are likely to become more complex, and the Council expressed an additional concern that the analysis component is under-resourced as proposed in the concept document. After substantial discussion, Council strongly urged that the two activities of project management/coordination and data analysis/study design be split into two distinct FOAs.

Some Council members expressed concern that the decision to include study design and data analysis activities in an FOA that is separate from the CMG and CDVD sequencing components might hinder the ability of these two components to achieve their goals. Dr. Felsenfeld clarified that the CMG and CDVD investigators would have the primary responsibility to determine their study designs and perform the data analyses. The coordinating center investigators may participate in the analysis work, but their responsibility would be to provide coordination among the centers, particularly when coordination was required between the CMG and CDVD centers. Council noted that NHGRI staff would have to be vigilant that 'mission creep' on the part of the coordinating center did not complicate and hinder the ability of the CMG and CDVD

investigators to plan their studies and analyze the data they produce. As an example, Council noted that early on, there should be multiple study designs going forward because at this time, we do not know the correct approach that should be taken for each disease that will be studied. If there is a coordinating center that insists on a single approach for all investigators, this would become counter-productive.

Dr. Green noted that participants at the July workshop expressed the view that it would be valuable to have additional funded investigators working outside of the production centers that bring a fresh analytical perspective to the analysis challenges and to coordinate cross-project analyses. The workshop participants felt there have been missed opportunities in NHGRI's Genome Sequencing Program stemming from a lack of coordination across the different components. He asked the Council if they concurred with that perspective for the current FOAs. Some Council members pointed to the TCGA program and noted that collaborations among the analysis groups and cross-project analyses were successfully conducted without a formal coordinating center. Other Council members concurred that there have been missed opportunities in the past, but the proposed coordinating center concept is not properly structured to address the kinds of cross-project analyses that will need to be done. Rather than having a single coordinating center, it would be better to involve several smaller groups to participate with the production centers to tackle the data-analysis challenges.

Council concurred that an administrative coordinating center should exist, but a substantially revised concept needs to be developed. A new concept for cross-analysis center(s) or analysis groups will be brought back to Council in February 2015, as the time delay for this activity is not critical, and it may even be beneficial to determine what data types will be produced before funding them.

The concept was rejected by Council with 13 votes to disapprove, no votes for approval, and 5 abstentions.

"Center for Inherited Disease Research" contract renewal presented by Larry Brody

Dr. Larry Brody gave a presentation on the contract renewal for the Center for Inherited Disease Research.

Council was curious how the CIDR program (and its costs) compares to companies that offer similar genotyping services. Dr. Brody answered that CIDR's genotyping cost is comparable to commercial services, but CIDR produces better quality data and only charges for samples that produce data. They also provide ancillary services (such as data cleaning and DNA fingerprinting of samples) to ensure quality control throughout all steps of the process. CIDR is not currently cost-competitive in whole-genome sequencing, largely because of their small capacity for that service.

Council questioned whether in 2015/2016, it will be worth it to spend ~$200 on a GWAS chip when for a few hundred dollars more, one could obtain whole-exome sequence data. Dr. Brody replied that if the cost of array chips remains fixed, then in the not-too-distant future, the demand for arrays will decline and CIDR will move to genome sequencing. But if the costs of arrays can be driven down significantly, then arrays can be used in combination with genome sequencing in economical ways for association studies and for variant-discovery work. However, CIDR does not have a large-enough production capacity to influence the commercial costs of genotyping arrays.

Council approved the concept with 13 votes to approve, none opposed, and 5 abstentions.

PRESENTATIONS

The NHGRI Division of Genomics and Society and the ELSI Research Program

Dr. Larry Brody gave a presentation on the Division of Genomics and Society and his vision as its Director.

Council asked if the Division of Genomics and Society has much interaction with the Office of Human Research Protections (OHRP). The Council noted that members of IRBs have expressed the desire to receive more guidance and training information from a centralized source, such as OHRP. Most of NHGRI's interaction with OHRP has been through the Division of Policy, Communications, and Education (DPCE). As for resources, NHGRI is about to launch a database of sample protocols involving genetics/genomics research and appropriately developed informed consent language. The two divisions are also periodically asked to work with the Office of the Director to develop policies.

Council also enquired about interactions with the Veterans Administration. The ELSI Program has not interacted with the VA; however, Dr. Manolio has had a number of discussions and consultations with the VA around several of their studies. Dr. Nussbaum is on the advisory board and commented that while there have been consent discussions for the Million Veterans Project, there has not been much discussion about ELSI research issues in this project's advisory meetings.

Council wondered about strategies for cost sharing with other institutes. Dr. Brody described two traditional approaches. The first involves providing some funding to add an ELSI research component to an existing project sponsored by another institute. The second is to try to induce other institutes to sign onto an NHGRI RFA or Program Announcement. Both approaches involve using personal relationships established with program directors from other institutes.

Council complimented the Division of Genomics and Society on the extensive consultations they have provided to other institutes and agencies, and asked if priorities had been aligned to the five goals that Dr. Brody has set for the Division of Genomics and Society. Dr. Brody identified the goal to align investigator-initiated research to the current NHGRI strategic plan as a key interest, but also noted the desire to retain flexibility to address new issues that may arise. While the Division of Genomics and Society's program directors do encourage application submissions that are responsive to specific topics, they ultimately fund the proposals that do the best in the peer review process.

Council asked if there are specific initiatives directed at bringing in the perspective of patient advocacy groups. Dr. Brody responded that NHGRI has not funded much research on this topic, but he has personally witnessed the interesting influence such individuals have when they participate in peer review panels.

NACHGR Genomics and Society Working Group Update

Dr. Pamela Sankar presented an update on the activities of the NACHGR Genomics and Society Working Group.

Council noted that the challenges facing the current ELSI review committee regarding conflict of interest are the same challenges affecting all review committees, and thus conflict is a challenge that must be addressed as in any peer review setting.

Council also asked about the development of the boundaries of what constitutes ELSI research in the context of making the determination if an application is responsive to the goals of the ELSI Research Program. Drs. Sankar and McEwen explained that these boundary decisions are largely based on the language in the more recent ELSI Program Announcement, and stem from the challenge of how to make funding decisions with the limited resources for funding at NHGRI. Regarding the specific case of research projects that are focused on a single disease, it seems appropriate to consider that other institutes are better-suited to support those research projects that are focused on a disease that is highly relevant to their institute goals.

Council singled out the debate on whether health services outcomes should be considered a component of ELSI research. Dr. Sankar explained that while this topic has begun to be debated by the Working Group, it will be brought back for further deliberation over the next year. While health services research is a part of the greater 'genomics and society 'umbrella, there is a question of how much it should be supported, and what agency should support it.

Finally, Dr. Brody mentioned that the conversations with the FBI have been very positive, and that the FBI has been very forward-thinking in its approach to understanding the ELSI issues in its law enforcement matters.

ENCODE Project Update

Dr. Elise Feingold presented an update on the ENCODE Project.

Dr. Green commended the ENCODE program directors for working to implement the new Genomic Data Sharing policy in the ENCODE Project before the policy was released and officially implemented.

Council noted that the ENCODE Project has been a great success and asked if the program directors plan to bring a discussion to Council in February 2015, ahead of the concept clearances that are planned for May 2015. In particular, Council asked if NHGRI staff is considering opportunities to leverage other research activities, including the Genome Sequencing Program. Dr. Feingold noted that the planning workshop will not take place before the next Council meeting in February, but the staff will be happy to report on planning efforts at that time. Council further asked if there are plans to coordinate and integrate the variant discovery work that will be done by the Genome Sequencing Program with functional projects that the staff will plan in 2015. Dr. Feingold assured Council that the projects will be looking to synergize as much as possible, though there may be logistical or technical issues that limit the degree to which the programs can be coordinated. Looking ahead, Council suggested that when sample selection is considered for the Genome Sequencing Program, additional thought should be given to issues like informed consent and whether additional tissues should be collected to enable functional studies to be performed.

GWAS and common disease studies have shown that 90% of GWAS hits are in noncoding regions of the genome. Returning to the discussion of the Common Disease Variant Discovery concept from earlier in the day, Council asked why NHGRI should continue to emphasize whole-exome over whole-genome sequencing. The rationale is largely based on power and cost issues. Another Council member predicted that within two years, there will be a major shift to

whole-genome sequence approaches as DNA sequencing costs continue to decline. In addition, a collaboration between ENCODE and the CHARGE Consortium is focused on using ENCODE data and additional genome-sequencing data to try to understand the biological consequences of the GWAS associations that have been discovered in disease cohorts to date. Other Council members pointed out the potential value of a completed ENCODE catalog and the utility of ENCODE data to help interpret GWAS hits that map to non-coding regions.

COUNCIL-INITIATED DISCUSSION

Council expressed concern over the FDA's involvement in implementation research involving the use of genomic information in clinical trials. Even though the FDA has expressed that it does not intend to influence the research, there is concern that investigators will alter their research plans to avoid the need to obtain an investigational device exemption (IDE) from the FDA. Council expressed concern that it may have influenced and caused changes in projects, such as those within the Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) Program. Council expressed interest in a two-way conversation with representatives from the FDA at the next Council meeting to hear their perspective.

Council requested an update on NHGRI's plans for the technology development program – for DNA sequencing technology and more broadly. Staff plans to bring a concept clearance on technology development to the Council in May 2015, following a workshop that will take place earlier in 2015.

A presentation from PCORNET highlighting their biorepository was also requested by Council.

ANNOUNCEMENTS AND ITEMS OF INTEREST

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

1) American College of Medical Genetics and Genomics Quarterly Report to Council
2) National Society of Genetic Counselors Quarterly Report to Council
3) American Society of Human Genetics 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 to them.

REVIEW OF APPLICATIONS[1,2]

In the closed session, the Council reviewed 168 applications, requesting $86,383,249 (total cost). The applications included: 106 research project grants, 10 ELSI Research Program applications, 7 research center applications, 5 conference applications, 2 career transition award applications, 23 research scientist development award applications, 8 SBIR Phase I applications, 4 SBIR Phase II applications, and 3 STTR Phase 1 applications. A total of 82 applications totaling $30,441,861 were recommended.

02/10/2015
Date

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

02/11/2015
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, R25, and U54 applications were submitted in response to BD2K initiatives and were temporarily assigned to NHGRI.