

**Department of Veterans Affairs
Genomic Medicine Program Advisory Committee Meeting (GMPAC)
March 16, 2007**

EXECUTIVE SUMMARY

The Department of Veterans Affairs (VA) Genomic Medicine Program Advisory Committee (GMPAC) convened its second meeting at 8:15 AM on March 16, 2007, in the Sonny Montgomery Conference Room at VA headquarters. During this meeting, the committee was welcomed by both Secretary of Veterans Affairs James Nicholson and Executive in Charge Michael Kussman. Committee members received briefings on data access and discussed their views on a variety of issues, including privacy, data security, and data accessibility.

Welcome by Dr. Wayne Grody, GMPAC Chair

Dr. Wayne Grody from the University of California at Los Angeles welcomed the committee members. Committee members present were Ms. Christine Burt from CQB & Associates; Dr. Annette Taylor from Kimball Genetics; Dr. Jonathan Perlin from Hospital Corporation of America; Dr. Geoffrey Ginsburg from Duke University; Col. Brion Smith from the Armed Forces DNA Identification Laboratory; Dr. Michael Watson from the American College of Medical Genetics; Dr. Daniel Masys from Vanderbilt University; Dr. Guttmacher from the National Human Genome Research Institute, attending for Dr. Francis Collins; and Mr. David Gorman from the Disabled American Veterans. Also in attendance were Dr. Joel Kupersmith, Chief Research and Development Officer, and Dr. Timothy O'Leary, Director of the Biomedical Laboratory Research and Development Service.

Introduction by Dr. Joel Kupersmith, Chief Research and Development Officer

Dr. Kupersmith thanked the committee members for their service. He stated that the committee will be working through many of the issues related to genomic medicine and that the VA will be setting the standard for everyone else.

Presentation on the VA Cooperative Studies Program's Biospecimen Repositories

Dr. Mary Brophy, Director, MAVERIC Core Laboratory, VA Boston Healthcare System, spoke about biospecimen banking in VA Cooperative Studies Program (CSP) research. The MAVERIC Core Laboratory was established at the Boston VA to serve as a central biorepository for CSP trials. Clinical data and patient identifiers are maintained at one of the CSP coordinating centers, and the bank receives only de-identified samples. The databases that exist as part of the multicenter trials are high-quality, large-scale clinical databases, with well characterized study populations, longitudinal follow-up, validated endpoints, and disease progression treatment outcomes. In addition, the VA electronic medical record is available for long-term follow-up of the study participants. Dr. Brophy gave a brief description about operations and procedures for banking samples. Sample collection has been streamlined using customized kits, which enables the bank to get a sample into the freezer within 36 hours from the time it is drawn.

A DNA Bank was established to standardize genetic research within CSP trials. The value of genomic data is how it is linked to the clinical data. To protect patients, no data is released from the coordinating center, and clinical data is used only for the parent trial. Scientific Advisory and Ethical Oversight Committees were established to monitor and plan trials and to steer the future direction of the bank. A Veterans Advisory Group was established to inform veterans about what is being done and what the next steps are for the bank.

Access to the DNA bank is determined through the submission of a Statement of Research Intent, which is reviewed by the Scientific Advisory Committee. If accepted, a full proposal is reviewed by the Scientific Advisory and Ethical Oversight Committees. Investigators must then get local Institutional Review Board (IRB) approval and have a material transfer agreement in place before samples will be released.

A new CSP initiative is to establish a population-based collection and to obtain more diverse types of samples. To do this, a charitable trust model for operation of biobanks was established. There is a very active governance system in place to ensure that the samples are used in accordance with the donor's intent. A board of directors was established to manage the operations of the bank. The plan is that, eventually, a donors committee will be established

Ms. Burt asked why some people decline to donate samples. Dr. O'Leary indicated that there will be a follow-up on why people decline to participate, especially those with amyotrophic lateral sclerosis (ALS). Dr. Watson questioned the local IRB approach, to which Dr. Kupersmith responded that a central IRB is in the works.

Dr. Kupersmith emphasized that a lot of what the VA is doing is to establish trust with the veterans.

Comments by Dr. Michael Kussman, Executive in Charge

After a brief introduction by Dr. Kupersmith, Executive in Charge Michael Kussman welcomed and thanked the committee members. Dr. Kussman recognized new committee member Dr. Jonathan Perlin.

Comments by the Honorable James Nicholson, Secretary of the Department of Veterans Affairs

Secretary Nicholson welcomed the committee members, asking them to discuss the best use of VA resources and to be aware of the ethical challenges involved in this program. He said that someone suggested to him that the VA could be the "lifeguards of the gene pool." He then presented Certificates of Appointment to the Committee to Drs. Perlin and Masys.

Discussion on the VA Cooperative Studies Program's Biospecimen Repositories

Ms. Burt said that she had the impression that there is an established level of trust between the VA and veterans. Dr. Brophy confirmed that veterans are trusting and willing to participate in research. That level of trust must be maintained for this program to succeed. Dr. O'Leary reported that it is not just trust among veterans, but also their generosity that is important. Dr. Kupersmith thinks the VA will be "the pioneers (in)

making contact with the public." Col. Smith briefly discussed the history of the DNA repository for the military. They receive between 25 and 40 requests per year to destroy blood samples from those who retire or leave the military. That is out of 5.02 million cards in the repository.

Presentation on Genotyping Disability in Schizophrenia and Bipolar Disorders

Dr. Larry Siever, Director of the Mental Illness Research, Education and Clinical Center (MIRECC) at the Bronx VAMC, spoke about the problem of disability in schizophrenia and bipolar illness. There are approximately 100,000 veterans with schizophrenia and a slightly lesser amount with bipolar illness. About 98% of these veterans are eligible for full VA care, with a total cost of about \$15 billion per year.

Some genes that have been implicated in cognitive impairment are shared between bipolar illness and schizophrenia. There are tests to directly measure functional domains, such as the UCSD Performance-Based Skills Assessment and a medication management ability test.

There are phenotypes that are important for outcomes of veterans, such as treatment resistance and metabolic syndrome. There have not been any published studies on the genetics of functional phenotyping, but there are two underway that do not include veterans. A uniform phenotype assessment of a large sample of veterans is needed. Dr. Siever has submitted a proposal for a CSP clinical trial to examine functional disability in schizophrenia and bipolar disorder. Blood samples from 5000 patients in each group would be collected. This proposal is still in the early stages. Dr. Siever discussed MIRECCs, which were established for the mental health care of veterans, as well as for research purposes and would provide the framework for this type of initiative.

Ms. Burt asked if the military screens for schizophrenia and bipolar disorder when people enter into service. Dr. Siever said that for schizophrenia, the age of onset varies, so it is not always possible to predict whether or not someone will develop the disease. For bipolar disorder, the age of onset is later than that for schizophrenia. Genetics would lead to the understanding about which patients may respond better to which treatments; this would be very valuable.

Dr. Kupersmith said that a question that will keep coming up is "What are the differences between veterans and the general population for any given disease?" Dr. Siever believes that for schizophrenia, there will be characteristics specific to veterans.

In response to a question about obtaining informed consent for this special population, Dr. Siever replied that most patients can provide their own consent and that the patients are quizzed later about the consents. Patients must be able to explain the consent in their own words. This is different than patients with Alzheimer's disease, where a family member or proxy is needed to provide the consent.

Presentation on Veterans, Privacy and Trust

Laura Damschroder, VA Health Services Research and Development (HSR&D) Center for Practice Management & Outcomes Research, VA Ann Arbor, presented the results of a multidisciplinary study with the purpose of obtaining recommendations from veterans about privacy issues and the reasons for their recommendations. While the study was

not about genomic medicine, Ms. Damschroder said that inferences could be drawn from some of the findings.

The study was conducted in light of the HIPAA Privacy Rule, which was implemented in 2003. They set out to obtain recommendations from veterans about access to medical records for research, without getting explicit permission in some cases. A deliberative democracy approach was used to give the study participants the chance to discuss the issues with their peers and to come to a group consensus. A baseline survey was conducted, followed by deliberations, and then a follow-up study. Of the veterans who participated in the study, 73% were concerned about privacy and 39% wanted to be asked to consent to every study. Ninety-six percent said they would allow VA researchers to access their medical records to study a serious medical condition, which reflects the high level of trust between veterans and the VA. Veterans want a say in how their medical records are used for research purposes. They are more willing to allow VA researchers to access these records, relative to non-VA entities, such as universities and pharmaceutical companies.

Trust involves confidentiality, transparency, security of systems, and the welfare of veterans. Veterans said they were more likely to participate in research if they received feedback at the end of the study. Transparency is an important issue. Veterans want to know who is accessing their medical records and for what purpose. There is a concern about stigmatized conditions.

Mr. Gorman mentioned that the average age of the veterans in the study is outside the Vietnam, World War II, and Korean cohorts. He asked if any younger veterans participated. Ms. Damschroder said that the study was done from 2003 to mid-2004, prior to the current conflicts; therefore, a large number of younger veterans were not involved. Mr. Gorman pointed out that there are generational trust issues and asked if the veterans in the study were receiving disability compensation. He added that people think disability compensation will be compromised if they participate in research and that more education is needed. Ms. Damschroder said that the participants in the study had not been asked about disability compensation.

Dr. O'Leary said that every encounter with the VA is a proxy for VA research. Dr. Kupersmith said that research results need to be sent to the study participants, especially those in genomics.

Presentation on Approaches to Sharing Genomic Data

Dr. Teri Manolio, Director, Office of Population Genomics, National Human Genome Research Institute, gave an overview of the National Center for Biotechnology Information's database of Genotype and Phenotype (dbGAP). She described what a genome-wide association study entails. One of the challenges is that these studies produce a huge amount of data and that many of the initial associations are likely to be false positives. Replicating the findings in another cohort is the best way to determine whether or not the associations are real.

Data sharing strategies are being established, with the understanding that the greatest public benefit will be to make the data available to the most researchers, while still maintaining privacy for the participants.

One can look at population frequencies of different alleles, which is all available through the internet because none of the data is individually identifying. In the publicly available portion of dbGAP, one can search for studies on specific diseases. Researchers can also look for protocols and questionnaires on phenotypes. Phenotype and genotype measures summary data can also be viewed.

Prior to downloading genotype and phenotype data for individuals, a request must be submitted and approved. A data security plan must be submitted with the request, which indicates who has access to the data, how long the data will be kept, and how it will be destroyed. There is a Data Access Committee and a Data Use Review Board.

They are now reviewing responses to a Request for Information. Privacy has been one of the biggest issues, with one concern being access to data by law enforcement agencies.

Dr. Masys pointed out that there is no context-free de-identification formula. Dr. Manolio said that the dates are reset. Dr. O'Leary reported that the VA has asked some of their statisticians to look at statistically acceptable de-identification, as opposed to safe harbor.

Dr. O'Leary said that for the VA, central access will be through an appointment mechanism, such as without compensation (WOC). These appointments are VA employees in terms of everything except salary. Dr. Masys suggested that a security threat analysis might be useful. Dr. Perlin expressed the concern that the use of data can be in conflict with veterans' trust of the VA and of the federal government as a whole.

Dr. O'Leary indicated that there are two mechanisms for translation into clinical medicine: formal and informal. Dr. Kupersmith said that information from the database will be available to clinicians through the electronic health record, even if it is not made public. He also suggested that the committee think of other ways to disseminate information, besides publications.

Open Public Comments

None

Presentation on the Marshfield Clinic Personalized Medicine Research Project

Dr. Catherine McCarty, Senior Epidemiologist and Interim Director, Marshfield Clinic Research Foundation, gave an overview of the Personalized Medicine Research Project at the Marshfield Clinic. The purpose of the project is to translate genetic data into knowledge about clinically relevant diseases to improve patient care. Research is being conducted in two areas: genetic epidemiology and pharmacogenetics. There are three phases to the project. Phase I was the initial enrollment. Phase II is the creation of the infrastructure and Phase III involves the discovery projects. Phases II and III are running concurrently.

There are three advisory boards: the Ethics and Security Advisory Board, the Scientific Advisory Board, and the Community Advisory Group. To ensure the privacy of the data, one-way encryption is used. This enables the researchers to update data and to re-

contact participants. The database is not on their network, but instead, it is on a stand-alone computer in a locked room. Researchers cannot access a merged database and the phenotypic information at the same time. This prevents the identification of research subjects.

The Marshfield Clinic's website has all of the study information, consent form, questionnaire, newsletters, upcoming projects, and publications. The newsletter will have research results.

The similarity between the Marshfield Clinic and the VA is that they are the provider for a group of people that do not go in and out of the system.

Presentation on Public Consultation on Large Cohort Gene and Environment Studies

Ms. Joan Scott, Associate Director, Genetics and Public Policy Center, Johns Hopkins University, spoke about a study centered around public attitudes regarding prospective large cohort gene and environment studies. When complex, scientific issues are involved, people may be asked to give their opinions on subjects with which they have little experience, such as genetic technologies.

A deliberative democracy approach is useful in eliciting opinions from people who have the opportunity to learn more about the particular area of research, listen to a variety of perspectives, and think about all of this for a period of time. When people participate in person, different demographic information is collected than when the person participates online.

The design of the study involves the enrollment of 500,000 people; collecting DNA, as well as medical, environmental, and lifestyle information; and having the ability to contact them periodically for updates. De-identified data and sample information will be entered into a database. Researchers can then apply to access the information.

They are interested in obtaining the public's opinions about participating in such a large study, why they would or would not participate, what their expectations are concerning data return and compensation, use of a central or local IRB, and who should be able to access the data. Educational videos will be used in focus groups. These videos will help in the actual research design by providing uniformity in the dissemination of information.

People understood the importance of studying genes in relation to the environment. Obtaining feedback about what was happening with the study was something that the participants identified as being very important. People felt that the study was asking a lot of participants and that there would need to be strong incentives.

While researchers are not selecting for educational level, they are collecting this information. Education is correlated with socioeconomic status.

Program Updates

Dr. Timothy O'Leary, Director, Biomedical Laboratory and Clinical Science Research & Development Services provided updates. Ethics and privacy issues will be discussed by a separate working group that includes people representing various religious groups, people from the VA Office of Ethics, and individuals from minority groups. This working group will report through the GMPAC.

In future GMPAC meetings, technical issues—such as control groups, general frameworks, and how to use scarce resources—will be topics of discussion. Dr. Grody asked about a timeframe for this work. Dr. Kupersmith said that the timeframe is affected by resources. Focus groups with veterans will be used. The strategy is to establish trust first. Early research will be in pharmacogenomics.

Panel Discussion of Genomic Medicine in VA Clinical Care

Dr. O'Leary asked how better quantitative data can be collected. Ms. Burtt suggested talking with community leaders and Mr. Gorman suggested Veterans Service Organizations. Ms. Burtt pointed out that there is a distrust of our leaders in the general public, but Mr. Gorman said that this is not as big a problem among veterans because the priorities are somewhat different, with the focus on what is best for our veterans.

Ms. Burtt asked the committee if HIPAA results in stripping out too much information. Dr. O'Leary pointed out that not everything goes into the electronic medical record and that research can be done under a HIPAA waiver. Dr. Grody said that clinical stripping can compromise the value of the data.

Dr. Grody thanked the committee members and the meeting was adjourned at approximately 4:50 PM.

Attendees

Wayne Grody—University of California at Los Angeles (Chair)
Christine Burtt—CQB & Associates (Member)
Geoffrey Ginsburg—Duke University (Member)
Dave Gorman—Disabled Veterans of America (Member)
Alan Guttmacher—National Human Genome Research Institute, attending for Dr.
Francis Collins (Member)
Daniel Masys—Vanderbilt University (Member)
Jonathan Perlin—Hospital Corporation of America (Member)
Brion Smith—Armed Forces DNA Identification Laboratory (Member)
Annette Taylor—Kimball Genetics (Member)
Michael Watson—American College of Medical Genetics (Member)

VA Attendees

The Honorable James Nicholson—Secretary of the Department of Veterans Affairs
Michael Kussman—Executive in Charge
Joel Kupersmith—Chief Research and Development Officer, VHA
Timothy O'Leary—Director, Biomedical Laboratory Research and Development Service, VHA

Invited Guests

Mary Brophy—Director, MAVERIC Core Laboratory, VA Boston Healthcare System

Larry Siever—Director, MIRECC, Bronx VAMC; Professor of Psychiatry, Mt. Sinai School of Medicine

Laura Damschroder—Implementation Research Consultant, Diabetes QUERI, VA HSR&D Center for Practice Management & Outcomes Research, VA Ann Arbor

Teri Manolio—NIH Senior Advisor to the Director for Population Genomics; Director, Office of Population Genomics, NHGRI

Catherine McCarty—Senior Epidemiologist & Interim Director, Marshfield Clinic Research Foundation

Joan Scott—Associate Director, Genetics and Public Policy Center, Johns Hopkins University

Timothy J. O'Leary, MD, PhD

Director, Biomedical Laboratory Research & Development

Director, Clinical Science Research & Development

Wayne Grody, MD, PhD

Chair

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