NATIONAL ADVISORY COUNCIL FOR HUMAN GENOME RESEARCH
SUMMARY OF MEETING[1]
February 12, 2007

The open session of the National Advisory Council for Human Genome Research was convened for its forty-ninth meeting at 8:32 A.M. on February 12, 2007 at the Fishers Lane Conference Center, Rockville, MD. Francis Collins, Director of the National Human Genome Research Institute, called the meeting to order.

The meeting was open to the public from 8:32 A.M. until 12:00 P.M. on February 12, 2007. In accordance with the provisions of Public Law 92-463, the meeting was closed to the public from 12:00 P.M. on February 12, 2007 until adjournment for the review, discussion, and evaluation of grant applications.

Council members present:

Eric Boerwinkle, *ad hoc*
Andrew Clark
Marilyn Coors
Sean Eddy
Vanessa Gamble
Richard Gibbs, *ad hoc*
Mary Hendrix
Deirdre Meldrum
Jeffrey Murray
Stephen Prescott
Harold Shapiro
Paul Sternberg, *ad hoc*
Richard Weinshilboum, *ad hoc*
George Weinstock

Council members absent:
Geoffrey Duyk

Ex officio members absent:
Gerard Schellenberg

Staff from the National Human Genome Research Institute:

Solome Abebe, DER
Maggie Bartlett, OD
Catherine Bennet, DER

[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".

Saveri Bhattacharya, DER
Christianne Bird, DER
Vivien Bonazzi, DER
Joy Boyer, DER
Lisa Brooks, DER
Comfort Browne, DER
Brian Campbell, DER
Debbie Chen, DER
Cheryl Chick, DER
Monika Christman, DER
Francis Collins, OD
Chris Davis, OD
Karen DeLeon, OD
Gwendolyn Dudley, DER
Adam Felsenfeld, DER
Greg Feero, OD
Colin Fletcher, DER
Phyllis Frosst, OD
Barbara Fuller, OD
Peter Good, DER
Mary Glynn, OD
Bettie Graham, DER
Alan Guttmacher, OD
Mark Guyer, DER
Linda Hall, DER
Emily Harris, DER
Christopher Juenger, DER
Laura Liefer, DER
Carson Loomis, DER
Raymond MacDougall, OD
Teri Manolio, DER
Jean McEwen, DER
Keith McKenney, DER
James McWilliams, DER
Jessica Melone, DER
Ken Nakamura, DER
Kenneth Ow, OD
Brad Ozenberger, DER
Carmen Perera, OD
Jane Peterson, DER
Rudy Pozzatti, DER
Michael Rackover, OD
Ed Ramos, OD
Eddie Rivera, OD
Jerry Roberts, DER
Cristen Robinson, DER

Laura Rodriguez, OD
Anna Rossoshek, DER
Jeff Schloss, DER
Geoff Spencer, OD
Tanya Stevens, OD
Jeff Struewing, OD
Gary Temple, DER
Elizabeth Thomson, DER
Kris Wetterstrand, DER
Diane Williams-Bey, DER

Others present for all or a portion of the meeting:

Mary Affeldt, NIDA/NIH
Diane Baker, Genetic Alliance
Joann Boughman, American Society of Human Genetics
Deborah C. Dietz, Social & Scientific Systems, Inc.
Camilla Day, CSR
Mike Gilbreth, Social & Scientific Systems, Inc.
John M. Greene, SRA International
Susanne Haga, Duke University
Nancy Moy, SRI
Sharon Olsen, International Society of Nurses in Genetics
Angela Sharpe, Consortium of Social Sciences Association
Branka Sekis, Social & Scientific Systems, Inc.
Wendy Uhlmann, National Society of Genetic Counselors
Michael Watson, American College of Medical Genetics

INTRODUCTION OF NEW MEMBERS AND STAFF, LIAISONS AND GUESTS

Dr. Guyer introduced four *ad hoc* council members: Eric Boerwinkle from The University of Texas Health Science Center at Houston, Richard Gibbs from the Baylor College of Medicine, Paul Sternberg from the California Institute of Technology, and Richard Weinshilboum from the Mayo Clinic.

Dr. Guyer introduced new NHGRI staff: Ms. Debbie Chen from the Grants Management Office and Dr. W. Greg Feero, Senior Advisor to the Director, NHGRI, for Genomic Medicine.

Dr. Guyer welcomed liaisons from professional societies: Joann Boughman from the American Society of Human Genetics, Diane Baker from the Genetic Alliance, Wendy Uhlmann from the National Society of Genetic Counselors, Sharon Olsen from the International Society of Nurses in Genetics and Michael Watson from the American College of Medical Genetics

Dr. Guyer welcomed other visitors: Deborah Dietz and Branka Sekis from Social & Scientific Systems, Inc, Susanne Haga from Duke University, Angela Sharp from Consortium of Social Sciences Association.

APPROVAL OF MINUTES

The minutes from the September 2006 Council meeting were approved as submitted.

FUTURE MEETING DATES

The following dates were proposed for future meetings: May 21-22, 2007, September 10-11, 2007, February 11-12, 2008, May 19-20, 2008, September 8-9, 2008, and February 9-10, 2009.

DIRECTOR'S REPORT

I. GENERAL ANNOUNCEMENTS

Ten years ago on January 14, 1997, then Secretary of Department of Health and Human Services, Donna E. Shalala, signed the documents that created the National Human Genome Research Institute (NHGRI, formerly the National Center for Human Genome Research, NCHGR) as the 19th institute of the National Institutes of Health (NIH). Each Council member received a pin commemorating this event. More recently, the NIH Reform Act, in which the NHGRI was legislatively authorized, was enacted and signed into law by the President on January 15, 2007.

On September 19th, 2006, David A. Relman, M.D., was awarded a 2006 National Institutes of Health Director's Pioneer Award.

Princeton University President Shirley M. Tilghman, Ph.D., has been awarded the Genetics Society of America Medal. A member of the National Research Council's committee that set the blueprint for the U.S. effort in the Human Genome Project, Dr. Tilghman also was one of the charter members of the National Advisory Council for Human Genome Research.

Ellen Wright Clayton, Alta Charo, Raynard Kington and Paul Sieving were elected to the Institute of Medicine of the National Academies.

Dr. Joan Bailey-Wilson, co-chief of the Inherited Disease Research Branch, NHGRI, recently received the 2006 Leadership Award conferred by the International Genetic Epidemiology Society (IGES). The award recognizes her research, teaching and service and was presented at the 15th annual IGES meeting in Tampa Bay. Dr. Bailey-Wilson was also named President-Elect of IGES for 2007.

Dr. Elias Zerhouni has announced the appointment of Alan M. Krensky, M.D., as the first NIH Deputy Director for Portfolio Analysis and Strategic Initiatives. In this position, Dr.

Krensky will be the Director of the Division of Program Coordination, Planning and Strategic Initiatives (DPCPSI) in the Office of the Director, NIH. This appointment will be effective July 8, 2007.

II. NEW NHGRI INITIATIVES

Two Requests for Applications (RFAs) for the ENCODE project have been issued. RFA-HG-07-030, "Creating the Encyclopedia of DNA Elements (ENCODE) in the Human Genome," solicits applications for projects to scale up the ENCODE analysis to the entire human genome. RFA-HG-07-031, "A Data Coordination Center for the Encyclopedia of DNA Elements (ENCODE) Project," addresses the need for centralized tracking and collection of project data. Letters of intent for both RFAs are due February 27, 2007 and applications are due March 29, 2007.

Another new RFA is a training announcement that is jointly being issued with NIEHS. RFA-ES-07-002, "Human Genes and the Environment Research Training Program," focuses on encouraging training of individuals in both the environmental sciences and genetics. The application receipt date is June 29, 2007.

III. EXTRAMURAL PROGRAM

Large-Scale Sequencing: Council was provided with a summary of the sequencing status of all organisms whose sequencing is funded by the NHGRI and has been previously approved by Council. Council was also provided with a press release announcing the new sequencing targets that were approved during the September 2006 Council meeting. The projects include full shotgun coverage of the skate, coelacanth, spotted gar, painted turtle, hagfish genomes; full coverage of the genomes of eleven species of strongylid nematodes; full coverage of the genome of one species and 2-fold coverage of three species of cichlid fish; and refinement of the cow, opossum, rat, marmoset, and macaque Y chromosomes.

The Honey Bee Genome Consortium, led by George Weinstock of the Baylor Sequencing Center published an analysis of the full coverage draft sequence of the 260 Mb honey bee genome in *Nature*.

The genome of a male California purple sea urchin was sequenced and analyzed by the Sea Urchin Genome Sequencing Project Consortium, also led by the Human Genome Sequencing Center at Baylor College of Medicine. That work was published in *Science*.

In addition, the Broad Institute announced the completion of the horse sequencing effort. The genome of Twilight, a horse from Cornell University School of Veterinary Medicine, has been sequenced to 6.8-fold coverage.

In November, NHGRI announced the latest round of awards for the Large-scale Sequencing center grants. The awards were made to the Broad Institute, the Washington

University at St. Louis Genome Sequencing Center, the Baylor College of Medicine Human Genome Sequencing Center, and the NIH Intramural Sequencing Center (NISC).

The annual NHGRI Research Network for Large-scale Sequencing and the NHGRI Sequencing Advisory Panel meeting occurred in Cambridge, MA on January 9th and 10th, 2007. The meeting was hosted by the Broad Institute. Much of the discussion at this meeting addressed new sequencing technologies.

Sequencing Technology Development: On October 4th, 2006, NHGRI announced the latest round of grant awards, totaling more than $13 million, for additional or renewed research projects to develop innovative sequencing technologies that would reduce the cost of DNA sequencing and lead to the expanded use of sequence analysis in medical research and health care. Awards were made to nine investigators developing revolutionary technologies that may make it feasible to sequence a genome for $1000, plus two investigators who are developing "near term" technologies to sequence a genome for $100,000. A meeting of the laboratories funded through this program was held in Florida on February 5-7, immediately before the Advances in Genome Biology and Technology Meeting at Marco Island.

Medical Sequencing: NHGRI policies for the Medical Sequencing Program are now available on the NHGRI website. Considering the unprecedented scope of genomic information to be obtained in these projects, it has been paramount in the development of policies to ensure protection of participant privacy and address issues of informed consent. A web-based data access request system for the Medical Sequencing Program was implemented recently. NHGRI staff have coordinated the development of data access procedures with NIH staff administering other projects producing large-scale genomic/genetic datasets (e.g. GAIN, TCGA). Policies, documents, and processes will be as consistent as possible across these projects. Adam Felsenfeld has spent a considerable amount of time looking into this, and the Council was provided with a document that describes the discussions and conclusions. The goals of the policy development process were to both advance research and protect study participants.

Public Consultation on a Large-Scale Cohort Study: Based on the outcome of peer review, NHGRI has funded the Genetics and Public Policy Center, headed by Kathy Hudson, to conduct a two-year pilot public consultation study to assess public attitudes about the possibility of a large-scale longitudinal cohort study to analyze the role of genetic and environmental factors in health and disease. The consultation activities will include focus groups, interviews, a large national survey, and town hall meetings in five American cities. A Citizen's Advisory Panel that has been set up for the project held its first meeting on January 8th. There has been a vigorous debate about the possibilities of using existing cohorts or developing a new one for such a large population-based study; Council was provided with copies of correspondence in *Nature* discussing the pros and cons of a large-scale national cohort of incident cases of common diseases. At the moment, further activity is waiting for, among other things, the results of the survey of public attitudes before further attempts are made to raise funds for this expensive project.

ENCODE: The ENCODE Consortium has submitted a manuscript that reports the generation and analysis of datasets produced in the ENCODE Pilot Project. The manuscript contains integrative analyses carried out by members of the five ENCODE analysis groups. The manuscript is under review.

As noted earlier, two RFAs for the scale up of the ENCODE program have been released. Applications submitted in response to the modENCODE RFA will be considered in the closed Council session. The modENCODE program is intended to identify functional elements in the *C. elegans* and/or *D. melanogaster* genomes.

KOMP: As reported at the last Council meeting, awards to support the Knock-Out Mouse Project mutant production, data coordination center (DCC) and ES cell development were issued during the first week of September 2006. There are regular interactions among the groups. The production teams are making good progress with well over 300 targeting vectors constructed, a number of which are now being electroporated into ES cells. We are tracking progress closely to ensure that milestones are achieved. A problem arose recently concerning the identification of the strain to use in KOMP. The goal is to make mutants in the C57BL/6 strain, but problems with the existing J substrains have been discovered, and the project will likely switch to the N substrain.

MGC: The Mammalian Gene Collection (MGC) has reached 83% coverage with fully validated clones representing 28,000 human and mouse genes. Although this is a large majority of the genes being targeted by the programs, it is expected that clones for approximately 2500 defined human and mouse genes will fail to be obtained by the current approaches.

To address the remaining human and mouse genes, an RFP for the *de novo* synthesis of these clones was issued. It requested a throughput capacity of at least 450 RefSeq sequences per month over approximately 6 months. Each coding sequence is to be synthesized in two versions, one with and one without a stop codon. The clones will be prepared in the same expression-convenient Gateway vectors used by MGC in its pilot gene synthesis study, which completed in early 2006.

As a result of the peer review of the proposals received, a contract with GeneArt was signed in December. The first 1200 RefSeq sequences have been assigned and their synthesis is underway. Completion of synthesis of all ~2500 RefSeq sequences is anticipated by July 2007.

CEERs: The Centers of Excellence in ELSI Research are holding their third annual investigators meeting on February 22-23. A one-day workshop organized by the University of North Carolina will take place before the meeting to address training for the next generation of ELSI researchers. This Spring, the existing P50 Centers will be undergoing their required third-year site visits to determine if they will be invited to submit a competing continuation application and if full funding will be awarded for years four and five. Ellen Clayton will serve as the chair of this review.

Minority Action Plan: The Minority Action Plan training program coordinators meeting on February 16 brought together the coordinators of all of the training programs participating in the MAP to discuss ways to identify 'best practices'. Vanessa Gamble commented on how impressed she was by the coordinators' commitment to the program.

The Cancer Genome Atlas: The TCGA project, which will apply the tools of genomics for the comprehensive characterization of the genomes of individual tumor types, has begun. A kickoff meeting was held in December 2006; PIs and additional staff from the sequencing centers, the Cancer Genome Characterization Centers, the Biorepository and the informatics groups participated in the meeting. Samples of the first tumor to be analyzed, glioblastoma multiforme (GBM), are currently being characterized prior to the generation of the DNA and RNA samples. In addition to GBM, the TCGA pilot will analyze squamous carcinoma of the lung, and cystadenocarcinoma of the ovary.

An NHGRI-supported effort known as the Tumor Sequencing Program (TSP), which can be thought of as a prelude to TCGA, has been on-going for about a year and has made a number of interesting observations about the genomics of adenocarcinoma of the lung. Publication of the initial results of TSP is expected in the next couple of months. From the TSP results, it is clear that the use of genomic approaches to study cancer is going to put a new light on the disease. A copy of an article from Scientific American about the TCGA by Anna Barker and Francis Collins was provided to the Council.

The Molecular Libraries Initiative: This Roadmap program is jointly led by the NIMH and NHGRI for the NIH. As part of the continuation process, a Mid-Course review in December 2006 assessed the project's accomplishments during its initial phase. The expert external review committee was very enthusiastic about the program and its accomplishments to date, and also had a number of constructive suggestions about how to make improvements. The results of the review will be presented to the Roadmap Implementation Coordinating Committee as part of the package it will consider for the transition of the program from its Pilot Phase to a Formal Phase in 2008.

IV. INTRAMURAL PROGRAM

On October 11th, researchers from 12 institutions, including the NHGRI, announced the results of the first genome-wide linkage study of prostate cancer in African-Americans. Using genetic markers, researchers identified several regions of the human genome that likely contain genes that, when altered, increase the risk of developing prostate cancer.

Eric Green will present a DIR update in the Open Session of the May 2007 Council meeting.

V. OFFICE OF THE DIRECTOR

As described at the September 2006 Council meeting, a trans-NIH policy development process for genome-wide association studies (GWAS) is being developed under the leadership of NHLBI Director, Dr. Elizabeth Nabel. NIH released a draft policy proposal

for public comment at the end of August 2006. The proposed policy focused on data sharing practices for GWAS and the critical questions around human participant protection that are integral to these datasets. The ultimate goal of the policy is to ensure that the important opportunities that the GWAS approach will bring to biomedical research are available in a way that maximizes public benefit. During the public comment period, the NIH received nearly 200 comments. These included discussion of the technical issues (both scientific and information technology-related), of concerns related to bioethics and participant protection, such as the potential ramifications for individual privacy, and of issues related to intellectual property interests, and of issues around the professional credit for the scientists conducting the studies and subsequent analyses.

In addition to the open call for public comments, Dr. Nabel, along several other senior NIH leaders including Dr. Collins, hosted a Town Hall Meeting in December 2006 to provide an opportunity for additional stakeholders to discuss the proposed policy with the NIH. Over 250 individuals participated in this event in person and through the internet. In consideration of all this public input, the policy is now undergoing final development and review within the NIH, with a goal of finalizing and releasing the policy by March 2007, in time for applications coming in to the June 1st grants submission cycle.

On October 3-4, 2006, the NHGRI sponsored a workshop on Privacy, Confidentiality and Identifiability in Genomic Research. The workshop was led by NHGRI Consultant in Health Research Policy, Bill Lowrance. The conclusions from the workshop are summarized on the NHGRI website, and a report is being prepared for publication.

Since the Surgeon General's Family Health Initiative began in November 2004, more than one million users have accessed the Web-based version or downloaded copies of the "My Family Health Portrait" tool from the Department of Health and Human Services Web site. On November 15th NHGRI named two new Family History demonstration projects. Each of the one-year projects will receive $100,000 to develop community-based models to increase awareness among the public and health care professionals about the value of family history information in promoting health and preventing disease. In the first, a multi-institution team will work with the urban Appalachian populations now living in the greater Cincinnati metropolitan area. A major goal of this project is to develop ways of educating people with low levels of literacy about the importance of family health history. The second project will be led by the Southcentral Foundation, an Alaska Native health care organization located in Anchorage. The primary goal of this effort will be to develop tools and methods for creating a common understanding about the role and importance of family health history among Southcentral Foundation's staff.

The University of Michigan will host the 3rd annual Community Genetics Forum in 2007.

This year, the DNA Day Ambassadors program will send 60 ambassadors to schools in the Southeast, including Georgia, Florida, South Carolina and North Carolina, as well as the DC Metro area.

On March 29-30 NHGRI will host a meeting with key leaders from the four U.S.-based Physician Assistant organizations; the meeting is entitled "Physician Assistant Competencies for Genomic Medicine: Where We Are Today and How to Prepare for the Future." This one-and-a-half day meeting will focus on developing an outline for how physician assistants can utilize current and anticipated genetics and genomics tools and approaches as the basis for making personalized medicine a regular part of patient care.

The translation of genetic/genomics to clinical care has major implications for the 2.9 million registered nurses. In general, these health care professionals have had little preparation in genetics. To prepare the nursing workforce to deliver genetic/genomic competent healthcare, a monograph describing essential competencies has been published. Forty-seven professional nursing organizations have endorsed the document, *Essential Nursing Competencies and Curricula Guidelines for Genetics and Genomics* (available at http://www.genome.gov/17517037). Jean Jenkins of NHGRI has been involved in this effort.

VI. POLICY

Jim Greenwood, President and CEO of BIO, former Congressman from Pennsylvania, and former Chairman of the Subcommittee on Oversight and Investigations, visited the NIH on January 11th. Mr. Greenwood toured the NIH Vaccine Research Center and the Collins laboratory, and also met with NIH Director Elias Zerhouni and David Lipman, Director of the NCBI.

Senator Ted Kennedy (D-MA), chair of the Senate, Education, Labor and Pensions Committee, visited the NIH Clinical Center on Thursday December 14th. The Senator heard several scientific presentations, including one from Dr. Chris Austin entitled "A Multi-Agency Collaboration Applying High-Throughput Chemical Screening to Environmental Toxicology". Other participants included Drs. Collins, Zerhouni, Nabel, Alexander, Fauci, Niederhuber, Gottesman and Green.

President Bush visited the NIH on January 17th to participate in a roundtable on advances in cancer prevention with Secretary Leavitt, Drs. Zerhouni, Niederhuber and Collins, as well as two cancer advocates. In his remarks, President Bush urged Congress to pass legislation to protect Americans from having their genetic information about cancer and other diseases used against them in health insurance or employment.

The 109th Congress adjourned without passing the Genetic Nondiscrimination Information Act, H.R. 1227, in spite of the fact that it was co-sponsored by 244 members of the House. On January 16th, the bill was reintroduced into the 110th Congress by Congresswoman Louise Slaughter, along with 143 original co-sponsors. It is H.R. 493, the Genetic Nondiscrimination Information Act of 2007. On January 22, 2007, Senator Olympia Snowe introduced S. 358, the Genetic Information Nondiscrimination Act of 2007, with 22 original co-sponsors. This year, for the first time, there is significant momentum in both the House and Senate to move the bill quickly. On several occasions, most recently at the NIH as noted above, the President has also conveyed his willingness

to sign the bill into law. A lot of the credit for current progress goes to the Coalition for Genetic Fairness.

The FY2007 budget is in the process of being finalized as a year-long continuing resolution (officially referred to this year as a Joint Resolution). As a result of efforts made to ensure that medical research got some extra attention, the NIH received an additional $620 million. This money is intended to allow funding of additional 500 research grants, to create a new $40 million program to support innovative research, and to provide $91 million for grants to first-time investigators. The resolution also includes $69 million for the National Children's Study, which will be funded through the NIH Office of the Director.

The NHGRI FY2008 budget request will include increases for the medical sequencing and translational genomics programs, and compensating decreases for the rest of the large-scale sequencing and genomic function programs. Appropriations hearings for the FY 2008 budget will be held in early March.

A Council member asked about the percentage of funds that will go to intramural and extramural. Dr. Collins noted that the proportionalities will stay about the same across NIH as they have been for several years: approximately 85% will go to the extramural program and 10% will go to the intramural program, with the rest for administrative support.

On January 15th, the President signed the NIH Reauthorization Act, following unanimous support by the Congress. This action affirms the importance of NIH and its vital role in advancing biomedical research to improve the health of the Nation. The legislation authorizes a new process to facilitate trans-NIH research with the establishment of the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) in the NIH Office of the Director. The DPCPSI will develop processes to distribute resources from the Common Fund, which was also authorized in the law. A Council of Councils will advise the DPCPSI.

In addition, the NIH Reauthorization Act establishes the Scientific Management Review Board (SMRB) to conduct periodic organizational reviews of NIH, and make recommendations on the use of NIH organizational authorities. This act authorizes, but does not appropriate, an increase in NIH funding for each of the next 3 years. It requires a public process for reorganizing NIH programs and many of the reporting requirements are eliminated or subsumed in a new biennial report.

An a*d hoc* Working Group will chaired by Raynard S. Kington, M.D., Ph.D., NIH Deputy Director to implement this legislation. The Working Group membership includes IC Directors and senior leaders in legislation, policy, management, communications, extramural and intramural activities, budget, and the Office of the General Counsel. The charge to the Working Group is to complete a careful, detailed analysis of the legislation and propose plans for its implementation that will aid NIH in serving the public and our scientific community more effectively.

REPORT FROM THE NIH OFFICE OF PORTFOLIO ANALYSIS AND STRATEGIC INITIATIVES (OPASI)

Dr. Collins introduced Dr. Alan M. Krensky, who has been appointed to be the NIH Deputy Director for the Office of Portfolio Analysis and Strategic Initiatives (OPASI). At the Stanford University School of Medicine, Dr. Krensky most recently served as Professor of Pediatrics, Chief of the Division of Immunology and Transplantation Biology, Associate Chair for Research in the Department of Pediatrics, and Associate Dean for Children's Health. Dr. Krensky brings to his new position a great deal of experience in organizing research, as well as being a leading investigator in the field. His role as the NIH Deputy Director of OPASI will help facilitate interactions across the NIH. Institutional planning and assessment is critical as the interdisciplinary nature of biomedical science evolves. Dr. Collins welcomed Dr. Krensky to NHGRI and NIH and expressed his delight in Dr. Krensky's appointment.

Dr. Krensky began with an explanation of the organization of OPASI. There are three divisions. The first is the Division of Resource Development and Analysis (DRDA), which is responsible for analyzing and coding systems for research grants in terms of the disease(s) being studied. NIH is responsible for both regular reporting to Congress on the amount of funding being spent on a large number of diseases and other categories of biomedical research, and for responding to individual requests for that type of information. One of the goals will be to develop ways to take information about burden of disease as an economic indicator into account in developing research priorities. There has never been a single computerized system for disease coding at the NIH, and the DRDA will now be responsible for establishing one with the goal of consistency in coding and reporting all of NIH research in terms of disease.

The second is the Division of Strategic Coordination (DSC), which conducts the Roadmap and other trans-NIH initiatives. Dr. Krensky will act as a facilitator to try to develop more trans-NIH initiatives. The third branch, the Division of Evaluation and Systematic Assessments (DESA), coordinates the formal government evaluation programs, such as GPRA and PART.

Dr. Krensky then discussed the development of a new set of Roadmap initiatives, known as Roadmap 1.5. In developing Roadmap 1.5, the NIH sought advice from the scientific community in several ways. A series of meetings was held last summer with more than a hundred scientists. Staff from each institute was also asked for suggestions. The ideas that came from these two efforts were then put up on the web for community comment and broad solicitation of other suggestions. These three approaches led to the identification of more than three hundred and forty ideas. The Institute and Center Directors then met in January and decided to pursue the most appropriate five ideas as Major Roadmap 1.5 Initiative Proposals; these were the Human Microbiome Project, Common Mechanisms of Inflammation (Immunology), Proteome (new technologies to

look at various aspects of proteomics), Phenome, and Epigenetics. After each of these is developed further, the IC Directors will meet in May 2007 to make a final decision about which one(s) to implement. At the January meeting, the IC Directors also recognized two other concepts that were highlighted through the idea nomination process (the Connectivity Map and Transient Molecular Complexes). These were considered to be potentially important, but not appropriate at this time for selection as major Roadmap Initiatives. These were designated for consideration to develop through smaller pilot studies. Three other areas of research not considered for development as Major Roadmap Initiatives were highlighted as areas where additional information about the current research portfolio and efforts to coordinate activities across NIH were needed; these were bioinformatics, regenerative medicine, and pharmacogenetics. Finally, the IC Directors identified Health Disparities, Training, and the Science of Science Administration as Roadmap Strategic Planning Activities in which broad strategic thinking and planning were necessary to fully address the needs expressed by the community.

For Roadmap 1.5, there will be $30M available for FY2008 and an additional $50M in FY2009. Both Dr. Krensky and Dr. Collins emphasized that the objective of the Roadmap is to create venture space for developing new, transformational approaches for biomedical research. None of the Roadmap programs will last more than ten years (five plus five at the most) in the incubator space, on the assumption that that will be enough time for an area to be developed to the point at which it can be supported through IC funds.

Council member Andy Clark asked about the role of model organism studies in Roadmap 1.5. Dr. Krensky replied that the emphasis will be on human studies.

The Council was enthusiastic about the ideas presented by Dr. Krensky and thanked him for his presentation.

CONCEPT CLEARANCE - INFORMATICS FOR THE ANALYSIS OF ENCODE DATA

Peter Good presented a proposal for concept clearance to solicit applications to establish a Data Analysis Center for the ENCODE Project. A January 2006 meeting with the ENCODE Scientific Advisory Panel had made specific recommendations regarding data handling and analysis for the ENCODE Project, which the advisors thought should include strong local groups at the production centers, a centralized data coordination center, and a separate data analysis component. The first and second recommendations were addressed in concepts approved by Council in May 2006. The third is addressed in this Concept Clearance that proposes implementation of a Data Analysis Center (DAC) that would coordinate the analysis of the ENCODE Project data. The DAC would provide an informatics resource to facilitate the integrative analysis of the data from the multiple platforms that will be used to generate data for different functional elements in the ENCODE Project. The DAC would help coordinate the integrative analysis of the ENCODE Project data in ways that would enhance the value of each individual dataset

and ensure that the ENCODE Project produces an essential annotation resource for the scientific community. The DAC would be supported through the U01 Cooperative Agreement mechanism at a level of $1.0 million per year in total costs for three years.

Sean Eddy asked about an alternative of funding this program with two or three R01 grants, as he was concerned about the possibility of a "silo" effect when only one group is involved. Dr. Good responded that one of the problems encountered during the pilot project was that the analysis subgroups often worked in isolation from each other and that the proposal was intended to promote a more integrative approach to the analyses. Andy Clark commented that a single DAC would give more confidence in the data and analysis of validation of data.

The Council voted to approve this concept.

CONCEPT CLEARANCE – LINKAGE OF GENOME-WIDE ASSOCIATION DATA TO ELECTRONIC MEDICAL RECORDS IN EXISTING BIOREPOSITORIES

Teri Manolio presented a proposal for concept clearance to support investigative groups affiliated with existing biorepositories to develop methods and procedures for, and then to perform, genome-wide studies in participants with phenotypes and exposures defined by electronic medical records (EMR). The goal of this proposal is to develop and apply approaches for using U.S. biorepositories with EMR systems for large-scale genomic research including, but not limited to, genome-wide association (GWA), sequencing and structural variation. The goal of a collaborative biorepository program would be to share expertise and experience, and to raise general standards for genomic research across biorepositories. Investigative groups would be supported to develop methods and procedures and then, using what had been developed, to perform large-scale high-throughput genomic studies. Each applicant would propose a GWA study of 1,000-1,500 cases and suitable controls. Other technologies might also be proposed, as might joint studies with 300-500 cases coming from each repository. A steering committee would be responsible for the development of criteria to be met before genome-wide studies and data sharing proceed.

The concept proposed that this venture would be funded for $25 million over a four-year period to support 3-5 biorepository-based efforts, an Administrative Coordinating Center and genomic laboratories, and to use the U01 Cooperative Agreement mechanism.

The Council was enthusiastic about this concept and had several comments. Mary Hendrix noted that her institution is attempting to address the problem of platform interoperability and had hired an IBM group to work on it; she recommended that an "IBM type" of person be included on the Steering Committee to provide a global perspective of coordination on multiple platforms. Eric Boerwinkle commented that a clear definition of an electronic medical record is needed. Dr. Manolio noted that the intended targets are clinical care electronic records. Harold Shapiro asked if this was for existing medical records, or ongoing records. Dr. Manolio noted that the current thinking

is that the records would be frozen and de-identified, but that this would be a good issue for the Steering Committee to consider. Jeff Murray noted that the ELSI program could also provide guidance in this. He also noted that prisoners and the poor would benefit a lot from electronic medical records.

The Council voted to approve this concept.

CONCEPT CLEARANCE – HIGH-PRIORITY PHENOTYPE AND EXPOSURE MEASURES FOR CROSS-STUDY ANALYSIS AND GENOME-WIDE ASSOCIATION STUDIES

Teri Manolio presented a proposal for concept clearance to support the identification, development, and dissemination of readily standardized and implemented phenotypic and environmental exposure measures suitable for addition to ongoing genome-wide association (GWA) studies. The goal of this concept is to increase the value obtained from costly GWA genotyping performed for investigation of specific diseases or traits by facilitating collection of selected additional standardized phenotypic and exposure measures. There is a great deal of potential for obtaining additional information from GWA studies that are carried out characterize the vast majority of inter-individual variation across the genome with respect to a specific disease or trait. Very few current GWA studies include phenotype and exposure data on a wide variety of traits. Even if studies do attempt to compare the same risk factors, the potential for cross-study comparisons and replication are restricted by the lack of comparability of the measurements made in different studies. Often, even basic measures (age, sex, self-reported race/ethnicity) are defined differently.

The aim of this proposed effort would be to select a small subset of phenotypic/exposure measures that are easily standardized and implemented. A single awardee would be selected to consult with ongoing bioinformatic efforts, review the current literature, survey expert opinion, and convene appropriate working groups to define 15-20 high priority phenotypic and exposure domains for GWA studies. For each domain, 10-15 high priority measures for GWA studies would be identified using the consultation, survey, and working group processes. It is estimated that this could be done for a single domain for about $400,000, so over a three-year period, approximately $8.5 million would be needed to support the proposed effort, with roughly 20% of the money spent in year one and 40% spent in each of years two and three. This effort would be funded by a cooperative agreement (U01) mechanism. NHGRI will also attempt to encourage the participation of other NIH ICs and could consider co-funding in the determination of the priority of domains of interest to these other ICs.

Eric Boerwinkle asked about the analysis of stored specimens from existing studies and Dr. Collins commented that it would be good to have a standardized set of measures that would be recommended for those stored specimens.

The Council voted to approve this concept.

SCIENTIFIC PRESENTATION: NEW SEQUENCING TECHNOLOGIES

George Weinstock, a Council member and the co-director of the Human Genome Sequencing Center at the Baylor College of Medicine (BCM-HGSC) gave a presentation on new sequencing technologies. The previous week, a group from the sequencing centers had met at Marco Island, Florida, to discuss new sequencing technologies. This topic was also addressed at the NHGRI Large-scale Sequencing Research Network meeting held at the Broad Institute in early January. Potential applications of the new technologies include whole genome shotgun sequencing, expression profiling, cDNA sequencing, amplicon sequencing, paired end genome structure mapping and other mapping. Solexa and 454 are both marketing instruments currently. Instruments from Applied Biosystems and Helicos are expected to be on the market soon. In support of yet further advances in sequencing technology, there are currently thirty grants in the NHGRI Sequencing Technology grant portfolio.

Two projects to sequence multiple human individuals were announced at the AGBT conference in Marco Island. 454 Life Sciences will sequence the genome of James Watson at 3-fold coverage. Solexa will sequence a Yoruba HapMap individual to 3-fold coverage. These two projects are expected to be completed in the next couple of months. There are also media reports that sequence reads are being removed from the Celera assembly and additional sequence information is being obtained to fill in the sequence of another person, Craig Venter.

A first generation 454 Life Sciences instrument, the GS20, produces 100 base reads with 200,000 – 600,000 reads per run; the total output is somewhat less than 60 Mb per run. The FLX is a second generation instrument that produces 250 base reads with 400,000 reads per run, generating 100 Mb per run. The data from the FLX are more accurate than the data from the GS20 (Q25 raw, aligned~10^{-4}). Both machines cost approximately 12 cents per kb, or $7000 per run for the GS20 and approximately $12,000 per run for the FLX). Sanger sequencing costs are currently 40-50 cents per kb, so the 454 instrument allows a significant decrease in sequencing cost. Projected 454 technology developments to upgrade the instrument project 500 base read lengths, higher sample density, and 10X increased throughput (1 Gb per run). The current cost for human shotgun sequencing is $360,000 per 3 Gb, which equals 1-fold coverage at current pricing. 454 claims "human genome sequencing (at 8-fold coverage) for $100K on the current FLX platform," but this would seem to require a 3X reduction from current costs.

A first generation Illumina-Solexa instrument produces 32 bases per read with 32M reads per run, for a total of 1 Gb per run, with 90% of the bases of quality greater than Q20. Each run takes two to three days. BCM-HGSC just received a Solexa machine this month. The direct reagent cost is $3,000 per run, or 0.3 cents/kb. This cost figure is not loaded with labor and other associated costs. With Solexa, we could be close to the $100,000 genome, although the reads are short. Competition can be anticipated to lead to further cost reductions.

Applied Biosystems is developing an instrument based on the Agencourt technology that AB purchased. Their "early access" instrument produces 20-40 bases per read, 25M reads per run, and 600 Mb per run. The base quality is greater than Q20 and a run takes approximately two to three days. To date, only bacterial and fungal genomes have been sequenced. The cost is uncertain but the target output is 3 Gb per run.

Helicos BioSciences is developing an instrument using single molecule imaging (no PCR). The instrument is producing 30 base reads and is set to be marketed in September 2007. Helicos has sequenced a virus with this instrument.

Jeff Schloss added that he confirmed with 454 Life Sciences that a number of the key improvements in the FLX machine were based on NHGRI support, both directly and because of NHGRI-supported centers working with the 454 machines. He also noted that early development of the Agencourt technology was also supported by NHGRI. According to Dr. Weinstock, some of the technology development grants are for building a piece of the technology and not a whole sequencing machine. It seems that the findings and lessons learned from NHGRI grants are being incorporated into commercial ventures.

Steve Prescott suggested that an interesting article could be written about how the public effort in new sequencing technology has had a significant economic impact.

Joann Boughman, from the American Society of Human Genetics (ASHG), commented that there is opportunity for abstracts that highlight the use of these technologies to be accepted for the American Society of Human Genetics meeting.

Andy Clark asked about the development of technology for sequencing a specific 1 Mb region from each of 1000 individuals. Dr. Weinstock replied that all of the technologies allow multiple samples to be done at the same time. He noted that if each of the samples were to contain pools of the regions of interest, that kind of data density can be obtained. There are also technologies to put on tags that will allow internal tracking of individual samples.

UPDATE: ELECTRONIC SUBMISSION OF R01 APPLICATIONS

Bettie Graham reported to the Council that 95% of the applications that were submitted were successfully received.

UPDATE: NHGRI SCIENTIFIC PRIORITIES & BUDGET REALITIES

Mark Guyer reminded the Council of the scientific prioritization process that was discussed during the September meeting. At that meeting, Dr. Guyer presented an analysis of potential spending priorities ($422M) compared with the actual budget for FY2007 (estimated at that time at $362M). Since the September Council session, NHGRI has been actively taking steps to solve this problem, taking Council's advice into

account. The approaches that have been taken funding include focusing on the highest priority programs, funding certain NHGRI programs (including the large-scale sequencing program, modENCODE, ENCODE and population genomics) at levels lower than proposed in the September plan, implementing the NIH-wide policy to not give inflationary increases to non-competing renewals, and taking an average 15% reduction on all new and competing NHGRI awards. In making its funding decisions, the NHGRI continues to address NIH priorities by paying special attention to new investigators and first-time renewals.

One Council member asked about the number of new investigators receiving grants. Dr. Collins commented that the situation is grave across the NIH, not only because the NIH budget has been flat for the past couple of years, but also because the number of applications has gone up as well over this same time period. Council asked for a report and data on this issue in a future meeting.

Another Council member asked if there is any interest in a NIH-wide specific formula for handling the current budget crunch. NHGRI currently does not have a specific over-arching policy and would like to consider grants individually. The institute has a small enough applicant pool that it does not have to use pay lines. Each grant is discussed one at a time to monitor how much we are spending. This issue will be discussed in more depth during the closed session.

Joann Boughman from the American Society of Human Genetics requested that Council take a look at the peer review process. Francis Collins reported that an IC Directors' retreat is being planned about the peer review process.

ANNUAL REPORT TO COUNCIL ON POPULATION TRACKING

Bettie Graham presented a report on the make-up of the population samples collected in NHGRI clinical research studies (both DER and DIR) clinical research in FY2005 and FY2006. Clinical research is defined as patient-oriented research whose outcome affects basic science and health services research. Additional information about this requirement can be found at: http://impacii.nih.gov/applications/apps_pop.cfm.

In FY2005, approximately NHGRI studies enrolled 5062 individuals, 14% of whom were self- reported as from minority populations. In FY2006, the DER extramural program reported that 41% of enrolled individuals were minorities, although the absolute numbers were reasonably small.

Francis Collins commented that the numbers presented here were slightly hard to understand and were probably driven by one or two projects. He stated that as NHGRI is heading towards the field of population genomics, the Institute has to try to focus more attention on minority participation than we have in the past. Good minority representation is essential to a good population genomics study. Vanessa Gamble

commented that the discussion about this topic in study sections is not very good and that it might be useful to have a discussion about this topic in a later meeting.

COUNCIL-INITIATED DISCUSSION

Harold Shapiro requested that a handout be created that explains the actual numbers in the budget.

Stephen Prescott urged staff to carefully look at Population Tracking. According to him, important decisions need to be made especially in regard to Genome Wide Association studies.

Vanessa Gamble discussed recent news that the Department of Justice has approved making a DNA database of immigrants who have been arrested. Francis Collins assured Gamble that he is aware of this, and considering talking to the Department of Justice. His hope is that NIH databases are not going to be mined for criminal information. Within the Department of Health and Human Services, NHGRI is having conversations with the FDA and the CDC.

Vanessa Gamble discussed her concern about DNA test kits that help one determine their roots or "race". She voiced concern about how physicians will use this kit. Dr. Vence Bonham, from the Office of the Director, is actively working in this area. Unfortunately, there is not much data about this at present. The group agreed that this item should be discussed during a future Council meeting.

NHGRI will try to get Ann Barker, Ph.D. from the NCI to come and meet with Council in May. Dr. Barker is involved with The Cancer Genome Atlas (TCGA) and could give a presentation about the TCGA program.] In addition, Council will hear the results from the CEERs review in May. We may also need to talk more about population tracking. Dr. Eric Green will give a presentation about the NIH Intramural program as well.

REVIEW OF APPLICATIONS

In closed session, the Council reviewed 107 applications, requesting $83,569,758. The applications included 27 regular research grants, 8 pilot projects, 16 ELSI grants, 24 RFA grants, 13 center grants, 2 conference grants, 1 continuing education training program grant, 6 SBIR Phase I grants, 4 SBIR Phase II grants, 1 fellowship grant and 1 other. A total of 69 applications totaling $71,997,864 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	Francis S. Collins, M.D., Ph.D. Chairman National Advisory Council for Human Genome Research