NATIONAL ADVISORY COUNCIL FOR HUMAN GENOME RESEARCH
SUMMARY OF MEETING[1]
September 8, 2008

The Open Session of the National Advisory Council for Human Genome Research was convened for its fifty-fourth meeting at 8:33 A.M. on September 8, 2008 at the Fishers Lane Conference Center**,** Rockville, MD. Alan Guttmacher, Acting Director of the National Human Genome Research Institute, called the meeting to order.

The meeting was open to the public from 8:33 A.M. until 5:00 P.M. on September 8, 2008. In accordance with the provisions of Public Law 92-463, the meeting was closed to the public from 5:00 P.M. on September 8, 2008 until adjournment for the review, discussion, and evaluation of grant applications.

Council members present:

Eric Boerwinkle
Andrew Clark
Jorge Contreras, Jr.
Vanessa Northington Gamble (9/9/08 only)
Richard Gibbs
Geoffrey Ginsburg
Caryn Lerman
Deirdre Meldrum
Patrice Milos
Pilar Ossorio
David Page
Stephen Prescott
Harold Shapiro
Paul Sternberg (by teleconference)
David Valle
Richard Weinshilboum

Ad Hoc Members present:

Sean Eddy
Claire Fraser-Liggett

Ex Officio Members absent:

Gerard Schellenberg

Staff from the National Human Genome Research Institute:

[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".

Ajay, DER
Maggie Bartlett, OD
Tsega Belachew, DER
Vivien Bonazzi, DER
Vence Bonham, OD
Joy Boyer, DER
Lisa Brooks, DER
Comfort Browne, DER
Debbie Chen, DER
Cheryl Chick, DER
Monika Christman, DER
Christine Cutillo, DER
Karen DeLeon, OD
Laura Dillon, DER
Gwen Dudley, DER
Greg Feero, OD
Elise Feingold, DER
Adam Felsenfeld, DER
Colin Fletcher, DER
Phyllis Frost, OD
Peter Good, DER
Alan Guttmacher, OD
Mark Guyer, DER
Bettie Graham, DER
Linda Hall, DER
Lucia Hindorff, DER
M.K. Holohan, OD
Ephraim Johnson, DER
Chris Juenger, DER
Heather Junkins, DER
Mike Kabatt, DER
Rebecca Kohlberg, OD
Carson Loomis, DER
Teri Manolio, DER
Omar McCrimmon, OD
Jean McEwen, DER
Keith McKenney, DER
Lisa McNeil, DER
Anika Mirick, DER
Janis Mullany, OD
Ken Nakamura, DER
Vivien Ota Wang, DER
Brad Ozenberger, DER
Carmen Perera, OD
Jane Peterson, DER
Rudy Pozzatti, DER
Ed Ramos, OD
Erin Ramos, DER
Cristen Robinson, DER
Laura Rodriguez, OD
Anna Rossoshek, DER
Sara Selgrade, OD
Jeff Schloss, DER
Geoff Spencer, OD
Jeff Struewing, DER
Gary Temple, DER
Elizabeth Thomson, DER
Susan Vasquez, OD
Lu Wang, DER
Chris Wellington, DER
Kris Wetterstrand, DER
Louise Wideroff, DER
Diane Williams-Bey, DER
Julia Zhang, DER

Others present for all or a portion of the meeting:

Diane Baker, Genetic Alliance
Terry Brennan, Social and Scientific Systems
Sharon Olson, International Society of Nurses in Genetics

INTRODUCTION OF NEW MEMBERS AND STAFF, LIAISONS AND GUESTS

Dr. Guyer noted that five members are scheduled to rotate off after this Council meeting, but they have been asked to be available for another year as the new Council slate has not yet been approved. They are Andy Clark, Vanessa Gamble, Deirdre Meldrum, Stephen Prescott, and Harold Shapiro.

Dr. Guyer introduced Clare Fraser as an ad hoc member of the Council pending her appointment, and welcomed former Council member Sean Eddy back as an ad hoc member. He introduced new NHGRI staff: Ebony Bookman of NIEHS, who is working with the Office of Population Genomics; Christine Cutillo, Program Analyst, DER; Sara Selgrade, ASHG policy fellow; Louise Wideroff, on detail from NCI with the Office of Population Genomics; and Julia Zhang, Program Analyst, DER.

Dr. Guyer welcomed members of the press and liaisons from professional societies: Diane Baker from the Genetic Alliance, Terry Brennan from Social and Scientific Systems, and Sharon Olson from the International Society of Nurses in Genetics.

APPROVAL OF MINUTES

The minutes from the May 2008 Council meeting were approved as submitted.

FUTURE MEETING DATES

The following dates were proposed for future meetings: February 9-10, 2009, May 18-19, 2009, September 14-15, 2009, February 8-9, 2010, May 17-18, 2010, and September 13-14, 2010.

FAREWELL FROM FRANCIS COLLINS

Dr. Francis Collins, who recently resigned as Director of NHGRI was invited to say farewell to the Council, and expressed his gratitude for the opportunity to say goodbye today.

Dr. Collins noted that one of the tasks he had had to complete before leaving NHGRI was sorting his old papers for those of interest to the historical record. He noted NHGRI's many scientific opportunities and accomplishments, and pointed out that the Institute's efforts had not diminished with the completion of the Human Genome Project. At present there are nineteen major production-oriented projects under way. He also

expressed two regrets -- that the AGES study, a large, population-based prospective cohort study, and the development of therapeutics for rare and orphan diseases, are not among those nineteen.

Dr. Collins congratulated the Council for being unusually active among NIH Councils, in terms of its substantive participation in the Institute decision-making process. He also expressed the opinion that the staff of NHGRI is unusually scientifically skilled, bold, and ingenious in their development and management of programs. He endorsed the new Institute leadership, and expressed confidence that the transition to new leadership of NHGRI will be smooth, pointing out that he and Dr. Guttmacher are similar in mindset and that the rest of the senior staff is well prepared for the transition.

Dr. Collins finished his remarks to Council with six exhortations:

1. Push the boundaries – don't be complacent; continue to seek new ways in which NHGRI can set the course. Take advantage of the planning process, and don't lose momentum while waiting for the appointment of a permanent Director.
2. Seek out partnerships – Partnerships are imperative for genomics to make its full impact on biomedical research; be at the head of the line with new projects for the Common Fund.
3. Continue to nurture the next generation of scientists, both as trainees and young investigators. These are the investigators who will tackle the next set of hard scientific questions.
4. Continue to attend to the broader social context – Much progress has been made with the passing of GINA, but careful attention will be needed to ensure that research will be done in ways that will protect the public and provide them with the educational tools to understand what their genomes mean.
5. Continue to push for open data access.
6. Be bold in all things – Don't settle for the science that is only "kind of exciting."

Dr. Collins will continue his research lab as a special volunteer. He will also be working on a personalized medicine book which is intended for the general public. He is not sure what his next calling will be, but he wants to go where he can make the most significant and meaningful contributions.

Dr. Guttmacher and members of the Council thanked Dr. Collins for his many contributions over the past fifteen years. They hope that Dr. Collins will continue to be involved in NHGRI.

DIRECTOR'S REPORT

I. GENERAL ANNOUNCEMENTS

Alan Guttmacher M.D., Acting Director

Alan Edward Guttmacher, M.D., a nationally recognized pediatrician and medical geneticist who has played major leadership roles at NHGRI for nearly a decade, became Acting Director of

NHGRI on Aug. 2, 2008. He replaced Francis S. Collins, M.D., Ph.D., who stepped down after 15 years at the helm of NHGRI to pursue other professional opportunities.

NIH plans to conduct a broad search for a permanent NHGRI Director, but the details of that search process have not been finalized.

There have been two other changes in the Office of the Director attendant upon Dr. Guttmacher's change in position:

- Laura Lyman Rodriguez was appointed Acting Director of the Office of Policy, Communication and Education. She is also Senior Advisor to the Director for Research Policy.
- Susan Vasquez was appointed Acting Chief of Staff to the NHGRI Director. She was formerly Special Assistant to the Deputy Director.

Victor A. McKusick, M.D., "Father of Medical Genetics," 1921-2008
Victor Almon McKusick, M.D., University Professor of Medical Genetics at the Johns Hopkins University School of Medicine, a towering international figure the history of genetics research, diagnosis, and treatment, died Tuesday, July 22 at home. He was 86.

NIH Director's Awards
At an awards ceremony in June in the Natcher Auditorium, NIH Director Dr. Elias Zerhouni recognized the work of several NHGRI staff members. The NIH Director's award recognizes employees who exhibit superior performance or special efforts significantly beyond their regular duty requirements, but directly related to fulfilling the NIH mission. Awards were given to:

<u>The Genome Wide Association Studies Policy Development Team</u>
Lisa Brooks, Mark Guyer, Jean McEwen, Elizabeth Thomson, Emily Harris, Teri Manolio, and Laura Rodriguez

<u>The Human Microbiome Roadmap Project Team</u>
Vivien Bonazzi, Jean McEwen, Jane Peterson, Jeff Schloss, and Lu Wang

<u>NIH Biennial Report Leadership Team</u>
Phyllis Frosst

<u>Job's Syndrome Group</u>
Mary J. Davis

Michael Rackover Receives Award for Physician Assistant Education
Michael Rackover, PA-C, M.S. has recently received the 2008 outstanding service award from the Physician Assistant Education Association for his leadership in promoting genetics education activities in the Physician Assistant community. Mr. Rackover recently spent a sabbatical at NHGRI, and continues as a consultant to the Genomic Healthcare Branch in NHGRI's Office of the Director.

Commissioned Core

Dr. Guttmacher recognized the seven NHGRI staff that are members of the Public Health Service Commissioned Core, and thanked them for their involvement in the recent hurricane relief efforts.

NHGRI Planning Process
It has been almost seven years since NHGRI began its last planning process, which culminated in the publication in April 2003 of our "Vision for the Future of Human Genome Research" in *Nature*. While that document has worn well over time, the phenomenal advances in genomics and related fields convinced NHGRI leadership that it is now time to embark on a new planning process for the future. In April of this year, NHGRI invited many senior NHGRI staff and a small number of external experts to a day-and-a-half retreat to help define the content areas that should be addressed in a new plan. The group also discussed the best means for gathering public comment about the future of genomics, including white papers, wiki-like discussions, webinars and in-person meetings. Several white papers will be posted for wiki comment later this fall, and the responses will help frame future planning activities. The goal is to complete the process in October 2010, in time for the 20th anniversary of the start of the Human Genome Project. The planning process is expected to be underway, but not completed, before the next permanent NHGRI Director is selected, so that s/he can have ample input.

II. NHGRI - EXTRAMURAL PROGRAM

Funding Opportunities. Dr. Guttmacher reported to Council that NHGRI is involved in several new funding opportunities, which are listed on the genome.gov and nihroadmap.nih.gov websites.

Sequencing Status Update. The Large-scale Sequencing Network met with the Sequencing Advisory Panel on July 21st and 22nd in New York City to discuss current status and progress on the implementation of new sequencing platforms. A more detailed update on the meeting and the sequencing program will be presented later in the Open Session.

Sequencing Technology. A set of new awards were issued in August for development of new DNA sequencing technologies, including three awards in the $100,000 genome program and eight in the $1,000 genome program. A new set of RFAs for the $1,000 genome program were issued in August, with a receipt date of October 22.

International Cancer Genome Consortium – ICGC. The formation of the International Cancer Genome Consortium (ICGC) was announced in April (see http://www.icgc.org for more information). The ICGC will help coordinate the large number of cancer genome studies being conducted across the globe. NHGRI and NCI, serving as the funding agency representatives for the U.S., are sharing with the consortium the many lessons learned in organizing The Cancer Genome Atlas program. ICGC members will meet in November to formalize operational principles and to forge relationships to investigate specific diseases.

MGC. MGC-funded activities officially end on September 25, 2008. To date, the MGC has achieved full-length CDS cDNA clones for 17, 566 unique human RefSeq genes, 17,555 mouse

genes, and 6,182 rat genes. The results for human and mouse represent 93% and 90%, respectively, of the well-defined RefSeq genes.

Altogether the cDNA cloning programs supported by the MGC infrastructure have generated 111,346 full-CDS clones

The accomplishments of the MGC program will be reviewed during the final MGC External Steering Committee meeting, on September 22, 2008, in Rockville, MD. On September 23, an MGC Symposium will be held at the NIH Masur Auditorium, at which six prominent scientists will present their results from studies that benefitted by access to the MGC sequence and clone resource. Both events are open to the public.

The Human Microbiome Project (HMP). The 'Jumpstart' phase of the Human Microbiome Project has been underway for almost a year and we are seeing significant progress. Of the 900 microbes to be sequenced during the entire five-year project, nearly 200 have been completed. An IRB-approved protocol for collecting human samples is now in place at the two sampling centers (Baylor College of Medicine and Washington University School of Medicine). An interim Data Analysis and Coordination Center (DACC) is in place and provides access to the HMP data generated, as well as to the protocols and consent forms being used. The Jumpstart centers are holding a face-to-face meeting later this week to discuss challenges and approaches. The Jumpstart phase is now two-thirds complete and preparations are being made for the launch of the full project. Applications have been received in response to RFAs calling for:

- The HMP Data Analysis and Coordination Center,
- Technology development,
- Computational tool development,
- Human microbiome-specific ELSI studies,
- HMP reference genome sequencing, and
- HMP demonstration projects.

Applications for the first four of these will be reviewed in the Closed Session of this meeting and awards will be made later this year. The reference genome sequencing and demonstration project applications will be reviewed at the February Council meeting and awards are anticipated to be made in Spring 2009. An International Human Microbiome Consortium, in which the NIH plays a very active part, has been organized to coordinate the microbiome efforts now underway or planned in several counties.

The Genotype-Tissue Expression (GTEx) Program. Despite the rapid progress achieved using genome-wide association studies (GWAS) to identify genetic changes associated with common human diseases, such as heart disease, cancer, diabetes, asthma, and stroke, a large majority of these genetic changes lies outside of the protein-coding regions of genes and often even outside of the genes themselves, making it difficult to discern which genes are affected and by what mechanism.

The Genotype-Tissue Expression (GTEx) Program is a newly approved NIH Roadmap program led by NHGRI, NIMH and NCI. It will conduct an initial two-year pilot project with the primary goal of testing the feasibility of collecting high-quality RNA and DNA from multiple tissues

from approximately 160 donors identified through low post-mortem interval autopsy or organ transplant settings. A small subset of tissues collected from living surgery patients will also be analyzed to compare to the autopsy-derived tissues. By analyzing global RNA expression within individual tissues and treating the expression levels of genes as quantitative traits, variations in gene expression that are highly correlated with genetic variation will be identified as expression quantitative trait loci, or eQTLs. If the pilot phase of GTEx proves successful, the project will be scaled up to involve approximately 1000 donors. Comprehensive identification of human eQTLs will highlight genes whose expression is affected by genetic variation, providing a valuable basis on which to study the mechanism of that gene regulation.

The GTEx project will also involve research into the ethical, legal, and social issues raised by the research, support for statistical methods development, and creation of a public database to house existing and GTEx-generated eQTL data. The database will allow users to view and download computed eQTL results and provide a controlled access system for de-identified individual-level genotype, expression, and clinical data. The associated tissue repository will also serve as a resource for many additional kinds of analyses.

Statistical Genetics. The National Institute of General Medical Sciences (NIGMS) and the NHGRI hosted a workshop on May 21, 2008 to address a concern of NIH Leadership Forum participants that there is not a sufficiently large cadre of scientists trained to develop methods and analyze the vast amount of data generated from population genomics studies employing current and rapidly emerging technologies. A small group of leaders in the fields of statistical genetics and genetic epidemiology (from both the extramural and the intramural communities) were convened to discuss the issues. The group was unanimous in the opinion that more individuals trained in these two areas are needed and that part of the problem stems from the fact that most US students have weak backgrounds in mathematics. Some of the action items for staff and invitees to address were: discuss ways to effectively "brand" this field, work with scientists in the field to develop core competencies, assess whether applications submitted to NIH receive objective peer review based on the competencies of the review panels, discuss ways for faculty in schools of public health and agriculture to become involved in human genetics/genomics studies, consider providing additional training opportunities in statistical genetics/genetic epidemiology by targeting pre-doctoral fellowships and supplements to train individuals in statistical genetics and genetic epidemiology, consider developing a post-baccalaureate program focused in this area, and encourage R01 support for research in statistical genetics/genetic epidemiology.

III. NHGRI – INTRAMURAL PROGRAM

Undiagnosed Diseases Program. The Undiagnosed Diseases Program (UDP) was launched on May 19, 2008 as a clinical research program of the NHGRI and the NIH Office of Rare Diseases. Under the direction of Dr. Bill Gahl, the program's two goals are to provide answers to patients with mysterious conditions that have long eluded diagnosis, and to advance medical knowledge about rare and common diseases.

The Clinical Center has established a dedicated information telephone line to handle inquiries about the program. Funding of $280,000 from the Office of Rare Diseases enabled initial

staffing of the program by two nurse practitioners. The medical review board of more than 30 specialists from 25 services of the Clinical Center meets monthly to review cases.

Since the announcement of the UDP, 700-750 inquires (among more than 1,200 calls to the information line) have been received regarding potential participation in the program and 250 sets of records have been reviewed. Five pediatric and one adult patient have been accepted. Six additional patients were accepted and referred to other Clinical Center services. Among those, a confirmation of a prior tentative diagnosis was made for one.

Each UDP patient visiting the NIH is to be evaluated by a multidisciplinary team custom-designed based on their presenting symptoms and the results of prior medical evaluations. Medical data collected during the UDP evaluation will be returned to the referring provider, regardless of whether a definitive diagnosis was achieved during the visit. In addition to the potential for diagnosis, participating patients may benefit from the elimination of possible diagnoses and additional ideas for treatment of ongoing medical problems. Data from the patient evaluations are to be used to as the basis for continuing research.

Intramural Site Visit. Last week, the Inherited Disease Research Branch underwent its quadrennial review and site visit. A group which included members if the NHGRI Board of Scientific Counselors BSC) will present the results of the review and recommendations to the NHGRI Director and the Scientific Director of the Institute.

IV. NHGRI OFFICE OF THE DIRECTOR

Population Genomics.
Genetic Association Information Network (GAIN) Analysis Workshop III. The third and final GAIN analysis workshop will be held in Philadelphia, PA, on November 10-11, 2008, immediately preceding the American Society for Human Genetics meetings. Abstracts based on GAIN data are currently being accepted from data users approved for access to GAIN data through dbGaP. The workshop is open to the scientific community (see http://www.fnih.org/index.php?option=com_content&task=view&id=407&Itemid=505). Several GAIN publications are submitted or in press, and others are expected to be submitted shortly.

PAGE. Awards supporting the program on Epidemiologic Investigation of Putative Causal Genetic Variants (RFA HG-07-014) were awarded in late July to four cohort study sites and one coordinating center.

NHGRI Catalog of Published Genome-Wide Association (GWA) Studies. The Office of Population Genomics has developed an interactive catalog and website (http://www.genome.gov/26525384) showing results from newly published GWAS attempting to assay 100,000 SNPs or more. As of 8/8/08, the catalog included 168 papers and 348 SNPs.

Consensus Measures for Phenotypes and Exposures (PhenX; https://www.phenx.org.). NHGRI awarded RTI International a three-year cooperative agreement to develop a toolkit of standardized measures for use in genome-wide association studies (GWAS) and related research to facilitate cross-study analysis in the future. The PhenX Steering Committee has selected

twenty research domains that will be the focus of the PhenX project. Expert working groups that comprise both NIH and non-NIH scientists have been convened for the demographics, anthropometric measures, and substance use research domains. Each working group has identified a set of commonly used, low burden measures that are important to include in GWAS and are currently vetting these measures with the relevant research communities.

Trans-NIH Communications Group on Genetics and Common Disease. The Trans-NIH Communications Committee on Genetic Testing for Common Disease was organized to develop an authoritative resource for the public, which is now receiving direct-to-consumer marketing for genomic scans from private companies such as 23andMe and Navigenics. Such testing is outside the traditional medical model, often leaving consumers to deal with complex results without much support.

The committee's principal responsibility is to develop a public information website on the NIH domain. Before construction of the site, however, the research subcommittee will conduct the following activities:

1. Focus groups and individual interviews to gather qualitative information from the public about what they know about genetic testing and what kind of information they would like to receive about their genetic information. NCI is providing in-kind services (through a contractor) to perform the studies; work will not begin until December because OMB approval is needed.
2. Literature review/environmental scan. The work will be performed by a contractor and overseen by the Technical Evaluation Panel. This project is expected to last eight months, once the contractor is in place.
3. The content development group of writers and editors has been working on developing basic content for the website. Pieces of content are being developed for the site, which will be tested later.
4. User-centered research on web site: This evaluation program will test the NIH.gov website providing this information to determine user-friendliness. This work will be conducted at the NCI OCE User-Centered Design Lab once funding is secured.

V. NHGRI – POLICY

Identifiability from Pooled Samples, and Changes to NIH Data Sharing Policies. On August 29, David Craig published a paper demonstrating that individual high-density genomic data could be used to identify an individual in a mixture of DNA. Dr. Craig and his group initially developed their method for forensic applications, but realized that the possibility for identification using public datasets was also an issue. Dr. Craig contacted staff at NHGRI prior to publication. When he confirmed replication of his method, dbGaP and other groups like Wellcome Trust pulled aggregate data from the open access website and moved it to controlled access. More details will be discussed following the Director's Report.

Appropriations Update. Congress adjourned for the August recess without completing the FY09 appropriations bills. Because there is not enough time to negotiate and pass all 12 of the appropriations bills, it is anticipated that the majority of the spending bills (and certainly the Labor/HHS/Education bill that funds the NIH) will be rolled into a large "continuing resolution" (CR) that would continue funding the government at the FY08 level ($486,779 million,

representing only a 0.1% increase from the FY07 level) at least until November and possibly until February or even later.

While Congress did pass a war supplemental appropriations bill for FY08 over the summer which provided $150 million for NIH, of which NHGRI received an additional $2.5 million, this was a one-time supplement and does not increase the NHGRI base budget ($486M).

Genetic Information Non-Discrimination Update. The Genetic Information Non-Discrimination Act (H.R. 493, S. 358) was signed into law on May 21, 2008. Regulations to implement the bill are currently being drafted by HHS, the Department of Labor, the Department of the Treasury, and the Equal Employment Opportunity Commission, and should be finalized by the statutory deadline of May 21, 2009. GINA's insurance provisions go into effect in May 2009, the employment provisions in November 2009. The law will provide important protection against the abuse of genetic information by health insurers and employers, with a broad definition of "genetic information" that includes genetic test results of an individual, those of their family members, and any information about family history of disease.

IDENTIFIABILITY OF INDIVIDUALS IN MIXED SAMPLES

On August 29, Drs. Craig and Homer published a paper, "Resolving Individuals Contributing Trace Amounts of DNA to Highly Complex Mixtures Using High-Density SNP Genotyping Microarrays" (*PLoS Genetics* 4:e1000167 (2008)) that described how summary level data, such as allele frequency, can be used to identify whether an individual's DNA is present in a complex mixture.

When Dr. Craig approached NHGRI staff with his manuscript, it was agreed that further investigation was warranted. Working with NCBI, Dr. Craig was given a dataset of allele frequencies from a mixture of 1,000 individuals. He was then given individual data for a subset of 100 of those individuals, and asked to identify whether they were in the mixture. Dr. Craig identified 38/38 in the mixture, 54/55 not in the mixture, and seven parents of individuals in the mixture. When his algorithm was re-run at NCBI, the results matched exactly; accordingly, NIH had all open access data moved to the controlled access side until more investigations could be completed.

Notifications were also made to other groups with relevant open access data, including the Wellcome Trust Case Control Consortium and NCI (CGEMS). Before moving its data to controlled access, CGEMS investigated whether any data could be left on the open access site, and attempted to define parameters for the release of group data. From their work, it is evident that since a SNP chip has about 250K SNPs, there is more than enough information available to resolve an individual in a mixture. More work is in progress.

The shifting of open access data to controlled access data includes only the summary level data files. Information on study description, etc, will remain on the open access site. Data that have been moved to controlled access will now need to be requested through relevant Data Access Committees.

GWAS policy was constructed to afford appropriate reaction to an event such as this. The Senior Oversight Committee was given the scientific authority to make decisions in the event of a data situation, and that committee made the decision in this case to move the open access data to controlled access. The committee has been meeting to discuss solutions and other approaches to the situation, and will continue to meet for more decisions on how to move forward. It hopes to finalize relevant decisions later this month.

There are also efforts to work with other groups in both the scientific community and industry. NHGRI has notified scientific journals and the investigators who have published GWA studies, trying to keep communication with the community open. Also, background documents have been created to keep the public educated about this situation, making it clear that even if a person is identified as having DNA in a mix, more work would have to be done to actually identify that person. It was noted that we also need to be prepared for the possibility that someone who has already accessed the open data could use it to further prove the identifiability issues. Several Council members expressed their endorsement of the controlled access procedures for all data types.

NHGRI RESPONSE TO THE ELSI ASSESSMENT PANEL (EAP) REPORT

At the May 2008 Council meeting, the ELSI Assessment Panel (EAP) presented its report on the NHGRI ELSI program. At this September Council meeting Dr. Guyer presented the staff response to the EAP recommendations.

The report stated that, overall, the establishment of the ELSI program was innovative and has been successful in promoting a great deal of thoughtful and interesting scholarship and in a number of other ways. At the same time, the EAP noted that there are a number of issues that have been around the program for some time, like lack of a clear definition of the role of the NHGRI ELSI effort and how the ELSI program should relate to other activities at NHGRI and NIH, and recognized that there are tensions surrounding the ideas of what ELSI should accomplish.

Dr. Guyer then summarized each of the specific recommendations and critiques and the NHGRI response:

1. To what extent is the ELSI program tied to principal components of DER? The panel supported a broad approach to the ELSI portfolio/mission but, at the same time, recommended that the ELSI program's role be well-defined. ELSI should better integrate with the overlapping efforts of NHGRI, OD, NIH and HHS. Within NHGRI, there is too little effective cooperation between DER, DIR and OD.

Response: To address the issue of improved cooperation, Laura Rodriguez has been designated as the OD point of contact for the DER ELSI program. She has been participating in DER staff meetings since the last Council meeting. Examples of efforts to increase communication were presented.

2. Is the ELSI research program is too broad or too focused? The EAP's answer is that it is both. On one hand, it is too broad and needs to do a better job of identifying priorities. On the other, it is too narrow in that it needs to include a wider set of scholarly methodologies common in social and behavioral sciences, not just bioethics. It also needs more sustained efforts to reach out to other institutes at NIH. The panel recommended that the program needs clearer leadership to foster a continuous and creative way to identify the best ways to mobilize the limited resources available to ELSI toward achieving the Institute's priorities.

Response: NHGRI has decided to establish a position of Director for the extramural ELSI program. The recruitment process for this position has been initiated.

3. To what extent should NHGRI set priorities and to what extent should they be set by investigator-initiated proposals? The panel suggested that senior NHGRI leadership and Council should set the priorities, with ELSI leadership having a significant role in the discussions. EAP recommended that NHGRI continue the current strategy of funding a diverse portfolio, while looking for new ways to ensure that NHGRI receives a sufficient number of grant applications. The current and projected FY2008 allocation for investigator-initiated research is too small.

Response: The institute's ELSI priorities will be a focus of the upcoming planning process. There are also two new approaches to notifying the community about areas of interest for the ELSI program as they arise. The first is that as each new RFA is developed, there will be a companion notice issued to discuss the perceived ELSI issues and research areas of relevance and to encourage interested investigators to contact ELSI staff and submit applications. The notice will be linked to the RFA and other appropriate ELSI grant solicitations in the Guide. In some cases a companion RFA may be appropriate instead of a notice. There will also be informational distributions on the NHGRI ELSI listserv.

The second approach is an internal process to identify emerging ELSI priorities. A staff working group, with broad membership across programmatic areas, will meet regularly to discuss emerging priorities and what is not being addressed. This group will also establish ways to communicate the issues to the community. A Council working group that the staff working group can interact with will be established.

4. What should be the relative roles of the CEERs within the overall ELSI portfolio? The EAP concluded that the CEER program should be capped at a proportion not to exceed the FY07 level (36% of the ELSI budget). NHGRI should be extremely rigorous in approving new CEER projects, and each CEER should only be eligible for one competitive renewal. More interactions among CEERs and between the CEERs and the community (for example, through a yearly conference) are needed, as well as a planning grant component.

Response: NHGRI staff accepted the recommendations for this point. Further details will be presented later in the Open Session with the concept clearance for the renewal of the CEERs program.

5. How should ELSI relate to other relevant NIH initiatives? The EAP recommended that NHGRI should look for ways to establish better on-going communications with the NIH OD and the SACGHS. Within NHGRI, there needs to be clarification of the ELSI research "policy portfolio" and more thorough integration with the policy issues of concern to the NGHRI OD.

Response: A request had been made to the NIH OD/OSP for quarterly meetings. The establishment of Laura Rodriguez as point of contact between DER and NHGRI OD is intended to establish better communications.

6. Are the ELSI staff and management functioning well? The EAP felt that there has been a breakdown of communication among ELSI extramural staff and senior NHGRI leadership.

Response: NHGRI will have quarterly meetings of ELSI program staff with DER Director, OD POC, and NHGRI Director.

7. What kind of advisory process is best for the ELSI program? The EAP concluded that there is currently no effective internal or external advisory process, and suggested the formation of a largely external advisory committee.

Response: Pending.

Dr. Guyer noted that the most important recommendation from the EAP was the need for improved management in the leadership and execution of the ELSI program. The ELSI leadership should consider alternative possibilities, welcome productive tensions, and make whatever creative adjustments are required to achieve ELSI's goals.

Council members expressed their satisfaction with the responses presented to the EAP report. They discussed the review process, and noted that they have seen that investigators who present studies that NHGRI stresses as priorities for the ELSI program are often not rated well in review. One Council member stated that perhaps there needs to be better communication between NHGRI and the review panel to establish the priorities of the ELSI program. However, the review process is organized so that there is a firewall between review and program. Central review is supposed to be focused on the technical scientific merit of proposals rather than program priority. Dr. Guyer suggested that summary statements should be clear on why an application scored the way it did, so that, if appropriate, issues can be addressed through the Council high priority process on an application that has been scored poorly. Council agreed, but suggested that a process of generating and clarifying ELSI priorities that can be built into the materials available for grant reviewers may also help diminish some concerns.

Council expressed satisfaction with the suggestion for parallel funding opportunities and notices that will help bring together clinical and basic scientists. There was also a suggestion to work more to bring ELSI and the Social and Behavioral Research branch of NHGRI's Division of Intramural Research closer together.

Council asked to what extent the ELSI program should be a trans-NIH strategy. NHGRI and ELSI staffs have been disappointed in the low level of enthusiasm for ELSI research in the other ICs. It was noted that the Trans-NIH Bioethics Committee was formed to assist with bringing the ICs together on ELSI-related issues.

PROJECT UPDATES:

Informed Consent Web Resource

NHGRI staff have developed a web-based resource to assist in the development of informed consent materials in the context of genomic research. The homepage includes an introduction to the project and a summary of elements within consent forms, including sample language, special considerations, and additional resources. Example consent forms have also been posted. NHGRI hopes that this will also become an important tool in forming best practices for consent form drafting. The resource is behind a firewall until it is ready to go "live." It will be available at www.genome.gov/policyethics.

Suggestions were made to clarify that the resource is meant as an aid to the development of research projects, rather than a policy document, and to simplify the reading level. Next steps will include the incorporation of comments, review by OHRP, and a workshop that might lead to best practices. Including international colleagues in the formation of the resource was suggested as a discussion topic for the workshop.

Molecular Libraries Probe Production Network

Molecular Libraries is a Roadmap project that was started in 2004 as a public-sector effort to use high-throughput screening as an approach to provide novel small molecule tools, termed probes, for biomedical research. It is expected that a subset of the probes developed will also be used as early-stage compounds in drug development, particularly in areas that are not commercially of interest to the pharmaceutical industry.

The Molecular Libraries program was designed as a two-phase effort: a three-year pilot designed to foster the development of screening centers and to gain experience in assay development, followed by a full-scale production phase. The project involves a number of components, including a repository, a public database, several routes to assay recruitment, screening centers, and chemistry capability. The Small Molecule Repository now contains over 300,000 compounds. Ten screening centers were supported during the pilot phase. The competition for the production phase was recently completed, with the

funding of four Comprehensive Screening Centers, two Specialized Screening Centers, and three Specialized Chemistry Centers.

The structure of the production phase Molecular Libraries Probe Production Network (MLPCN) was based on a number of lessons learned during the pilot. Probe development was refined to an 11-step system to take assays from implementation to chemical probe development. The average time from assay implementation to probe is about 18 months (six months to screen and 12 months to complete the chemistry), and only a third of the assays will produce a probe. Chemistry was a bottleneck during the pilot, and more resources were devoted to it in the production phase. There was a lot of input from the pharmaceutical sector in the development of this project over the pilot phase.

1000 Genomes

The goal of the 1000 Genomes Project is to provide a resource to support GWA studies comprised of a fraction of the variants in the genome sufficient to allow investigators to use the 1000 Genomes data instead of having to resequence their own samples. Three pilots are currently under way: a gene-region pilot with deep coverage in 1000 samples (this is just getting started with the implementation into production scale of newly developed methods for capturing specific regions of interest (e.g., the exome); a trio pilot with deep coverage of six individuals (two trios, one each from the Yoruba and CEPH samples); and a low coverage pilot that will cover 180 samples 2-4X.

The sequencing for the pilots is going very well, but is producing more data than can be analyzed at the same pace. The goal was to design the full project in November, but it is not clear that enough data will have been analyzed by then. The full project should be able to start in about one to two years.

Sequencing Program

The Sequencing Program held its biannual principal investigators meeting in New York City in July, combined with the annual interaction with the Sequencing Advisory Panel. A major topic of discussion was the progress of implementing the next-generation sequencing technologies in the centers and the development of reporting metrics. The first draft of the metrics was discussed, and NHGRI will begin to track production using the new technology in November.

Other important topics were developing ways to handle the large amounts of data being produced and how to best take advantage of the new technologies. The centers will prepare a statement of their vision for the program for discussion at the next principal investigators meeting (in December) and the sequencing planning meeting to be held in 2009.

ENCODE and modENCODE

The goal of the ENCODE and modENCODE projects is to compile a comprehensive encyclopedia of all the functional sequence features in the human genome (ENCODE) and in the genomes of *D. melanogaster* and *C. elegans (*modENCODE). Both projects are now in production phase. Many publications and collaborations have been generated.

Project management is extensive, including monthly conference calls, quarterly progress reports and annual review (and resetting, if necessary) of milestones. There is a panel of External Scientific Consultants (ESC) that is involved with both ENCODE and modENCODE. Both consortia are open to those who are not funded directly by the program, but who demonstrate some other source of funding. The consortium has a monthly conference call with all participants. There are also working groups, analysis working groups, and frequent progress meetings. The data release policy is being finalized. The group is currently discussing the implementation of next generation sequencing technology in expression and ChIP analyses.

Cancer Genomics Programs

The Cancer Genome Atlas is a partnership with NCI that arose out of a report in 2005 to the National Cancer Advisory Board. The goal of the program is to create a public catalog of all genomic alterations present at significant frequency for all major cancer types. The pilot phase began about two years ago, to investigate three cancer types. The TCGA Research Network recently completed an interim analysis on glioblastoma multiforme, which yielded many interesting results; the findings were published in *Nature*.

The Tumor Sequencing Project is a consortium of the three large-scale sequencing centers and several cancer groups to study lung adenocarcinoma. A manuscript from the project has been accepted for publication and will be available soon. Data for the manuscript were generated by PCR-targeted sequencing. The TSP is now actively trying to take advantage of new methods available for sequencing, and the TSP centers are currently benchmarking new methods against the old.

The International Cancer Genome Consortium has also been started. It includes ten countries, including the U.S., each of which will investigate at least one cancer. A major planning meeting is scheduled for this November in Bethesda.

1000 GENOMES ANALYSIS PLAN

The 1000 Genomes Project plans to provide support for certain analyses needed for the production of the 1000 Genomes datasets. To achieve an appropriate balance between fairness and competition for support on the one hand with the immediate need for starting the project, staff proposed to release both a limited-competition RFA and an open-competition RFA.

Council members expressed concern at the proposal of limited competition RFAs and the rapid speed proposed for this project (the pilot has been going since early 2008, and the

full project is aimed to start in early 2009). They noted that Program will need to prove that the resource needs to be provided immediately. Council also noted that it would probably have been beneficial to include analysis in the original RFA, since it is an important part of the project.

Council stated that while they are supportive of the idea that analysis is needed now for the project, the members were concerned that a limited competition proposal is problematic because it appears to allow only certain investigators to apply.

Discussion of this topic was continued to the discussion of the Concept Clearances for the 1000 Genomes Analysis RFAs (below).

CONCEPT CLEARANCE: 1000 Genomes Analysis

The 1000 Genomes Project was created to support genome-wide association studies by providing a resource of the genetic variants across the human genome with a frequency of 1% or higher, and of genetic variants with lower frequencies in gene regions. The pilot stage of the study has produced large amounts of data that need to be analyzed to determine how to structure the full project.

For the analyses of the 1000 Genomes data, Program staff proposes to release a limited competition RFA for the initial analysis of data collected in the project, with the focus on production topics like genomic coverage and data quality. It would be open only to the current 1000 Genomes participants. The reasoning behind a limited competition is that the timeline for this project is short, and a typical open competition RFA would take too long.

Council expressed concern about the use of limited competition, for fear of giving the impression that the competitive position of those who are already funded is being reinforced. Council noted that NHGRI needs to consider two things with a limited competition approach, the substance and the appearance. Council emphasized that it is important to avoid the appearance, especially with a research small community, of making deals.

It was proposed that, for the two objectives the analysis effort intends to address, the analysis needed to produce the 1000 Genomes resource and the analyses that make use of such a resource, RFAs be issued simultaneously – a limited competition RFA for the production analyses and an open competition RFA for the broader analyses. This would help the community understand the entire scope of the project goals. Council also recommended making it clear that funding from NHGRI for the production analysis component is not a requirement for participation in the 1000 Genomes Analysis Group, which should be as inclusive as possible, and then unanimously approved the proposal.

CONCEPT CLEARANCE: CEER Program Renewal

The Centers of Excellence in ELSI Research Program was initiated to encourage transdisciplinary research beyond the scope of that appropriate for R01 support, and has been in operation for about five years. The original four CEER grants are coming to the end of their initial funding period, and staff proposes to reissue the CEER RFA to allow them to apply for renewal as well as to allow others to submit new applications.

Council noted that the RFA concept reflects the EAP recommendations for the CEER program. Council unanimously supported the proposed RFA renewal.

CONCEPT CLEARANCE: Proteomics Database

UniProt is a centralized repository of curated protein sequences with high quality annotation of functional information, which is co-funded by NHGRI and NIGMS. The current award is coming to the end of its funding period and staff propose to issue an RFA to solicit applications for a new resource.

The proposal for a new database reflects staff's perceived need to refresh the project as well as increase the volume of the database. A workshop was held in July to engage the community, to understand their perspectives, to discuss how to keep the needed resources current, and to raise ideas on how to move forward. Some of the core needs identified for the database are scale, user accessibility, new data requirements, and community input and training. The workshop attendees also expressed the opinion that the database should contain sequence as well as functional information and high quality manual annotations, and should not duplicate what is currently being done by smaller databases. High throughput data will need to be handled carefully, and methods for addressing scalability of computational and manual curation are needed. It is important that the database be accessible for computer scientists and biologists.

Program staff requested approval of a concept for an open RFA soliciting applications for this resource. The funds available will be $5 million over three years, and the funding mechanism will be a U01 cooperative agreement. In the discussion, Council suggested the importance of making sure that the current balance of curation (SwissProt) and comprehensive (TrEMBL) is maintained. Noting that databases this large have the tendency, through their monopoly power, to dominate the field, Council suggested that one way to address this potential problem was to include a requirement for integrating new tools from the community, rather than providing support within the database award for the development of new tools. Council then unanimously approved this concept.

CONCEPT CLEARANCE: Community Consultation

A Community Consultation RFA was initially issued about three years ago to support a broad survey of community thinking about large cohort studies and other large-scale research studies. One award was made, as a cooperative agreement to ensure program staff involvement in the design of the study and the questions being asked.

The funded group would like to follow up immediately on several areas from the first consultation, including community views on return of results and consenting for broad research use of data. Program staff agrees that this is important to do and to do quickly, and therefore proposed issuing a limited competition RFA, for which only the current awardee would be eligible to ensure that the new effort returns comparable results to the initial results. Some Council members thought that a limited competition was appropriate in this case, but others were uncomfortable with the idea of a limited competition for reasons previously discussed. However, these members did agree that since the funds are available now and may not be available at a later date, this project should move forward quickly. Council suggested that the RFA be written to address a reduced scope of questions that specifically address areas of interest from the first consultation project. The Council then unanimously approved the concept for a limited RFA for focused research questions, but recommended that the community be informed, through a notice in the NIH Guide and/or a statement on the ELSI page of the NHGRI website that NHGRI would be interested in receiving investigator-initiated applications in this area. Council also noted more generally that NHGRI should consider developing community resources for the social and behavioral sciences.

COUNCIL-INITIATED DISCUSSION

Council requested that training in statistical genetics be discussed at the February Council session. Council also asked for a discussion of current NHGRI priorities, as this topic had not been discussed with Council for some time.

Dr. Guyer mentioned several other discussion topics. The presentation from Kathy Hudson, which was originally scheduled for this Council, could be rescheduled for February if Council is still interested. Also, presentations on sequencing informatics, MGC, KOMP, GTEx and eMERGE project updates were of interest to Council. .

ANNOUNCEMENTS AND ITEMS OF INTEREST

Dr. Guyer directed Council to the Council folders containing items of interest.

CONFLICT OF INTEREST

Dr. Guyer read the Conflict of Interest policy to Council and asked them to sign the forms provided.

REVIEW OF APPLICATIONS

In closed session, the Council reviewed 120 applications, requesting $41,577,932. The applications included 94 regular research grants, 14 ELSI grants, 1 research center grant, 1 career transition award, 1 individual training grant, 4 SBIR Phase I grants, 2 SBIR Phase II grants, 1 STTR phase II grant, and 2 mentored quantitative research grants. A total of 83 applications totaling $34,541,429 were recommended.

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

_____	_____
Date	Mark Guyer, Ph.D. Executive Secretary National Advisory Council for Human Genome Research
_____	_____
Date	Alan Guttmacher, M.D. Chairman National Advisory Council for Human Genome Research