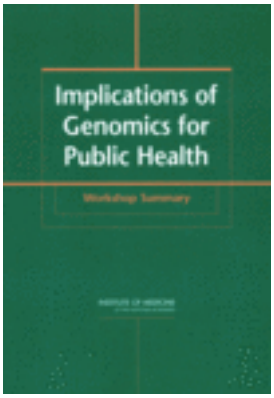

Implications of Genomics for Public Health: Workshop Summary

Lyla Hernandez, Editor, Committee on Genomics and the Public's Health in the 21st Century

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Implications of Genomics for Public Health

Workshop Summary

Committee on Genomics and the Public's Health in the 21st Century

Board on Health Promotion and Disease Prevention

Lyla M. Hernandez, *Editor*

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

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Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of the report before its release. The review of this report was overseen by **ROBERT B. WALLACE, M.D.,** College of Public Health, University of Iowa. He was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the author committee and the institution.

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Introduction

Genomics is the study of the entire human genome. Unlike genetics (the study of the functions and effects of single genes), genomics explores not only the actions of single genes, but also the interactions of multiple genes with each other and with the environment. As a result, genomics has great potential for improving the health of the public. However, realizing the benefits of genomics requires a systematic evaluation of its potential contributions and an understanding of the information and other factors necessary to facilitate the translation of research findings into public health strategies.

The Centers for Disease Control and Prevention, Office of Genomics and Disease Prevention (CDC) contracted with the Institute of Medicine (IOM) to convene a committee that would plan and conduct a workshop on the implications of genomics for the public's health. During the workshop, speakers were asked to discuss major scientific and policy issues related to genomics and public health, examine major supports for and challenges to the translation of genetic research into population health benefits, and suggest approaches for the integration of genomic information into strategies for promoting health and preventing disease. The CDC also requested that the IOM committee prioritize issues and approaches raised during the workshop.

In response to the CDC, the IOM convened the Committee on Genomics and the Public's Health in the 21st Century. Committee membership includes experts in genomics, epidemiology, pharmacology, social and behavioral health, public health, law, health care delivery, finance, and ethics. A workshop organized by the committee was held October 7

and 8, 2004, in Washington, DC. There were four panels that considered the following topics: the science of genomics, bridging genomics and public health, and gene–environment interactions; clinical use of genomic information, cost-effectiveness analysis, genomic information and behavior, and effecting population change; the public health system, international lessons, educating the public, and capacity; and data, financing and access, and legal and regulatory issues (see Appendix C for the workshop agenda).

This report summarizes the workshop presentations and commentary. It is important to note that, with the exception of the section entitled "Priorities," all material is taken directly from the workshop presentations. No additional material has been added, nor have analyses or interpretations of the presentations been made. As described in the charge to the committee, the "Priorities" section of the report does contain committee conclusions regarding prioritization of issues raised by the presenters with suggestions for next steps.

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Workshop Presentations

OPENING REMARKS

Lawrence O. Gostin, J.D., L.L.D.
Committee Chair

The speed and acuity of scientific innovation since the mapping of the human genome has been marvelous. However, it is important to remember that much of this scientific innovation has only been the means to a benevolent end. That end traditionally has been improving the health of individual patients through the use of genetics and family history for diagnosis, prognosis, and clinical interventions. Genetic testing and genetic information initially provided only modest but important benefits such as reproductive counseling and life planning. Today, the potential for clinical prophylaxis and treatment, including the possibility of genetic treatment, is stunning.

At the same time that genetics offers this remarkable promise of benefit in clinical medicine, it raises a host of ethical, legal, and social concerns. For example, should genetic information be kept strictly private, and should patients receive special legal protection against discrimination in employment and insurance? Do physicians or even patients themselves have an ethical or legal obligation to inform family members who may be at risk? In focusing so much attention on the importance of genetics to health, the question of whether genetics is really different from other areas of science and medicine has yet to be addressed. Is the importance of genetics sufficiently different to justify genetics exceptionalism? Fortu-

nately, Congress had the foresight to set aside 5 percent of all human genome funding to address the ethical, legal, and social implications (ELSI) of genetics.

There is another, deeply important benevolent end of the Human Genome Project, and that is improving the health of the public. Until recently, genetics has been primarily interested in discrete but rare genetic diseases such as cystic fibrosis and Huntington Disease, diseases with high penetrance but relatively low prevalence in the population. However, what if genomics could help explain the causes of and responses to common chronic diseases that affect so much of the population: diseases such as cardiovascular disease, diabetes, various forms of cancer, schizophrenia, severe depression, and so on? What if genetic knowledge was used not only to benefit individual patients, but to benefit whole populations? What if genomics could help illuminate the critical interactions that science has been trying to understand for decades, those dynamics between innate characteristics and such things as diet, the environment, and behavior? This would truly be a revolution in public health, and we may be on the cusp of that revolution.

Public health genomics would bring new meaning to the Institute of Medicine's famous definition of public health as being "what we, as a society, do collectively to assure the conditions in which people can be healthy." Public health genomics may bring new and deeper understanding of important problems in medicine, science, and public health. For vaccines and pharmaceuticals, for example, public health genomics can help us answer such questions as why vaccines and pharmaceuticals work on certain people but not on others, why they are more effective in some areas and not in others, and why they produce adverse effects in some areas but not in others.

Ethical, legal, and social implications of public health genomics must also be considered. A penetrating inquiry about social justice is needed. Will the benefits and burdens of population-based genomics be distributed fairly throughout society or concentrated with a privileged few?

During this workshop, these important, but very difficult questions will be asked. It is the hope of the committee that the information presented will help provide a blueprint for future research, planning, and understanding in this exciting area at the intersection of medicine, public health, law, and ethics.

GENOMICS AND PUBLIC HEALTH: A VISION FOR THE FUTURE

Gilbert S. Omenn, M.D., Ph.D.

The emerging and important field of genomics bridges many disciplines. There is an avalanche of new genomic information, including new knowledge about single nucleotide polymorphisms (SNPs), haplotype blocks, and candidate genes and alleles, as well as their association with disease. However, effective linkages with much better environmental and behavioral data sets are necessary so that ecogenetic analyses (i.e., the combination of interactions of environmental and behavioral factors with genetic variations) can occur. Ecogenetics has a long overdue role in occupational, environmental, and regulatory decision making. Credible privacy, confidentiality, and nondiscrimination policies are essential to advancing this field. Breakthrough tests, vaccines, drugs, behavioral initiatives, and regulatory actions are envisioned to reduce health risks and treat patients more cost effectively in this country and globally.

Recently, a state policy guide was developed by the Partnership for Prevention group entitled "Harnessing Genetics to Prevent Disease and Improve Health." The goals of the report were to help state policy makers protect consumers; monitor the implications of genetics for health, social, and environmental goals; and assure that genetic advances be used not only to treat medical conditions but also to prevent disease. One of the key recommendations was that genetics and genomics be integrated into existing health, social, and environmental policies rather than establishing stand-alone genetics programs. There are many reasons for integrating genetics into existing policies. First, virtually all health conditions have a genetic component. Second, most common diseases arise from gene–environment interactions; therefore, genetic advances are likely to extend and expand current practices in medicine, public health, and environmental protection. Third, some genetic variations are associated with greater health risks than others, and covering this wide variability with a one-size-fits-all genetics policy would be inappropriate.

A combination of science, ideas, and technology facilitates new ways of thinking that bring about new kinds of experiments. The grand vision is one of personalized, predictive, and preventive health care and community health services in both medicine and public health.

There are a number of key challenges in this genomic era. The first challenge is to strengthen the sense of commitment to prevention along our public health and clinical medicine continuum. The second challenge is to think of ways we can apply new technologies and new knowledge to global infectious and chronic disease, not just those we already recognize in this country. The third challenge—one very important to our entire

understanding of human health—is to recognize the heterogeneity among patients within any diagnostic category and among populations. Another challenge is to use the interpretation and computational analysis of gene expression profiles, microarray experiments, comparative genomics, and proteomics in the development of mechanism- and evidence-based medical practice. Finally, there is the challenge of integrating genetic, environmental, and behavioral factors in preventing and treating illnesses. In chronic diseases, there is a need to know a lot more about variation, risk, and how to motivate people to take actions within their own control by providing knowledge about their risks and the modifiability of those risks. Concomitantly, credible privacy, confidentiality, and nondiscrimination policies are necessary to effectively translate genetics research into population health benefits.

Supporting the whole endeavor are information sources about genetic variation. For example, the International HapMap Consortium aims to genotype at least 1 million SNPs from 270 individuals to facilitate the study of direct associations of individual SNP alleles with disease phenotypes. This will include careful analysis of the linkage disequilibrium, which represents a more powerful approach than the traditional linkage-based analyses.

Another key support for translation of genetic research into population health benefits is the CDC-funded Centers for Genomics and Public Health. The leaders and staff in these institution-based centers have worked closely with the CDC to advance the whole field and are a major source of support for developing an effective public health workforce and infrastructure.

Sequencing and analyzing the human genome is generating genetic information that must be linked with information about nutrition and metabolism, lifestyle behaviors, diseases and medications, and microbial, chemical, and physical exposures. Genetics must be included in protocols for health promotion and disease prevention research (e.g., host–pathogen interactions, risk factors for chronic diseases, and drug or vaccine development).

Using the field of toxicogenomics as an example, risk assessment and risk management must move beyond consideration of one chemical, one environmental medium (air, water, soil, food), and one health effect (cancer, birth defect) at a time. This will require that multiple molecular signatures and biomarkers be integrated with a comprehensive public health view. It is important to take advantage of the fact that there are multiple sources for the same agent, multiple media/pathways of exposure, multiple risks/effects of the same agent, and multiple agents causing the same effects in order to understand the status and trends of disease, formulate

ecological models of health, and take into consideration social, cultural, and environmental justice.

This is a golden age for the public health sciences. But the best way to reap the benefits of all the developments and advances in genetics and genomics is to bring this information together with other crucial non-genetic variables. One framework for pulling this all together comes from regulatory decision-making that begins with hazard identification, then moves to risk characterization, and finally focuses on risk reduction. Currently, attention is focused on identifying genetic variations and their accompanying disease susceptibilities. Regulatory laws should be used to advance the genomics research agenda. For example, the Office of Safety and Health Administration (OSHA) Act requires that health standards be set so as to protect—that is, no individual, even if exposed at the level of the standard for a working lifetime, shall suffer any adverse effect. Genetics should be used to identify and define those individuals at risk of suffering adverse effects. Another example comes from the Clean Air Act, Section 109, in which ambient air quality standards are set so as to protect the most susceptible subpopulations with an adequate margin of safety. Genetics can help define those susceptible subpopulations.

There are experts on most sides of contentious genetics issues. What is needed is better science and better risk communication. One of the ways risk communication might be improved is by identifying specific molecular signatures that would tell people whether they have been exposed to the agents or combinations of agents. If they have early effects, the effects might still be highly reversible. Research by the Center for Toxicogenomics at the National Institute of Environmental Health Sciences (NIEHS) and academic centers around the country is focused on identifying molecular signatures of the model compound acetaminophen. It is important to test other compounds, especially known carcinogens and chemopreventive agents, which could guide us to new ways to take action on the preventive side. In all of this work on environmental exposures, it is very important to move beyond the traditional regulatory approach of examining one chemical, one medium, and one health effect at a time.

In 1997, the Commission on Risk Assessment and Risk Management recommended that these issues should be put in broader contexts. Multiple sources of the same agent, multiple pathways of exposure, multiple risks of effects of the same agent, and multiple agents causing the same effects should be considered. Additionally, the Framework for Risk Management developed by this commission is an important model to emulate in genetics. The many different stakeholders need to be engaged from the start to put problems into their proper context, define risk assessment, investigate options, work up decisions, take action, and then evaluate what has been done.

From a policy point of view, there are many things that need to be done to facilitate translating genomics into improvements in the public's health. For example, the case was made above for integrating genetics into existing policies. Decisions about genetics policy involve many complex issues about ethics, costs, benefits, individual interests, and societal interests. Medical care decisions must be linked to research, to insurance policies, and to broader public health policies. The intersection between genetics and public policy is both immediate and long term, warranting close monitoring and timely actions. One area that needs particular attention is the criteria for population screening using genetic tests.

Several key recommendations for health policies advanced by the Partnership for Prevention should be implemented, including (1) increase consumer knowledge of genetics, (2) strengthen public health infrastructure to accommodate genetics developments, (3) add genetic competencies to licensing requirements for all health professionals, (4) increase supply of qualified genetic counselors, (5) invest in a broad genetics research agenda.

Several key recommendations for state policies include (1) protect individual privacy while meeting information needs for public health tracking systems and approved research; (2) put one state agency in charge of handling reports of discrimination and privacy breaches; (3) help state universities expand genetics education and training; (4) convene insurers, employers, consumer groups, and health professionals to resolve barriers to timely availability of affordable genetic services; (5) require that genetic services financed by the state are valid, reliable, and useful; and (6) establish a coordination process to integrate genetics into policy and programs, starting with the broad public health agenda.

Finally, greater effort must be made to engage communities in ethical, effective, and timely community-based studies. This includes involving community members from the earliest stages to have a real influence on the project. The research processes and outcomes should benefit the community, and community members should be part of the analysis and interpretation of the results. This type of investment should create productive partnerships that continue beyond a specific research project and should ultimately empower community members to define and initiate their own projects.

THE SCIENCE OF GENOMICS AND ITS APPLICATION TO COMMON DISEASES

Aravinda Chakravarti, Ph.D.

It has been widely predicted that genomics will soon allow us to unravel the genetics of most common diseases and will provide a mechanism for risk prediction for individuals susceptible to a variety of complex disorders. This presentation is intended to provide a background on the science of genomics while addressing the following questions: How can one gain information concerning complex disease genetics? How can this information be used in individuals and their families for risk prediction? How can this information be used to prevent disease, delay its occurrence, modify its severity, and/or develop specific therapeutic measures?

In assessing the application of genomics to common diseases, there are four perspectives outlined below: the importance of genome sequence to identify genes, identifying functions of genes through comparative genomics, identifying disease genes/processes through large-scale association studies and transcript analysis, and proving function by chemical genetics.

Genetics research is at a crossroads, evolving from work that focused primarily on rare Mendelian disorders to that of complex common diseases. Several old controversies have to be dealt with, including Mendelian versus biometrician approaches, the genetic load controversy, and biochemical/molecular versus evolutionary mechanisms.

The Human Genome Project and new DNA (deoxyribonucleic acid) sequencing data can provide numerous insights into disease mechanisms, and we are now beginning to understand gene function and disease pathogenesis. Common diseases appear to be caused by interactions of some genes with major effect and high penetrance, but also by multiple genes, each with small effect and low penetrance, all of which will interact with environmental factors. For these diseases, simple Mendelian inheritance will be the exception rather than the rule. For instance, research on Hirschsprung disease, which shows no simple Mendelian pattern of inheritance, indicates gender predilection and geographic and ethnic differences in prevalence. Now several genes have been identified, each with small effect, out of many that remain unknown.

In addition to our current knowledge of genes, which pertains primarily to the coding sequences of the genome, many other mutations must occur in the non-coding parts of the genome, which make up the vast majority of human DNA; there is still much to learn about the effect of mutations in these areas. The HapMap project, which will enable us to pinpoint millions of SNPs and many genes with small effect, will be con-

cluded in a few years, enabling the study of a great amount of human genetic variation. This new technology will facilitate efforts to sequence the genomes of multiple individuals, and the interpretation of these changes will likely be based on computational biology.

The interaction between these multiple genetic predispositions and specific environmental factors will provide important information about how to reduce the burden of these complex disorders on both individuals and the population. For example, recent data on the interaction of gene mutations with environmental factors in fetal alcohol syndrome show that some diseases previously considered to be totally environmentally based have differences in genetic susceptibility and may now be explained in part on molecular genetic grounds.

Thus, the genetic basis of complex common diseases, the specific environmental factors involved in each of them, and the molecular/chemical basis of these interactions will be important in developing population-based approaches to disease control and eradication.

BRIDGING GENOMICS AND POPULATION HEALTH

Sharon Kardia, Ph.D.

One of the biggest issues in the emerging genomics revolution is how to create a bridge between the great scientific advancements that are emanating from genomics and improvements in population health. Conceptually, it is necessary to consider the individual in the context of his/her environment. The genomics revolution, in the broadest sense, is bringing to our awareness the rich tapestry of the biological hierarchy, moving from the tremendous variation in an individual's genome to its manifestation in the expression of the genome (i.e., the transcriptome) that translates into the basic metabolic machinery (i.e., the proteome) and its impact on a person's metabolic profile (i.e., the metabolome) that underlies disease processes. It is important to recognize that the same processes that feed information from the genome to the disease process are also feeding information about a person's internal and external environment back through the metabolome to the proteome to the transcriptome. All of this is happening within the context of people's day-to-day lives.

The scientific and technological revolutions occurring right now are breaking down the barriers to gathering the high-dimensional biological information[1] needed to understand the continuum between health and

[1]High-dimensional biological information is all the data (i.e., information) obtained from the "omic" science and technologies (genomics, transcriptomics, proteomics, metabolomics).

disease. The availability of genome-wide and candidate gene SNP panels, gene expression array technologies, and proteomic and metabolic profiling are at an all-time high. However, the emerging data have not yet provided sufficient explanations for the chronic diseases and infectious diseases that affect the population's health, nor have the data been fully applied to concerns about occupational health and health behaviors. In building bridges between these worlds, it is important to monitor our advancements in terms of an overall conceptual map of the intersecting continua of research and practice that affect the continuum between individual and population health.

One model of genomic medicine—that is, one model of a bridge between genomics and the public's health—is to collect all the genomic, transcriptomic, proteomic, and metabolomic information on an individual that is possible. Then it is necessary to make the information available in a user-friendly fashion so that the average physician can improve diagnosis and treatment, thus reducing health care costs and improving health outcomes. In order for this model to work, there needs to be a tremendous amount of research behind the scenes. A major scientific issue is how to get such vast amounts of integrated information across the biological hierarchy in patient and population studies to provide the evidence base for transforming medical practice. Another key question is, How must linear, single-agent based concepts of disease be revised in the face of information about the huge collection of interacting agents that underlies human biology?

The "omic" technologies are revolutionizing our understanding of biology. New language and concepts are needed to convey and compress this high-dimensional data into useful information and knowledge. Molecular profiles, signatures, and patterns do not easily translate into current understandings of causality. What is causality when everything is related to everything else in the cellular milieu? This brings up new issues or principles in biology never addressed, such as redundancy in human genetic and metabolic systems or the concept of balance across multiple systems. Extensive genetic knock-out studies show that there is a large compensatory or adaptive aspect of human biological systems that must be understood in order to build a bridge between genomics and population health.

Many challenges exist in attempts to bridge the worlds of genomics and population health:

- The challenge of etiological heterogeneity of the common diseases.
- The need for better methods for measuring disease processes, environments, and behavior. The ability to collect high-dimensional "omic" data far exceeds the ability to measure the core aspects of disease and the

external or human factors that will form the interventions of tomorrow to improve human health.

- The daunting complexity of considering all the possible underlying gene–environment and gene–gene interactions.
- The need for large, expensive, clinical and population-based cohort studies that build the necessary evidence base for translation into practice.
- The need for improved informatic capacity to translate and integrate diverse sources of information and data into new knowledge, as well as the informatics support for translation into practice.
- The lack of high-dimensional statistical methods for analysis and compression of these rich data sources.
- The climate of fear about genetic information among the public and health professionals.
- The challenge of educating health professionals so that genetic information can be used appropriately and accurately.
- The lack of clear evidential standards set forth by the scientific community or federal agencies that could be used by a body such as the U.S. Preventative Services Task Force to inform medical and public health professionals about the level of confidence and the utility of genetic information.

Support for translating genomics into improvements in the public's health requires development and support of an emerging public health genomics model. The United States has great public health services, departments, agencies, and organizations. Schools, churches, hospitals, and community organizations help people throughout their lives by providing connections that allow health to be promoted, prevention efforts to be enhanced, and population-based screening approaches to be implemented. There are many ways in which the established public health infrastructure and other public and private networks can be used to support the translation of genomics into improvements in the public's health. For example, by partnering with academic institutions, departments of health can provide culturally responsible avenues for genetic research that utilize existing newborn blood spots, childhood and disease registries, and local environmental and behavioral risk assessments in order to provide research feedback about the local population's genetic risk and disease-prevention possibilities. In addition, departments of health are ideal partners for community-based participatory research programs that can be used to fill the gaps between health professionals in the community, academic partners, and public health practice.

Other types of support that are already available to help in this translational area are the population-based cohort studies such as the National

Health and Nutrition Examination Survey (NHANES), the Framingham Heart Study, the emerging National Childhood Study, and many others that have extensive longitudinal data and biological samples in hand. Importantly, some cohort studies already have mechanisms for distributing samples for "omic" measurements that are then compiled into central databases that can be used by the entire research community. These resources, as well as other biobanks, and data resources (e.g., clinical and behavioral intervention trials) are a very cost-effective way of conducting research critical to facilitating translational outcomes.

One approach to providing a solid evidential basis for genomic medicine and public health genomics, and moving beyond linear, single-agent–based ideas of disease, is to create a risk assessment framework to guide the trajectory of scientific investigation and to facilitate decision making. The risk assessment framework used in the environmental health sciences provides a useful template for creating genetic risk assessment standards in population health research.

The three main areas of research needed fall into the categories of genetic risk identification, genetic risk characterization, and genetic risk reduction. Genetic risk identification encompasses genetic epidemiological research, gene–environment interaction studies, animal genetic modeling, as well as bioinformatic research and ultimately complex system modeling. Genetic risk characterization focuses on understanding how genetic risk factors influence disease development and manifestation. This research focus necessarily involves longitudinal studies to characterize the genetic probabilities of developing disease, extensive "omic" analysis of the causal chain of events, in vitro studies of the identified processes, and development of animal models.

From this evidence base, novel methods for genetic risk reduction could then be tested in clinical prevention and intervention trials, population prevention and intervention trials, and pharmacogenetic trials. In order to support this type of research, medical and public health informatic systems will need to be developed. Furthermore, there is a need for new research paradigms such as community-based participatory research to address the psychosocial aspects of performing genetic studies in the public arena. In addition, high throughput "omic" measurement centers and the availability of biological samples and high-quality data from clinical trials and cohort studies will also be needed to facilitate an overarching scientific program that begins with genetic risk identification, moves to risk characterization, and then tests methods of genetic risk reduction.

The community-based participatory research paradigm is ideally suited for addressing the multitude of issues that arise in translational studies of genetics and genomics. By engaging community stakeholders in the development of research questions, in conjunction with academic

and clinical partners, many bridges can be built and crossed simultaneously. Community members can build trust with genetic scientists. The general public and health professionals can become more familiar with the language and concepts of genetics so as to be more informed consumers and decision makers about genetic information. Academic researchers can be more informed about how communities deal with genetics issues and their health. Community based participatory research will provide health professionals with practical experience on the impact of genetics on people's lives and behavior, as well as important data on the effectiveness of genetic risk reduction in communities. Overall, the community-based participatory research paradigm is important to explore as a strategy for health promotion, disease prevention, and individualized treatment of disease.

GENE–ENVIRONMENT INTERACTIONS

David L. Eaton, Ph.D.

The following includes an overview of research on gene–environment interactions, a summary of scientific advances to date, and a description of opportunities and challenges in this area of research.

Human genetic variation can now be characterized using a variety of types of DNA markers, including SNPs. Millions of such SNPs have been identified in the human genome, although only a fraction of these are frequent in the population. Polymorphic variants have been found to directly cause many relatively rare, highly penetrant diseases such as Huntington Disease, cystic fibrosis, and muscular dystrophy.

However, most common diseases in the population are probably multifactorial. That is, they involve several genes (i.e., are multigenic), and environmental factors and behavioral factors play an important role. Furthermore, the mutations that contribute to these diseases, including cancer, asthma, birth defects, cardiovascular disease, Alzheimer's disease, and Parkinson's disease, have limited penetrance, and the diseases are likely to be etiologically heterogeneous. Although some diseases may be entirely attributable to "high dose" environmental causes, most diseases are caused by the interaction of genes and environment. Specifically, risk among individuals carrying either disease "resistant" or disease "sensitive" genotypes is modulated by exposure to environmental and behavioral factors.

Examples of well-characterized diseases that involve gene–environment interactions include PKU, HIV infection and the CCR5 receptor variants, and adverse drug responses and CYP2D6 metabolism. Another important example is thiopurine methyl transferase (TPMT) deficiency and

toxicity/therapeutic benefit in leukemia treatment with thiopurine drugs. That is, while there is effective treatment of children who are carriers of the normal allele of this gene, those homozygous for the poor metabolizing TPMT genotype are at risk for serious toxicity or even death.

Several lines of evidence, including the increasing number of publications on the topic and relevant grant funding, demonstrate that research into gene–environment interactions is progressing rapidly. For example, the Environmental Genome Project and related grants funded by NIEHS are undertaking human DNA polymorphism discovery projects, are performing functional genomic analyses and population-based epidemiologic studies of these polymorphisms, and are developing relevant new technologies.

However, with the exception of a few single-gene examples, gene–environment effects have proven difficult to measure so far. This is due to a variety of factors, including the relatively low magnitude of the associated increased disease risk (usually odds ratios of 1.5 or less), modest frequencies of disease susceptibility alleles in the population (often less than 10 percent), and the low penetrance of these alleles. Other challenges include the accurate characterization of the risk factor or outcome phenotype, difficulties in quantifying the exposure involved, possible epistasis (gene–gene interactions), and the possibility that the genetic effect may only move an individual up or down on the dose–response curve.

When gene–environment interactions are identified, appropriate risk communication also needs to be considered. For example, when is the knowledge base sufficient to ensure that genetic susceptibility is real, who should have access to this information, and when should genetic screening be undertaken? Case examples that raise these issues include the interaction of the GSTM1 null genotype with smoking on the risk of lung cancer and the effect of the HLA-DPB1 Glu-69 genetic variant on risk of lung disease among beryllium workers.

Even with these challenges, advances in understanding gene–environment interactions promise to help discern the molecular basis of disease, to facilitate the identification of at-risk individuals, and to reduce uncertainty in risk assessment. Thus, these advances provide important potential avenues to prevent disease and improve the public's health.

COMMENTARY

Melissa A. Austin, M.S., Ph.D.

Three themes emerged from the presentations by Dr. Chakravarti, Dr. Kardia, and Dr. Eaton: There is a distinction between single-gene disorders and complex disorders; a great deal of additional resources must

be applied to understanding complex diseases and to developing ways to use what is known for improving public health; and efforts must be grounded in the context of communities and society.

First, tremendous progress has been made in understanding relatively rare Mendelian single-gene disorders. However, even preventive measures for these types of diseases have little effect on risks for the population as a whole. The challenge is to characterize the basis of common, complex disorders—those multi-gene disorders that are caused by multiple low-penetrance, relatively common mutations.

Second, some existing resources can be used to begin to address these challenges involved in translating what is known into population health benefits: the human genome, the environmental genome project discussed by Dr. Eaton, the HapMap, and all the "omic" technologies Dr. Kardia described. However, additional resources are needed, including large population-based studies that will facilitate understanding about the impact of these "omic" technologies on population health. Furthermore, there is a need to develop more sophisticated methods for synthesizing and integrating the vast amount of information obtained.

Third, addressing these challenges requires working in a societal context. Dr. Kardia discussed the importance of community-based participatory research and of understanding the social implications of genomic research. There are also ethical concerns, including privacy and confidentiality of genetic tests. Of major importance is the need to prepare the public health workforce to use genomics.

The Institute for Public Health Genetics at the University of Washington has developed both master of public health (M.P.H.) and doctoral (Ph.D.) programs to begin preparing the public health workforce in genetics. The institute's mission is to provide broad, multidisciplinary training for future public health professionals, to facilitate research and public health genetics, and to serve as a resource for continuing professional education. This multidisciplinary training program has three major components, described below, and the courses are taught by faculty from 12 different departments, located in seven different schools and colleges at the University of Washington.

The first major component of the program is referred to as the "fundamental areas of study." This component includes human genetics, genomics, population genetics, and molecular biology, as well as the core public health disciplines of epidemiology, biostatistics, environmental health, health services administration, and social and behavioral sciences. The second major component is "genomics in public health," which includes genetics; molecular epidemiology; ecogenetics, the study of gene/environment interactions; and pharmacogenetics. The final component of the program is an area called the "implications of genetics for

society," which includes ethics and social science, law and policy, and health economics and outcomes research.

The development of the public health workforce is crucial to realizing the opportunities that genomics can bring to improving the health of the population. Preparing such a workforce requires the multidisciplinary collaborations of academia, public health practice, and the private sector.

David L. Rimoin, M.D., Ph.D.

There have been a number of instances where the public health approach to genetic disease has been effective; examples include folic acid supplementation for neural tube defect prevention and neonatal screening. However, an overlooked area is genetic heterogeneity, that is, different mutations can result in the same phenotype. This can be locus heterogeneity (mutations in different genes producing the same phenotype) or allelic heterogeneity (different mutations of the same gene producing similar phenotypes).

When examining complex diseases one must distinguish between polygenic versus multifactorial inheritance. With polygenic inheritance there are multiple genes, each with small but additive effects. Disease occurs when the threshold is exceeded; this is called quasi-continuous variation. Mulitfactorial inheritance involves more than one gene plus environmental factors. There may be one or two genes with a major effect or various specific genes in different individuals or ethnic groups that produce the disease.

Currently, large populations with common disease are screened with many markers (e.g., SNPs), but phenotypes are not stratified; therefore, we include many heterogeneous disorders. Data showing that 20 percent of a study group is associated with a given genetic marker lead to important questions. Does the gene cause 20 percent of the polygenic genetic component in all individuals, or does this gene have a major effect in only 20 percent of the people in the group?

Genomic or personalized medicine addresses individual risks based on family history and attempts to provide an individualized risk assessment. This approach can address genetic heterogeneity, look for stratification of disease in clear examples of gene mutations that have high specificity, screen by gene mutations, and treat based on a gene-specific defect.

Personalized medicine differs from the typical public health approach, which searches for a common phenotype, pathogenetically grouped disorders rather than a single disorder, and high sensitivity rather than specificity. Screening is usually by a subclinical common marker rather than a specific gene mutation, and the treatment is based on a common endpoint.

Some examples highlight the complexity involved in making decisions about screening. Type 2 diabetes mellitus was originally thought to be one disease. However, as many as 70 different genes contribute to type 2 diabetes in the population, and at least 38 distinct genetic single-gene syndromes produce the same phenotype associated with type 2 diabetes. But is glucose intolerance really one disease? Should there be screening for mutations in over 70 different genes or simply screening for glucose intolerance? Is treatment very different depending on how screening is implemented?

Whether one screens for the genotype or the subclinical marker depends on the disorder and the current genetic and pathogenetic knowledge. For example, with hypercholesterolemia cholesterol is screened for because there are statin drugs that lower cholesterol in the general population regardless of the primary cause. However, with breast cancer the BRCA mutation is screened for because we do not have a common marker.

Anemia is another example. There are hundreds of different types of anemia. Some are purely genetic, for example, sickle cell disease. Some are purely environmental, as is the case with iron deficiency anemia. Some require a combination of genetic and environmental factors, such as G6PD deficiency. Although most types of anemia can be treated with a blood transfusion, one has to define the particular form of anemia in the population and individual in order to provide accurate and effective screening and specific therapy.

These questions also lead to the field of ethnogenetics. That is, different populations may have different genetic and environmental causes of the same phenotype. To be most cost-effective, one should target each population with its specific screening test, preventive measure, and treatment. For example, there is little benefit to screen African Americans for Tay-Sachs disease or Ashkenazi Jews for sickle cell disease. However, newborn screening programs screen all newborns for hemoglobinopathies. Is this cost-effective, or should screening be based on ethnic profiling?

In terms of cost-effectiveness, it is important to identify predisposed individuals in order to engage in prevention and early treatment. However, it is equally important to identify the 0 percent non-predisposed individuals in high-risk families who did not inherit the mutant genes in order to avoid expensive screening.

Modern genetics has taught us that one size does not fit all. Genomics and public health will not be able to use gene mutations to achieve the most effective screening until microarray techniques become robust enough to screen for all mutations. Many of the major advances in genomics as applicable to public health will probably be in the area of new knowledge of disease pathogenesis and heterogeneity, so that broad

as well as specific therapies can be developed for individuals detected by screening at the family history, gene, or subclinical level. Detecting genetic susceptibility to common diseases will be based on

- Understanding of pathophysiology and natural history of disease
- Clarifying genetic heterogeneity
- Individualizing disease risk
- Increased predictive value of screening tests
- Increased participant compliance with screening guidelines and therapies.

CLINICAL USE OF GENOMIC INFORMATION

Alfred O. Berg, M.D., M.P.H.

Genomic testing has the ability to greatly enhance or to further erode the quality of care provided in this country. There is an opportunity to enhance the quality of care by being explicit and intentional about how genetic tests are introduced into general clinical practice. There should be a focus on primary care because ultimately that is the setting where much of the testing will occur, and this is precisely the point in clinical medicine where testing is most likely to be useful in risk stratification and diagnosis—the goals of many genetic tests.

Clinicians need a good source of advice about appropriate test use. Therefore, a process for evaluating genetic tests should be developed. The first issue in such a process is selecting the tests to study. We need to choose clinical questions that have significant health consequences, that are of relatively common frequency, that have a test with excellent analytic validity, and that have an available and effective intervention. Genetic testing needs to add value to what already exists. This is a problem with current proposals for testing for chronic diseases, such as heart disease and diabetes, for which adequate tests already exist. The added value of genetic testing in such instances is unclear.

The most common genetic test in use today is the family history. However, from an evidence-based point of view, family history is not well developed. The instruments range from simple verbal questions in practice (e.g., Do you have any cancer, heart disease, or diabetes in your family?), to detailed instruments that can lead to a formal genogram. The reliability and validity of these instruments are not well defined, and the documentation of the results in most medical records is poor. Clearly, these issues will also need to be addressed for genetic testing.

If a process for evaluating genetic tests were developed, what would it look like? An evidence-based approach provides a valuable framework.

A typical evidence-based approach first would need to define carefully the population to be tested, the clinical features to be evaluated, and the intervention and its comparisons; indicate whether the comparison is no treatment or some other treatment; and provide clearly defined clinical outcomes. Clinical outcomes are particularly important and should be outcomes that patients would notice and care about.

Once the problems and questions are clearly identified, it is possible to review the evidence. Typically, an analytic framework is constructed. Key questions are proposed. There is a specific literature search strategy, a way of summarizing what is found, a way of assessing individual articles, making sure they are critically reviewed for quality, and then making an explicit link between the evidence and the rationale.

A relevant example of this process is the United States Preventive Services Task Force (USPSTF). The USPSTF produces scientific reviews of preventive interventions provided to asymptomatic patients in primary care clinical settings, using explicit, transparent, and publicly accountable methods. A panel reviewing genetic tests should similarly have its mission very clearly defined in terms of population setting and methods.

The USPSTF assigns letter grades to recommendations on the basis of quality of evidence—good, fair, or poor—and the net benefits—substantial, moderate, small, or zero or negative. An *A* recommendation for a test requires good evidence, and the benefits need to substantially outweigh the harms, for example, screening for colorectal cancer. A *B* recommendation requires at least fair evidence, and the benefits need to outweigh the harms; screening mammography earned a *B* recommendation. The *C* recommendation is a close call where the evidence is at least fair to good, but the benefits and harms are closely balanced, for example, screening young adults for abnormal lipids. A *D* recommendation against use is made when the intervention is found to be ineffective or harms outweigh potential benefits, for example, screening for cervical cancer in women who have already had a hysterectomy or screening for ovarian and pancreatic cancers. For a large number of interventions reviewed by the USPSTF, the evidence is insufficient to reach a conclusion or make a recommendation because of lack of evidence, poor-quality evidence, or good-quality evidence but with conflicting results. These receive an *I* grade.

An important outcome of the USPSTF process is that, at the end, it allows identification of the gaps in evidence, thereby defining a research agenda.

Use of an evidence-based approach is strongest when the evidence changes relatively slowly and when there is a common and serious disease, a clearly defined intervention, clearly defined outcomes, a substantial body of evidence produced by research with a range of study designs, and substantial literature on cost and cost-effectiveness. The approach is

weakest when the condition is rare, there are multiple interventions used (e.g., dealing with developmental delay in children), there are ill-defined outcomes, there is limited evidence, or there is rapidly changing evidence.

Although a process is needed for evaluating genetic tests proposed for clinical practice, there are concerns about the application of evidence-based methods to evaluation of genetic tests in routine practice. First, many conditions are uncommon to rare, and this has huge implications for the predictive value of testing, for false positives that require further evaluation, and for the likelihood of having sufficient resources to generate high-quality information on the effectiveness of an intervention. Second, interventions and clinical outcomes are often not well-defined. For example, there is no treatment for some of the conditions currently being screened for in newborns, and for some where treatment has been proposed, it is not known whether the treatment is effective.

Third, many genetic tests have inadequate sensitivity and specificity in unselected populations. Fourth, many tests are now being proposed and marketed on the basis of descriptive evidence and pathophysiological reasoning, with no clinical trials conducted. Without evidence of effectiveness, it is questionable whether such tests are worth the investment. Finally, there is concern about advocacy for tests from industry and patient interest groups.

The assertion that genetic tests are somehow fundamentally different does not stand up to the evidence. Genetic tests are like many other tests in providing risk information, making a diagnosis, making a prognosis, and predicting a response to therapy. The one area where genetic tests are probably exceptional is in that of the subjective overlay. That is, patients and clinicians attribute meaning to genetic tests that is different from the meaning attached to, for example, a blood test.

To evaluate genetic tests for clinical practice, several steps are needed. First, methods must be developed. The initial step would be to define a typology of genetic testing questions in clinical practice (e.g., reproductive counseling, prenatal testing, screening for risk or disease) with a goal of explicitly exploring, for each category, how these clinical scenarios systematically differ.

Second, there is a need to examine information as a clinical outcome. The evidence-based view is that information is not a relevant clinical outcome unless the individual gives it a value, either positive or negative, and the value can be measured. It is necessary to better define the benefits and harms of genetic information and to develop valid measures of the value of the information. We need to be able to recognize that this information may have different benefits and harms for the individual and his or her family members, that clinical context exerts an effect, and that there will be unintended consequences that should be named and measured.

Third, for each type of clinical scenario, there is a need to develop a generic analytic framework and a typology typical of key questions, specify the hierarchy of research designs, develop tools for assessing the quality of the research, specify links between evidence and graded conclusions, and very importantly, develop a coherent plan for communication and dissemination.

In summary, what is needed is support for a group that would be charged with evaluating genetic tests that are proposed for general use in the clinical setting. This group could focus on questions likely to come up in primary care, develop an overall typology of questions, propose analytic methods, and make sure that communication and dissemination plans are well developed. That is, there should be some system for decision making, akin to the USPSTF, that can be used for genetic testing.

COST-EFFECTIVENESS ANALYSIS IN DECISION MAKING

Scott Ramsey, M.D., Ph.D.

Given that there is a fixed amount of funds available, if society decides to spend more on genetic technologies, it will need to spend less on other medical services. Therefore, it is important to conduct a systematic evaluation that considers costs and outcomes.

Cost-effectiveness analysis determines whether a medical intervention, when used to prevent or treat a condition, improves health outcomes in patients enough to justify the additional dollars spent compared to another intervention. It is important to note that cost is not congruent with cost-effectiveness. A costly genetic test with high clinical utility may be cost-effective whereas an inexpensive test may not if it is not clinically useful. Furthermore, the idea that the genomic revolution will result in an overall savings in health care costs has been suggested. On the contrary, the genomic revolution will likely increase the cost of care. The question is what additional health benefits are obtained for that added cost?

Relatively few economic evaluations of genetic technologies have been conducted, and there is significant variation in the quality of those that have been published; therefore, there is tremendous uncertainty about the value of the tests studied. Much of this uncertainty is due to the fact that information needed to assess value is missing. A good cost-effectiveness analysis must have analytic validity and clinical utility. Analytic validity is the accuracy with which the genetic characteristic can be identified in the laboratory, and it determines whether the test measures what it is supposed to measure and also whether the results are reproducible. Clinical utility is the degree to which the test alters medical

management in a way that results in a net health benefit to the patients and is a function of the efficacy of an available treatment and the acceptance of the test by patients and clinicians. The lack of good data makes assessing effectiveness, let alone cost-effectiveness, challenging.

Cost-effectiveness analysis has not played a role in genetics to date. The development, marketing, and use of genetic tests often follows a less than ideal path. Frequently, a test is developed and (hopefully) validated, perhaps receiving some level of regulatory approval. It then diffuses into clinical practice. On the basis of what happens in clinical practice, information about the clinical context is obtained, and that information filters down into professional recommendations. Then individuals or health care payers make decisions about paying for these technologies.

If cost-effectiveness is not assessed, what can happen? Highly cost-effective tests could be underutilized. Marginally cost-effective technologies might be over-utilized. In a worst-case scenario, a test that is neither effective nor cost effective could be used. With this in mind, a systematic evaluation that considers costs and outcomes is important in order to obtain the most added value for the money spent on genetic technologies.

There appear to be several factors that inhibit practice of cost-effective genomic medicine. The marketplace incentive is to cash in on the genomic revolution, thereby leading to a plethora of technologies that have not been analyzed in terms of cost-effectiveness. Regulation of genomic technologies is minimal. Patients are usually not given a full picture of the complex issues surrounding genetic tests. Clinicians, who do not receive adequate training in genetics or evidence-based medicine, often make the mistake of assuming that clinical validity equals clinical utility. Delivery systems do not have a method for integrating genomic technologies into practice, and health plans and payers are not using cost-effective analysis for genetic technology coverage decisions.

Cost-effectiveness analysis might be used to address issues of genetic testing. In a perfect world of cost-effective analysis, a gene test would be developed and validated. Then, to understand the clinical context, data would be gathered on the prevalence of the disease and the mutation relevant to the test; the analytic validity of the test, particularly in relation to comparison tests that may not be genetic; the clinical utility, that is, what can be done for individuals to help them live longer or have lower morbidity; and the costs of screening, follow-up diagnostics, and treatments. This information would then be filtered into a cost-effectiveness analysis that examined the value for dollar spent. If the test was deemed cost-effective, recommendations would be developed, and it would diffuse into clinical practice.

In terms of a research agenda, a better understanding is needed of issues that influence an individual's acceptance of these tests. Why do

people, even when they are at risk, choose not to take tests? What are the psychometrics involved? What are the patients' preferences (using the language of economics); that is, what would people prefer to learn about their own genetics?

INTERSECTION OF GENOMIC INFORMATION AND BEHAVIORAL SCIENCES

Ellen R. Gritz, Ph.D., and Susan Peterson, M.P.H., Ph.D.

The desired goals in providing genomic information are to improve understanding of individual and family risk, identify persons at increased risk of disease, target interventions to specific high-risk groups, motivate individuals to engage in preventive health behaviors, mitigate psychological distress, and facilitate informed decision making about short-term and long-term behavior and lifestyle modifications. However, there is a tremendous challenge in personalizing information and in developing a prevention and treatment plan that then translates into behavior change to reach the desired outcomes.

How do people understand and use genetic information? Surveys about genetic testing for cancer found several factors associated with interest in testing, the same factors that are found in many behavioral studies of adoption of interventions. These factors include higher distress; cancer worries; higher perceived cancer risk; perception that benefits outweigh limitations; prior practice of preventive behaviors; awareness of inherited cancers and testing; desire to learn whether children are at risk; being Caucasian; older age; higher income; and education.

When actual uptake rates of cancer genetic testing were measured against hypothetical rates, they were found to be much lower. Research conducted to date shows us that initial interest in genetic testing often exceeds actual uptake; that testing uptake may vary based on study population and setting; and that individual differences in psychological variables (e.g., perceived risk, distress) may influence use. Physician's influence on test decisions is understudied, and study populations generally lack diversity; however, cultural/ethnic differences in testing attitudes and uptake may exist.

How does genomic information influence health behavior? What, for example, is the impact of cancer genetic counseling and testing on behavioral outcomes? The behavioral outcomes focused on in current research are, for the most part, screening and risk-reduction interventions such as prophylactic mastectomy or oophorectomy. Findings are that notification of positive mutation carrier status may improve screening behavior and

risk-reducing surgery; psychological variables (perceived risk, distress) may influence ovarian cancer screening and prophylactic surgery decisions; and genetic testing information may be important in guiding risk-management decisions. The results of controlled trials evaluating cancer risk counseling methods show a definite increase in knowledge, not much change in perceived risk (which is not necessarily good), and no increase in perceived distress.

What are the opportunities for integrating genomic information into health promotion? Opportunities exist, but to realize those opportunities requires tremendous effort. Theory-driven interventions to evaluate the impact of genomic information on short- and long-term behavioral outcomes are needed. It is important to understand how psychological characteristics influence behavioral change and how various risk factors and health-promoting behaviors interact. Furthermore, it is necessary to better understand risk communication and family and social network influences. The role of the health care provider; the influence of socioeconomic status (SES), culture, and ethnicity; and access to health care services must be explored. Importantly, the ethical, legal, and social implication issues must be addressed.

One framework for integrating genomic information into behavioral interventions calls for linked, multi-level interventions to promote health behavior change and adoption in the context of genomic information at the individual level, the interpersonal level, the familial level, the level of the health care system, and also at the societal or population level.

HOW TO EFFECT CHANGE IN THE POPULATION

William Foege, M.D., M.P.H.

The expectation is that genomics will be used for the improvement of both individual and collective health. Improving health is accomplished through two primary strategies, both of which have been based on developing broad messages for everyone. The first strategy is to provide information and expertise to an individual for use in reducing the risk of adverse health effects in that individual's life. The individual then uses this information to improve his or her own health, for example, by deciding to quit smoking or to eat healthy foods. However, personal use of science correlates with education and wealth; thus, inequalities in health have increased in many areas. The public health philosophy is to use science for the benefit of all and to reduce inequalities.

The second strategy involves improving health through use of the law. In this strategy, scientific information is used for the benefit of all;

examples include regulations on occupational exposure, pollution, and food safety. Sometimes the laws are direct (e.g., requiring use of seat belts), sometimes incentives are built into tax laws, or sometimes unhealthy behaviors are made more difficult, for example, through bans on smoking in public places. Occasionally the laws, regulations, rules, or social norms are applied globally, as with smallpox eradication; sometimes they are applied nationally; but usually the approach is state by state, county by county, or even school district by school district.

In asking how genomics can be used for the benefit of all, it is sobering to analyze how poorly and inequitably knowledge and tools have been used in the past. Genomics will certainly expand the opportunities but will probably widen the disparities, resulting in unbelievable advances and unbelievable inequities. Some think genomics will lead to a single-payer system because of problems in maintaining privacy and difficulties of insurance companies in determining which individuals to insure at what rates. It has been said that within a decade many of us will be carrying our own genetic code around on a small card that will be taken to every physician visit. There is an opportunity to bring science benefits to bear on the individual; the hope is that genomics will lead to a new world of prevention as each person becomes able to obtain a specific prescription for what must be done in order to be as healthy as possible.

The bottom line is that the first approach, individual use of science to improve one's own health, is likely to blossom. What will be much more difficult is to apply genomic knowledge for the benefit of everyone. Despite the fact that much time is spent thinking about errors that might be made, that thinking is almost totally about errors of commission. Yet historically, the greatest harm has been through errors of omission: things not done, the science not applied, the vaccines not given, the medications not available in Africa because of their cost, the water supplies not treated, and so on. There will be dilemmas about how to use the tools and power of genomics, but the greatest challenge will be in a widening equity gap, the failure to use science for the poor, the foreign, the unnoticed.

The tools that are needed must be clearly identified and their cost made cheaper. The questions must be, Where is a test needed, and how can that test be made available more cheaply? For example, about a quarter of a century ago, it cost $10 to do a lead test, and it took days to get the results. So every child had to go in to have blood drawn and then come back for the results. However, when attention was focused on this issue, within months the price had dropped from $10 to 10 cents and the time from days to minutes. If things are done correctly, current actions can harness the basic tools of science not only for the benefit of the rich and the powerful, the leaders, but as a way of giving the very poorest people a chance for optimal health.

Unless there is public funding to narrow the gap between the rich and the poor, we are unlikely to succeed in providing everyone with a chance for health. The most important decision we can make is to declare that, to the best of our ability, we will use genomics for the benefit of both individuals and society. We need to persuade the funders that we need research on population use, genetic risk reduction, and biomarkers for the biggest problems, both in this country and in the world. We need global approaches to understand the interaction of everything in an environment, but also to understand disease problems in poor countries.

The challenge to public health genomics is to overcome inequitable allocation of benefits, the tragedy that would befall us if we made the promise of genetics only for those who could afford it and not for all of society. Social evolution as a result of genomics will be what we want it to be, and now is the time to make our case.

COMMENTARY

Deborah Bowen, Ph.D.

The ways in which genomics will be used are even now being shaped in different ways. For example, the CDC evaluated the effect of direct to consumer and direct to provider advertising of genetic testing for breast cancer. The findings are both comforting and chilling; comforting in that there are not huge changes in purchase patterns, but chilling in that in a relatively short time one can see changes in the ways that women think about breast cancer genetic testing.

Social science disciplines have much to contribute to our understanding of human behavior. Dr. Gritz reviewed a body of research on how people react to genetic tests. The results were reassuring and surprising: reassuring because long-term outcomes of genetic testing were not found to be harmful; surprising because when faced with an actual decision, many people choose not to undergo genetic testing. Dr. Gritz presented some of the few existing data about use of tailored information to improve health, which make it clear that our use of such information is not yet effective. She called for basic social science research to help us understand why people are not reacting in ways that were anticipated.

Dr. Foege laid out a vision for moving genetics and genomics into both clinical medicine and public health practice, cautioning that there is potential for increasing existing disparities. However, public health practitioners in the field already are under immense pressure, overworked, and underfunded. A move to add genomics to public health means an increase in volume of work, further straining the system.

There will also be an increase in volume in terms of research, for example, in terms of need for increased sample sizes because of dealing with relatively small effects. Clinical practice will also see an increase in volume. It will take more than a few years to genotype every person in order to provide each individual with a card full of personal information. Furthermore, current clinical practice will need to change from the seven-minute primary care visit to incorporate the need for increased information collection, processing, and dialogue. Clinicians are being asked to integrate genetics into the primary care setting, yet research shows dismal results at actually changing provider behavior to incorporate preventive actions. A better understanding is needed of how to work with primary care systems, providers, and patients.

Finally, it is important to begin thinking about the evidence needed for regulatory processes and about how to shape such processes. In addition to evidence of effectiveness, good policy will also be based on rigorous social science research and attention to legal and ethical issues.

Kenneth Offit, M.D.

Genetics is used in diagnosis, prognosis, and prevention. In prevention there is some evidence of efficacy, but the necessary cost-effectiveness studies are lacking. The limiting factors in genetics are social and behavioral, not technological. The population implications are significant, and there are many barriers to overcome.

There are several cancer syndromes for which genetic factors are relevant (see Table 2-1 below), and the interventions for these syndromes are commonly surgical. Cost-effectiveness information about these areas is needed. It is important to note, however, that while genetic technology is

Table 2-1 Interventions for Cancer Syndromes

GENE	SYNDROME/INTERVENTIONS
BRCA 1 and 2	Breast–ovarian syndrome/imaging, oophorectomy, mastectomy
MSH2/MLH1	Hereditary non-polyposis colon cancer/endoscopy (in some cases), colectomy, and hysterectomy
RET	MEN 2A: thyroidectomy
APC	Familial adenomatous polyposis/endoscopy, colectomy
CDH1	Hereditary gastric cancer: gastrectomy
VHL	Von Hippel Lindau syndrome/imaging
KIT	Gastointestinal stromal tumors/Gleevac

expensive, advances in oncologic care may make these expenses worthwhile. For example, an MRI is an expensive test, yet it may be worthwhile for all women with BRCA mutations.

There are companies that are marketing extensive genetic testing to individuals; some of this testing is legitimate, but some of it is highly questionable. When commercialization begins to influence public expectations about genetic tests, there should be concern. The major barrier to effective use of genetic information is not technological, it is social and behavioral. Furthermore, the perception of genetic discrimination is a profound barrier, as is lack of education about genetics. These social and behavioral challenges must be addressed so as to realize the benefits of genomics for improving health.

Nelson Freimer, M.D.

There needs to be a greater focus on the phenome. The phenome is the comprehensive representation of phenotypes. One of the difficulties in trying to relate genotype to phenotype is that we have taken phenotypes one by one. Furthermore, the current approach to implementing genomics in medicine and the health care system is on a disease by disease basis.

The way in which genomics is going to influence public health is through behavior. The same approach to understanding is required, both in understanding behavior and understanding the phenotype. A new science of behavioral phenotyping must be developed. A phenomic approach is an attempt to bring scale, scope, and standardization to phenotyping. To implement a phenomic approach requires developing a more comprehensive approach to all types of phenotyping, particularly for behavioral phenotyping. This will involve the application of both qualitative and quantitative measures and new modalities for assessing behavior, for example, neural imaging. Furthermore, the phenomic approach can work only if one has large samples.

Genetics studies and studies that have led to the identification of disease-related genes have been based almost entirely on disease diagnoses. It is increasingly clear for all kinds of phenotypes that disease categories are an incomplete and imprecise representation of phenotypes. A real challenge will be addressing the increasing mismatch between the use in research of phenotypic definitions that are not disease diagnoses with their application in clinical practice, which will still rely on disease diagnosis categories.

This problem is also relevant to pharmacogenomics. Drugs act on biological pathways, not on diseases. It will require new processes of phenotyping to identify relevant pathways for pharmacogenomic drugs. Once

the pathways are identified, we are much more likely to find meaningful variation in genotypes that relate to drug response and adverse effects.

Research funding is also affected by the disease-related approach. Much of the work accomplished to date has been funded by various institutes at the National Institutes of Health, where funding comes from an institute focused on a specific disease or disease category. Future progress will require examination of many phenotypes together, not on a disease by disease basis.

What is needed is a new type of phenotyping. The scale of phenotyping must be increased. Comprehensive databases must be developed. International efforts are necessary. Increased scope is needed in terms of the phenotypic measures that are selected, but how we select these measures is a huge issue. Unless this process is standardized, it will be impossible to compare information that comes from different sources. Finally, there is a need for individuals interested in and trained to examine phenotypes. In short, a Human Phenome Project should be undertaken.

STRATIFICATION, JUSTICE, AND OPPORTUNITY

Alexandra Shields, Ph.D.

Perhaps nowhere else has the challenge of translating new knowledge into improved health been more evident then when addressing racial disparities and health. Health services research and public health efforts have rigorously documented racial differences in the prevalence of common diseases, in the quality of care provided, and in access to care and occurrence of subsequent disease outcomes. However, the levers needed to reduce those very same disparities are still lacking. In the context of genetic research, the challenge of using this new knowledge to reduce health disparities has become even more intense and fraught with conflict.

In part, this is due to the recognition of both the social and environmental underpinnings of health disparities and the demonstration of racial differences in the frequency of disease susceptibility alleles and alleles that alter response to treatment. The intersection of these two potential components remains to be reconciled in ways that have potential for improved health and reduced disparities. For example, what new groups will genomic information create, and how will these be used in public health and clinical practice? Will research on genetic variation enable people to be grouped in new constructive ways to better tailor treatment and prevention, or will it reinforce existing patterns of racial, ethnic, or socioeconomic stratification?

The classification scheme used to define differences in genetic risk of developing disease or in responding to treatment is critical for developing concrete strategies to translate genetics into public health practice. Although there are several possible strata along which to assess risk now, race is perhaps the most salient rubric of stratification in U.S. society.

In anticipating a widespread integration of genomics into public health, the many challenges to come include ensuring critical evaluation of the scientific evidence for specific genetic effects on disease and the clinical validity and utility of genetic tests. This integration can be thought of in terms of three different moments in the translation process. First, there are the research practices that produce and frame the new knowledge that must be evaluated. Second is clinical integration. That is, what are the appropriate applications of this new knowledge in clinical practice and public health? And then, third, is monitoring the impact of these interventions on the public's health.

The constructs appropriate for monitoring health disparities are not necessarily the same ones that are appropriate for genetic studies of disease etiology. For example, the rubric of continental ancestry that is used in some genetics studies is an arbitrary categorization scheme that may not be applicable in public health, especially since continental ancestry actually reflects a continuum of human variation across the globe. Furthermore, the majority of genetic studies do not distinguish between self-identified race and continental ancestry.

In general, researchers should avoid the use of self-identified race in genetic studies and rather use self-reported ancestry or empirical assessment of ancestry. Even more importantly, every effort should be made to measure directly the many environmental factors for which race is often used as a gross proxy, including everything from environmental exposures to stress and the way it affects hormones, to overcrowding. These measures are likely to be much more informative while avoiding the problems of stigmatization and the racializing of disease.

To the extent that genomics research can contribute to understanding how specific environmental and social factors intersect with genes in producing disease, genomics may offer both new levers for reducing health disparities and new frameworks for developing effective new public health interventions.

THE PUBLIC HEALTH SYSTEM

J. Michael McGinnis, M.D., M.P.P.

In addition to the extraordinary scientific advances, speakers at the conference made interesting broad observations about public health genomics. Gilbert Omenn maintained that it allows us to expand our vision of public health. Sharon Kardia emphasized that it is about understanding people in their living spaces and their day-to-day lives. David Eaton pointed out that public health genomics is not about single genetic variants or single environments, but rather about complex relationships among genes and among genes and environments. Bill Foege cautioned that the national tendency is for health inequalities to become larger as our tools improve. Nelson Freimer suggested that a missing link in understanding how genetic events affect population health is an understanding of the nature and structure of our phenotypes. David Rimoin stated that major advances will derive from knowledge not just of the polygenic, but of the multi-factorial nature of disease, requiring broad rather than specific therapies. Human genomics plays out in accordance with principles of redundancy, balance, and causality, and therefore we are fundamentally dependent on large-scale databases.

The implication of all this is that ultimately insights are dependent on understanding the patterns, not the point-to-point relationships involved. This is the stuff of public health: dealing with those patterns, understanding how they impact our health destinies, and taking action to change them.

The 1988 IOM report *The Future of Public Health* defined the mission of public health as "what we do collectively to fulfill society's interest in assuring the conditions in which people can be healthy." Although the IOM intended this mission statement to apply broadly to the involvement of multiple institutions and players that shape the population health, this presentation focuses on the role of official public health agencies at the local, state, and national levels of the public health system. The traditional way to think about the functions and activities of these public health agencies is in terms of the conditions with which they work and the risks they try to reduce: conditions such as infectious diseases, sexually transmitted diseases (STDs) and HIV, maternal and infant illness, heart disease, and injuries. These agencies also work to reduce risk through initiative such as sanitation, work site safety, immunizations, tobacco control, and screening programs.

The three core functions of public health are assessment of health status and program effectiveness, assurance of the access and quality of programs, and future-oriented policy development. How do the issues of genomics and genetics relate to these functions? The answer is: monitor

the influence of genetic factors on population health (assessment); assure access, quality, and appropriateness of genetic services (assurance); and establish policies and guidelines that support sound and efficient application of genetic tools to improve population health (policy development).

Traditionally, the 10 essential services of public health are to

- Monitor health status
- Diagnose and investigate health problems
- Inform and educate about health issues
- Develop and enforce health and safety protection
- Link people to needed medical care
- Mobilize community partnerships for health
- Foster health-enhancing public policies
- Assure a competent health workforce
- Evaluate the quality and effectiveness of services
- Conduct research for new insights and innovation

How do the issues of genomics and genetics fit into these 10 services? We need to

- Monitor: *the prevalence of known genetic susceptibilities*
- Investigate: *unusual results of gene–environment interactions*
- Inform: *the public about emerging genomic insights*
- Protect: *the vulnerable against exposure and discrimination*
- Link: *people to the genetic services they need*
- Mobilize: *partnerships key to genomics understanding and action*
- Foster: *appropriate, equitable application of genetic advances*
- Assure: *a genomics savvy public health workforce*
- Evaluate: *the quality and effectiveness of genetic services*
- Conduct research: *to reveal the intricacies of the gene–environment relationships that can be used to improve health for individuals and society*

The health of populations and of individuals is determined by the dynamics of events in five domains: genetic predispositions, social circumstances, behavioral choices, environmental exposures, and medical care. It is the province of public health, and only public health, to deal with all these domains. Of course the issue is not how each of these domains plays out independently, it is how they interact to determine our health. The real action occurs at the intersections, and it is the role of public health to understand and act at those intersections.

The public health system, charged with addressing and acting within each of these domains, is a vastly heterogeneous enterprise. There are more than 3,000 local health departments that serve populations ranging

from a few to nearly 10 million individuals. The territories covered by a local health department vary from a few square miles to more than 94,000 square miles, and budgets range from essentially zero to $1.3 billion for the health department in New York City. The median annual budget is $620,000; the mean is $4.5 million. The number of employees ranges from zero to 6,000 with a median of 13 and a mean of 67. State health departments also vary, serving populations that range from half a million to 35.5 million individuals.

Meeting the challenges for public health and public health genomics requires the involvement of many stakeholders, including the public, public health officials, medical providers, payers, schools, businesses, community leaders and elected officials, academic institutions, and the media. The challenges facing us are many. They include

- Ability to deal with patterns
- Data set linkages
- Confidentiality
- Discrimination
- Disease-dominant paradigms
- Training needs
- Principles for screening
- Dealing with heterogeneity
- Incorporating advances
- Involving the community
- Equity

Despite the challenges, there is great creativity, brilliance, and commitment being brought to bear on these issues. Such action will help us achieve the vision for public health genomics of a society in which understanding and effective public health action turn our knowledge about the intersecting influences on health to the benefit of healthy people in healthy communities throughout the nation.

INTERNATIONAL LESSONS: BIOBANKS

Bartha Maria Knoppers, Ph.D., with Clementine Sallée

Research has advanced tremendously since the early 1990s, from rare single-gene disorders to common complex diseases, from national research to regional and international collaboration, and from traditional research biobanking to studies relying on Human Genetic Research Databases. A Human Genetic Research Database (HGRD), or biobank, is a collection of

information organized in a systematic way for research purposes and from which genetic material and related data can be derived. Recent developments have increased the pressure to develop these databanks, and there is a trend toward proliferation and specialization of national and international policies to govern HGRDs that range from principles governing research involving human subjects to genetic or genomic database management.

A few countries (e.g., Estonia, Sweden, Iceland, and Norway) have implemented legislation that specifically regulates HGRDs in terms of establishment, governance, structure, collection, processing, storage mechanisms, and so on. Other jurisdictions have applied existing legislative schemes pertaining to traditional research, data protection, and public health issues. The lack of rules, taxonomy, and nomenclature that are internationally agreed upon is quite detrimental to research collaboration, database compatibility, and exchange and transfer of information and researchers. Harmonization of principles and terminology is sorely needed.

At the national level (that is, within a particular country), there is a move toward a coherent and comprehensive approach, for example, acknowledgment that HGRDs differ in important ways from traditional databases, including long-term storage and the consent process; identification of the limits of traditional personal data and privacy legislation; and a call for a regulatory framework that will protect participants while avoiding strict regulatory mechanisms.

There is also an emerging consensus on some ethical principles such as the need to tailor traditional consent mechanisms to the specificity of databases; the correlation among the degree of data identifiability, the need to re-contact, withdrawal of consent, return of results, and access; the need for adequate ethical oversight from the inception of a database as well as monitoring mechanisms; the need to initiate, promote, and strengthen the professional/public dialogue; and the need to develop a benefit-sharing policy, that is, giving back to the community or population while opening the door to the possibility of commercialization.

One controversial issue relates to funding for these databases. Some of these databases are supported by public/private funding partnerships because they are costly and need stable funding beyond traditional government grant periods. Another issue relates to informed consent. Can there be an original informed consent or authorization that suffices for future use subject to ethics review? How can privacy be protected? Some propose removing identifiers, thereby rendering the data anonymous. Anonymization is shortsighted scientifically because then data are frozen in time and cannot be clinically updated.

The status of genetic materials remains controversial. For example, words such as ownership or property cannot be used in European coun-

tries, in Quebec, or in any country that has a civil law tradition where the human body is seen as extra-patrimonial. Some countries have specific laws or articles in their civil codes that state that the body cannot be a source of profit or be considered property. Other controversial issues are governance structure, ethical review for multi-center projects, ongoing monitoring, and involvement of industry.

Despite these controversies, there are ongoing efforts to develop genomic research databases at many levels. There are several efforts aimed at developing national population HGRDs, including one in the United States in Wisconsin, CartaGene in Quebec, the entire country of Estonia, and the United Kingdom. The Genomic Research in African Diaspora (GRAD) is an ethnic-based population HRGD that was developed to study the genetic variation of a particularly underrepresented ethnic group. There are also international population HGRDs such as the GenomEUtwin, which is building on existing twin cohort studies to analyze genetic and lifestyle risks associated with common physical and mental diseases. There are also HRGDs that are attempting to harmonize and standardize national biobanks for international collaboration, for example, the Public Population Project in Genomics (P3G).

What is needed to move from principles, existing laws, and frameworks to establishing, building, and governing HRGDs? Establishing HRGDs is difficult because there is no immediate personal benefit, they are expensive, and although many geneticists agree that these databases will yield a wealth of useful information, it is not clear that they will deliver on their most ambitious promises. Legislation can be used to establish the databases (as was done in Iceland and Estonia), but such laws should be preceded by a debate involving the community at large: scientists, representatives of the public, and legal experts. Another approach is for groups of scientists to initiate the project, adapting science to the desires and preferences of communities or populations. This is the case with the HapMap, the UK Biobank, and GRAD. A difficulty with this self-regulatory approach is the lack of uniform national standards. Transnational enterprises face the challenge of harmonization. In such cases there must, at a minimum, be agreement about scientific approaches, technologies, standards, measurements, ethical issues, and governance structure.

Once HRGDs have been established either through law or some other process, they must be built. This requires ensuring representation and building public trust. Furthermore, there must be data-collector participation and expertise, an acceptable privacy/consent process, and individual feedback and general results. Commercialization is an issue that must be addressed. Commercialization and free public access to the data can be

seen as common public goods. However, industry involvement as a financial partner makes it more difficult to keep the public trust.

Governing such databases requires a project framework and protocol assessment that is approved by authorities, that has the public as a true partner, and that has built-in review mechanisms and procedures for monitoring over time. The management structure must be accountable to both stakeholders and the public, have clear policies regarding commercial aspects, and have both independence and integrity. Data protection and security mechanisms must be monitored.

The research community is designing unique infrastructures with the potential to benefit the community as a whole. Among the issues that need to be addressed are political legitimacy and maintaining the public trust, the role of informed consent and feedback of results, protection of information, intellectual property rights, and oversight and governance.

EDUCATING THE PUBLIC

Vicki Freimuth, Ph.D.

Early research about public opinion on genetic testing focused on a very narrow group of consumers of either genetic information or genetic products, or participants in research studies. What was learned is similar to what is known about risk communication in general: People have trouble with numeric expressions of risk, they assess risk very differently than do professionals, and they have different priorities and values from the medical genetics establishment.

There are three sources of information about public knowledge and attitudes about genetics. First there is public opinion, measured for the most part through public opinion polls and focus groups. Public discourse is a second source of information and includes media coverage, particularly news, editorial coverage, and even entertainment. Finally, information is obtained by examining organized interest groups. However, there is currently little to be found regarding genetics from this last source; therefore, this presentation will not examine information from this source.

Between 2000 and 2002, a variety of public opinion surveys conducted and compiled by the Roper Center for Public Opinion Research showed fairly positive attitudes toward genetics. Results show that 59 percent of those surveyed think mapping the human genetic code is beneficial, 57 percent believe the benefits of genetic research outweigh the risks, and 65 percent are either very or somewhat likely to take a genetic test. This last response was given in a hypothetical context and, as mentioned by other speakers, when individuals are actually presented with the question of

whether or not to take a genetic test, they often decide differently than the results of the survey would indicate.

Opinion polls also demonstrate that the public has a number of concerns about genetic testing and genetic research. Eighty-eight percent believe a person whose genetic profile shows problems should not pay higher health insurance rates; however, 84 percent think it likely that health insurance companies would deny coverage to such individuals, and 69 percent think it likely that employers will deny people jobs on the basis of a genetic profile. Eighty-nine percent believe it is not acceptable to use cloning to reproduce humans, and 59 percent think it should be illegal to clone animals.

Focus groups that examine attitudes toward genetics by race or ethnic group have found some differences among groups. For example, African Americans and Hispanic Americans are more concerned than other groups about genetic research leading to racial discrimination. Furthermore, Hispanic Americans are much more likely to see genetic research as offensive to their religious beliefs, whereas European Americans are more likely to view the research as subject to government or corporate exploitation.

Public opinion research found that three factors shape public attitudes toward genetic research: amount of confidence in regulatory agencies, direct perceived usefulness of technologies, and moral frameworks. Those who believe their concerns (such as discrimination and privacy issues) will be managed successfully have much more positive attitudes than those who lack confidence in the abilities of regulatory agencies. Those who perceive genetic technologies to be of direct use or benefit, particularly personal usefulness, are more positive toward genetic research. Finally, an individual's moral framework is important in shaping and predicting one's attitude.

Research has also demonstrated that language is important in communicating genetic information. One study of how information about risk is presented found that terminology affects the degree of risk the public may feel. In this study, use of the phrase "gene that causes" conveyed a higher degree of risk than use of the term "family history of." Another study found that the term "mutation" evoked strong emotional reactions, probably based on entertainment, science fiction, or our historical experience with radiation. A better alternative to mutation was found to be "genetic alteration."

Public discourse, the second source of information about public opinion, also reveals important information. Genetics has definitely been on the public agenda. A content analysis conducted by Capella found that between 1997 and 2003 the *New York Times* published 3,300 stories about genetic influence on human behavior and disease, with the majority of

articles in one year focusing on genetics in a forensic application. Capella also found that the three major broadcast news networks produced 2,500 segments on genetics. A Google search of the World Wide Web found 10 million Web pages, of which the top 10 were scientifically credible. A content analysis of U.S. mass media magazines between 1980 and 1995 conducted by Condit found that most of the coverage of genetics was positive.

Results of research on public discourse tell us that genetics is on the public's agenda and that they know something about it, the public opinion polls do not demonstrate gross misunderstandings, and media coverage is frequent and fairly positive.

Turning to the issue of the effectiveness of public education campaigns on genetics, it is informative to examine what is known about effectiveness of these campaigns in general. It is easier to achieve awareness and provide knowledge than it is to change attitudes or behaviors. There are four basic models used for public education campaigns. The traditional public service model relies for exposure on public service time and donated time. An example of this kind of campaign is the National High Blood Pressure Education Campaign that has been ongoing for more than 30 years. The second model, the public–private partnership, brings the resources of the private sector to complement what the public sector is doing. The use of paid media by the government is the third type, an example of which is the White House's Anti-Drug Campaign. The final model, that which is used in genetics, is a public relations campaign. In this model one relies on the media to cover the issue.

Effective public education campaigns have been shown to include clear, specific objectives; targeted audiences; multiple channels; and adequate budget to ensure exposure to messages. For genetics this means that the public's concerns must be addressed, and material must be translated into personally relevant information. Audiences must be targeted and many channels used, from personal contact through television and the Internet. This requires adequate funding.

In conclusion, there are some critical questions that must be answered about genetics communication. Probably the most critical relates to determining the effects of being told that one has a genetic predisposition for a disease. Research provides conflicting results, with some studies showing that such information could lead to fatalism while other research indicates it leads to greater motivation for behavioral change.

What are the pivotal terms that make a difference to the public's understanding of genetics? More must be learned about the language and terms that can make a difference to the public's understanding of genetics. Some of that research is under way, but much more needs to be done. Finally, an improved understanding is needed of how probabilistic con-

cepts can best be conveyed. Research in these areas is needed because communication about genetics is critical.

CAPACITY

Kristine Gebbie, R.N., Dr.P.H.

Public health capacity depends upon the infrastructure, which includes data and information about the population; laws, organizational structures, and interorganizational relationships; and a workforce that is prepared in both general public health practice and specialty areas. Adequate infrastructure in the area of genomics includes genetic data about a population as well as genetic/genomic resources in a state or locale; updated laws (e.g., consent and confidentiality) and agreements among service or research agencies; and genomic competencies for the workforce.

This section focuses on the workforce and, more specifically, public health professionals. A recent IOM report, *Who Will Keep the Public Healthy?*, examined challenges to public health and developed a framework for how education, training, and research can be strengthened to meet the needs of future public health professionals. The report defined public health professionals as persons educated in public health or a related discipline who are employed to improve health through a population focus. A major challenge addressed in the report is globalization, including the movements of populations, of diseases, and of information. Another challenge relates to advances in scientific and medical technologies, including increasing surveillance and use of genetic information and communication technology. Demographic transformations were also examined.

The report proposed using an ecological model of health to address these challenges. An ecological model of health is aware of and takes into account the linkages and relationships among multiple determinants of health, including how genetic heritage fits into the model. Education about this model and about eight new content areas was deemed important for public health professionals in the 21st century, and the report recommended that competencies be developed for each area. One of these new content areas is genomics. However, an examination of the other seven content areas (informatics, communication, community-based participatory research, cultural competency, global health, ethics, and policy and law) shows that genomics-related information could very well be a part of the content in each area.

Genomics is a new challenge for public health professionals. Public health education programs and schools must provide their students with

a framework for understanding the importance of genomics to public health and with the ability to apply genomics to basic public health sciences. Access to lifelong learning must be assured. Compared to medical schools, nursing schools, and some other health profession schools, public health has been relatively weak in continuing education. Without strong continuing education programs, however, it will be impossible to close the workforce knowledge gap in genomics. Finally, it is necessary to have supervised practice opportunities, not just classroom learning.

Genomic education for public health should be based on competencies. Competencies are things people can do, not what one thinks, knows, feels, or believes. Competency statements can be used not only for education and training, but also for updating or revising job descriptions and as self-assessment tools. The CDC specified competencies in genomics for public health workers, separating them into three levels: competencies for all public health workers; competencies for all public health professional workers; and competencies for those in specialty or concentration-specific positions such as leaders/administrators, clinicians, epidemiologists, health educators, laboratorians, and environmental health workers.

Every public health worker should demonstrate basic knowledge of the role that genomics has in the development of disease, identify the limits of his/her genomic expertise, and make appropriate referrals to those with more genomic expertise. Public health professionals must have a greater facility in genomics, as should those in specialty positions. The complete list of competencies for each level can be found on the CDC Web site.

CDC has funded three major centers for genomics and public health at the University of Michigan, the University of North Carolina, and the University of Washington and has challenged those centers to translate what is known about genomics into real practice. CDC also provides a genomics guide and toolkit; has entered into cooperative agreements with state health departments in Michigan, Minnesota, Oregon, and Utah to strengthen programs for genomics and chronic disease prevention; provides a "Six Weeks to Genomics Awareness" course on the Web; and has many additional resources, including cases and curriculum training modules, family history tools, genetic epidemiology tools, and much more.

Collectively, the importance of public health workforce capacity in genomics is understood. Our public health professionals are needed to shape programs and policies to improve population health; they must not lose sight of their responsibility for helping to keep the public healthier in the 21st century.

COMMENTARY

Jean Chabut, M.P.H.

The contributions that genomics will make to the public's health over the next generation will be equally as important as the discoveries that led to vaccines and antibiotics. It is necessary to prepare for the use of genomics in public health by readying the workforce, examining the legal framework at the state level (for example, in terms of confidentiality and privacy), and identifying additional tools needed—tools, for example, that will avoid increasing disparities in public health.

Our experience at the Michigan Department of Community Health is, perhaps, relevant to what will be confronted as public health engages with genomics. Until 1999, our primary public health involvement with genetics or genomics was through our newborn screening programs. In 1999, Michigan was asked to host the Third National Genomics and Public Health Conference. At about the same time, CDC asked the Michigan Department of Community Health to pull together some chronic disease specialists who would ponder the relevance of the human genome project to chronic diseases. Unfortunately, it was extremely difficult to identify individuals to participate in this discussion, either because of a lack of knowledge or a lack of interest.

Ultimately, working with CDC, a collaborative workshop was organized for colleagues from state departments of health that focused on genomics and chronic disease. Participants included epidemiologists and chronic disease directors from department labs, and the discussion focused on five chronic disease areas: cardiovascular disease, cancer, obesity, diabetes, and asthma.

Several concrete advances have been made since that time. The Association of State and Territorial Health Officers (ASTHO) has developed and disseminated a toolkit for genomics and public health. Workgroups on the use of laboratory blood spots and workshops on the practical uses in public health of family history have been developed. We now encourage each of the chronic disease areas to prepare a genomics session for each of their conferences. CDC has now funded three centers for genomics and public health, at the University of Michigan, one at the University of Washington, and one at the University of North Carolina. These centers have a very collaborative and supportive relationship with each other. Additionally, four states were funded as demonstration sites for infrastructure development.

There are things states can do without a significant investment of resources. Michigan organized an internal workgroup composed of individuals from chronic disease specialties, the laboratories, and epidemiology to discuss and identify issues. A grant from HRSA provided funds

to implement a statewide assessment and develop a statewide plan. Working closely with the University of Michigan genomics center, a "Six Weeks to Wellness" brown bag luncheon discussion series was organized. Also with the help of the center, various legal issues are under examination. Discussions have been held with state legislators on the ethical, legal, and social issues related to genomics and public health. Public education, however, has fallen short, primarily because public health professionals are still in the process of educating themselves.

Ultimately, resources will be needed to be able to mount the kind of effort necessary to assure that genomics is used properly for the benefit of the public's health.

Sue Friedman, D.V.M.

The application of genetics and genomics has outlined a new emerging community—a community or population that knows it is at risk. A new vocabulary needs to be developed to work in this emerging field. Perhaps an example can best illustrate this point.

One of the members of FORCE (Facing Our Risk of Cancer Empowered) posted a message on the organization's Web site. This is an individual who carries a BRCA mutation but has not had cancer. She wrote, "I have to admit, I need a label. Do we have one? You know, those of us who have the BRCA gene but have not had cancer, the ones going through all this research and deciding on whether to have prophylactic surgery. We need more of a voice and a label, a name. I've never been one hung up on labels before but a lot has changed for me since this began. I feel if we had a label we could begin to have more of a voice. What are your thoughts?"

The medical community already has a label and that label is "unaffected carrier." When one thinks about this label, however, it does not begin to touch on the experience of this person or the community from which the person comes, but it does illustrate a recurring theme. The theme is that it is important to engage the stakeholders, not just in research, but also in developing the questions and the framework for the future of genomics.

Genomics is beginning to bring understanding that everyone is at risk for something based on their genes. As attention moves from disease treatment to disease prevention, many more participants, particularly healthy participants, will need to be involved in endeavors such as biobanks. Public input does affect funding priorities, and input from potentially affected communities can help keep research relevant, culturally appropriate, and sensitive to the community's needs.

An educated public that understands and supports the application of genomics and public health is needed. Such a public can be very effective

in helping generate much necessary legislative and financial support. The lack of public education efforts is not intentional. Rather, the focus has been on trying to educate the educators and the medical community. Although it is important to educate those groups, we should begin now with efforts aimed at educating the public.

Using what has occurred in the breast cancer community, it is important for the medical and research communities to understand that the source of some of the public's knowledge about medicine comes from consumer groups. It is as important to educate these consumer groups as it is to educate the medical community. Consumer groups are now being educated and funded by some of the same companies that are conducting direct-to-consumer marketing of genetic tests and products, which brings to the fore questions of conflict of interest. Furthermore, there is often a bias in the advocacy community against genetics. The following quote from someone attending a workshop on hereditary cancer was chosen to provide insight into the issue of conflict of interest: "As we all sat poised to focus our full day on genetics and how the study of it has shifted our paradigm for addressing epidemics, I was faced, not for the first time, with the disheartening reality that hereditary susceptibility accounts for no more than 3.5 percent of breast cancer cases. So, no matter how illuminating the findings, no matter how fantastic the progress in the field, our efforts will only apply to a minuscule percentage of women diagnosed with breast cancer. After the decades and dollars funneled into genetic research, almost 97 percent of the mysteries would remain. With this realization setting the tone for the day, I resign myself to concentrating on a fraction of the problem."

Professional societies must rise to the challenge of becoming more involved in advocacy training and advocacy oversight. Efforts might include developing mentorship programs like the Scientist to Survivor Program of the American Association for Cancer Research; organizing workshops with a specific consumer focus, not just a disease focus, in order to encourage attention on prevention, not just cure; developing mechanisms to share research outcomes with advocacy groups; and developing laws that preempt concern about genetic discrimination.

The time to educate and involve consumers was yesterday—we are late, but not too late.

Judith L. Benkendorf, M.S., C.G.C.

A major question is whether the current genetic counseling model, which focuses on helping individuals and families make informed autonomous choices, can be applied to a population-based public health approach that values motivating individuals to change health behaviors

in order to improve the health of society. There are five basic steps to providing genetic services in the clinical encounter. The first is to determine the diagnosis or condition and, second, to assess the role of genomics in that condition. The third step is to assess the risk for the individual, the community, or the public. The fourth step is to educate the public about its options. Finally, individuals, families, communities, and populations must be assisted to clarify their values and make the best possible decisions.

Meeting the challenges of the 21st century requires balancing the duties to individuals and families with a commitment to addressing and advancing public health interests. To do so requires preparing the professional workforce. As Dr. Gebbie indicated, preparing the workforce requires knowing the competencies that the workforce must possess. A set of core competencies in genetics was developed by the National Coalition for Health Professional Education and Genetics (NCHPEG). This set is similar to and consistent with the competencies developed by the CDC and has to do with appreciating the role of genetics in public health, with understanding one's own limits, and with knowing where to find further information or assistance.

The current workforce of genetic counselors is quite small; there is one board-certified genetic counselor for every 157,000 Americans. In addition to genetic counselors, there are about 1,520 active M.D. and Ph.D. degree geneticists who are certified by the American Board of Medical Genetics, bringing the ratio to one certified genetics professional for about every 85,000 individuals in the United States. Additionally there are about 300 nurses who are members of the International Society of Nurses in Genetics (ISONG). The bulk of this workforce is in hospitals and academic medical centers, and these professionals spend a great deal of time teaching.

Eight percent of geneticists spend more than one day a week teaching, and almost 80 percent spend some time teaching, which further limits the time available for genetic services delivery. Those whom they teach include medical students and residents, genetics residents and fellows, graduate students, practitioners, and the general public. Fifty-six percent of genetic counselors also identified teaching as a primary role, providing information to the same groups as the geneticists.

A major problem is that, with the exception of genetic counselors, the genetic workforce is not growing. In order to meet future needs, it will be necessary to develop a partnership between the genetics and public health communities. Genetic integration into newborn hearing screening provides an example of how a partnership is needed. More than 50 percent of hearing loss has a genetic component, yet the screening programs are not housed within genetics programs. Initial screening does not usually involve geneticists, and few follow-up programs include these professionals.

Yet there are many emerging benefits of providing genetic information to families and for ongoing management. For the future, an integrated model for newborn hearing screening will need to answer many questions, including how genetic services will be delivered, where the point of entry will be for genetic involvement, who will be rendering genetic health care on the front line, how genetics and public health will build partnerships, and how the involved professionals will learn about each others' disciplines and roles.

GENOMIC INFORMATION AND ITS APPLICATION TO POPULATION HEALTH

Michael Liebman, Ph.D.

In general, for all of the issues raised at the conference, informatics needs to be considered from both a technology perspective and science perspective. There are many repositories of information and samples that are important scientific resources to recognize in this endeavor of using genomic information to improve the public's health. However, the problem faced at this symposium is much deeper. What does all the collected information mean in terms of understanding and predicting disease? How will the growing opportunities in the field of informatics help in organizing various information sources so that lessons from genomics can be quickly applied to improving the health of individuals and the population?

There are many scientific issues related to using information resources to affect population health. Assuming it is possible to determine how to measure and store genetic and genomic information, the key question then is how can disease be modeled using these many different sources of information? For example, in Nigeria, sickle cell anemia is a public health issue. Twenty-five percent of Nigeria's population—almost 30 million people—are affected by sickle cell anemia, and there is no early detection and almost no treatment other than what might be associated with local medical procedures. From a population health perspective, the many patients that survive into their forties and fifties bring to light the issue that sickle cell does not present as a single disease but as a set of different diseases. In this case, even what is known to be a clear genetic disease is affected by modifier genes, environment, lifestyle, or other factors that make this a multifactorial or multigenic disease. Modeling disease is difficult because of the differing types and amounts of data that are being generated from a variety of sources. Despite the generation of enormous amounts of genomic data and now proteomic information, sequencing

information, and expression information, the problem is that the data generation tends to be from a technological perspective as opposed to a scientific perspective. These data do not immediately translate into clinical utility. One of the major scientific issues today is how to close the seemingly widening gap between data, information, and knowledge in order to translate research into public health benefits.

A major challenge in using informatics to bring clinical, genomic, and protemic information together to translate into population health benefits is the lack of uniformity in the quality of the data. Review of protocols for data collection and information storage from a scientific perspective is critical to maintaining a basis for scientific investigation that will guarantee reproducibility and high-quality information from survey methodologies. This is also critical for being able to extract valuable information from databases about risk factors for disease, ensuring the appropriate allocation of resources, and studying only the problems that are real in the population.

Another major challenge is that the informatic resources now used—for example, PubMed—do not recognize a continuum of information but focus on classification of information as discrete states. For example, the medical subject headings (MeSH) or Unified Medical Language System (UMLS) systems are focused on this classification of information and do not facilitate gathering information for the modeling of disease processes. There must be awareness of the underlying architectures of the information systems and their limitations as attempts are made to bring multiple information sources to bear on an important problem area. The PubMed example is just one of many examples where the utility of the information is compromised by its architecture.

One of the biggest challenges encountered in bringing clinical and genomic data together is the difficulty of modeling all the components of a disease and its impact on the public's health. From a data perspective, there is a need to consider the history of risk exposure and the clinical trajectory of a person in his or her genetic risk, early detection and stratification into a disease subtype (i.e., reflecting the stages of the natural history of disease), treatment options (e.g., pharmacogenomics), outcomes, and quality of life. It is important to recognize that when a patient presents to a physician they are in a slice of time reflecting multiple perturbed processes, only some of which are reflected in symptoms that are being reported and result in a diagnosis being made. This temporal issue is currently ignored when examining population health. Patients must be synchronized by the different stages of disease as they present in a clinic visit. This can be done by collecting and examining all the other disease parameters that the patient presented (e.g., life history events, previous clinical events, risk factors). Without the ability to synchronize patients,

there is no ability to accurately define phenotypes or subtypes of the disease. It is necessary to collect this type of data and treat all of the interactions between factors in a longitudinal manner so that it is possible to start to refine or identify which of these elements are critical and should be prioritized for general screening. It is critical to compare instances of exposure to the stages of disease development.

Data from patients over their lifetimes are needed to model the stages of disease development and determine the interactions among genetic, biological, and environmental factors. Self-reporting is a problem, but by developing some common mechanisms for recording information over a lifetime, it is possible to begin to determine how, for example, the risk of obesity or risk of smoking has differential effects at different times or at different ages. This will enable the linking of information to population health problems. Furthermore, information can be more accurately conveyed to individuals and education more appropriately targeted, for instance, by teaching that smoking at certain age intervals is more critical than at other age intervals.

One of the fundamental problems in integrating information to serve the public good is that there is not a mandated state-by-state harmonization or normalization of data. For instance, Pennsylvania recently commissioned a consortium of all cancer institutes within the state to integrate all cancer data across cancer institutes. Some major cancer centers do not generate registry data and those that do have registry data do not necessarily have data that is compatible with data from other centers. The kinds of data in registries and other public sources need to be brought to a level that can be integrated and serve the public good. Another example of the impact of standardization of information comes from a population study of kidney transplantation funded by the National Institute of Allergy and Infectious Diseases. In the kidney and renal transplant databases, we found that only 90,000 records in a database of 1.3 million people could be used in the analysis because of the way that the claims data had been collected. This indicates the magnitude of the problem of data heterogeneity and the need for public health informatic initiatives.

Assuming an eventual understanding of the genetics and genomics of disease, then it is important to anticipate next steps. Modeling of complex disease processes in people from a time-dependent point of view is essential. It will be necessary to create informatic systems that focus on the person and not just the basic research information typically derived from genomic or proteomic studies. Rather than personalized medicine, it is important to think about population-based medicine.

During the question-and-answer session, several points were made. The public health infrastructure at the state and federal levels has made important contributions that can contribute to the field of genomics and

its applications to improve the public's health. For example, assessment, one of the core functions of public health, provides good examples of use of information and data on populations. Furthermore, public health is taking a leadership role in moving relational databases, setting standards, and gathering public health information. Public health already has many population-based databases such as vital statistics, the cancer registries, and disease registries. In addition, it has household surveys (e.g., Behavioral Risk Factor Survey) that could include information on what people know about genetics, health behavior, use of genetic services, and so on.

There is a large movement to link public and private information under the confidentiality regulations of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Bioterrorism resources have enhanced the sharing of information across clinics, hospitals, and physicians. This revolution in information sharing and informatics will help mesh public health information systems and genomics in order to improve the public's health. In addition, the President of the United States has declared that the country will have electronic medical records within the next decade. Work on standards has begun, led by the CDC in the development of NEDSS (the National Electronic Data Surveillance System) and PHIN (the Public Health Information Network). In summary, the public health infrastructure and public health professionals have begun to incorporate informatics principles and tools to monitor and improve the health of the public. These efforts, which would be greatly advanced by an infusion of money and other resources, are poised to help with implementing the lessons of genomics research into public health practice at the local, state, and federal levels.

FINANCING AND ACCESS

Marc Williams, M.D.

There are many health care systems in the United States. There are managed care organizations of several types—for profit, not-for-profit, or self-funded—some of which operate a prevention model. A large number of individuals are insured through the indemnity model, which is essentially catastrophic coverage from which prevention is usually excluded. The government also provides Medicaid, which does cover some preventive services, but that coverage has focused more on women, children, the disabled, and the young indigent. The Medicare population is now being divided into the traditional fee-for-service systems, where preventive services are specifically excluded from coverage unless legislated by Congress, and managed care Medicare, which does have the latitude to cover

prevention unless it is specifically prohibited by law or rule. Finally, there is a large segment of the U.S. population that has no third-party coverage.

These payers have concerns. They want to know when genomics will be important, what it is going to cost, what the value added will be, whether testing will affect patient behavior, what the time frame for return on investment is, and whether there is a capable provider network. The answer to all these questions is that no one knows. Payers have to consider a number of factors: Medical care costs are escalating, new pharmacy is expensive, and new technology costs more and is additive (old technology is not eliminated when new is added). Payers must try to determine where to draw the line in terms of what is offered to an individual: Is it complete ascertainment, which is going to cost more, or is it what is reasonable for a population?

Two current programs can help us think about the financial and access questions surrounding integration of genomics into health care: newborn screening and population carrier screening. Newborn screening began in the 1960s, incorporated new technologies that became available, is a public–private interaction, is present in all 50 states (although the number of disorders screened for ranges from as few as 3 in some states to more than 60 in others), and is considered a successful program. Criteria for newborn screening require that disorders have a high relative frequency in the population; in addition, tests must be easy, inexpensive, reliable, and able to be performed on a blood spot. The tests have to have acceptable positive/negative predictive value, and effective treatment or cure must be available. Disorders that meet all the criteria and are tested for include phenylketonuria (PKU), galactosemia, congenital hypothyroidism, and congenital adrenal hyperplasia (CAH).

Selected population screening is also conducted, for example, Tay-Sachs, sickle cell carrier screening, and screening for Down syndrome in pregnant women of advanced maternal age. In this setting more problems begin to arise. It is sometimes the case that solutions involve highly charged issues; for example, the decreased incidence of Down syndrome in this country has been achieved by termination of affected pregnancies, which some find to be unacceptable intervention. Some insurers pay for testing only if a woman pledges to terminate the pregnancy. Other insurers are paying for pre-implantation genetic diagnosis in order to implant only those embryos that are known to be unaffected.

There is also the problem that screening is extended, sometimes because of political or legal pressures, to disorders for which interventions are less effective. Lawsuits are also being used to try to expand screening. For example, the parents of a child who died of MCAD (medium-chain Acyl-CoA dehydrogenase deficiency) are suing the state, claiming that

the child could easily have been screened for this disorder but was not screened, and as a result the child died needlessly.

Payment for screening is a blend of public and private funds that varies from state to state. Furthermore, in most states payment for follow-up treatment is provided by third-party payers, which can be problematic if treatment includes one of the standard insurance exclusions, for example, dietary supplements or hearing aids. There is great concern about the potential for discrimination. However, there have been no well-documented cases of genetic discrimination in health insurance, and many state laws already prohibit such discrimination.

In summary, it is important to recognize that rather than a well-organized health care system, what exists is complicated and includes multiple systems and multiple payers. Payers do not know what to do about genetic testing. They need a paradigm for screening that includes high relative frequency in the population, and they need easy, inexpensive, and reliable tests that can be performed on a blood spot or maybe a multiplex chip. Payers also want these tests to have acceptable positive and negative predictive values, and they want effective interventions or treatments. What payers are likely to get is pressure from industry to implement tests before answers are known, political coverage mandates, and pressure from consumers and lawyers that will result in increased cost with minimal increased benefit.

LEGAL AND REGULATORY

Ellen Wright Clayton, M.D., J.D.
with the assistance of Julie Schreiner-Oldham

The focus of this section is to identify legal and regulatory barriers to ensuring optimal use of genomics to improve the health of the public, specifically in the areas of surveillance, assurance, and policy development.

The provisions of HIPAA and the new interpretation of the Common Rule by the Office of Human Research Protection (OHRP) permit most surveillance activities. A number of states have passed genetic privacy laws that can be more stringent, yet they are often tempered by the state's desires to obtain information for public health purposes.

During this workshop, much has been said about the incredible importance of research that uses large databases with well-characterized clinical and exposure information. This past decade has seen much discussion about the ethical and legal controls for this type of research. Two months ago, however, OHRP issued a new guidance saying that if inves-

tigators have access to coded information that they believe cannot be traced back to an individual, then that information is not covered by the Common Rule; there need be no Internal Review Board (IRB) review even if the researchers abstract the information from an identified medical record. Furthermore, OHRP stated that because such research is not subject to IRB review, they recommend that health care institutions identify someone or some entity that would assure the coding was actually done in a way that protected the privacy of individuals. However, the OHRP exemption does not apply if one is creating a repository for research purposes, thereby creating incentives to use a hospital database or clinical record because it will be easier.

This OHRP guidance is a radical change that presents us with two major problems. First, individuals want to know when information about them is being used and, more importantly, they want ethical oversight. The change will undermine public trust in a major way. Second, good phenotypic information is important. However, all clinicians know that information in a clinical record is not very good; there are many mistakes. Given that this new guidance will move us toward using hospital pathology samples and clinical information, our data will not be as accurate.

Major problems exist in ensuring the appropriate use of genomic information. There is a long history of efforts to create guidelines for testing: the Watson/Holtzman committee of the mid-1990s; the Secretary's Advisory Committee on Genetic Testing (SACGT), which was dissolved and replaced by the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS); the efforts of the Institute of Medicine; plus the efforts of various professional groups such as the Cystic Fibrosis Foundation and the American College of Medical Genetics (ACMG). However, efforts to develop enforceable guidelines for the use of genetic tests have repeatedly failed.

A major issue is ensuring that information about genetic variation is used in ways that improve the health of individuals and the public. Furthermore, regulators need access to information about the impact of genetic variation. For example, if companies have pharmacogenetic information, they need to submit such information to the Food and Drug Administration (FDA). Finally, patients and providers must have access to reliable data about genetic tests. Currently there is a great deal of bad information and false and misleading advertisement. The FDA has declined to regulate in this area even though it has been urged to do so on many occasions. The result has been a proliferation of direct-to-consumer advertising and even sales.

Both litigation and advertising to providers have fueled demand for genetic information. However, in some cases, tests simply are not commercially available. In other cases, tests may be costly as a result of intel-

lectual property claims or are not covered by third-party payers. Furthermore, without major changes in the legislative background, it will be impossible to obtain uniformity in insurance coverage for genetic testing. At the same time, individuals' interest in using genetic tests has been dampened by fear they will suffer discrimination if they learn about their genetic makeup.

Can the law require that people use genomic information for health promotion, for example, information about a susceptible worker who will be made sick by going into the workplace? Important issues in this instance are the validity of the information, who receives the information, and who gets to decide what to do in response to the information. Does the employee get to decide, or the employer? The fact is that genomics will enable us to stratify, and the risk of stratification is always that the information will be used in ways that are socially unacceptable or discriminatory. Although many assert that genetic discrimination is not a major problem, it has not been easy to address in the legislative arena. The result is a patchwork of policies that are not consistent either internally or with each other.

The legal and regulatory framework exists to explore the impact of genetic variation on health and disease. However, more work needs to be done to ensure that providers and patients have access to clinically useful tests and accurate information. Furthermore, it is necessary to create a system in which people feel free to use this information to improve their health and to define the conditions under which third parties can appropriately use this information to constrain individual choice.

Overall, what is needed are efforts to address problems from a systems perspective, recognizing that the dilemmas posed by genetics are not unique, but rather intersect with and parallel many of the great debates currently going on in our society about how to treat others.

COMMENTARY

Ruth Katz, J.D., M.P.H.

Genomics promises to be both exciting and complex for the field of public health over the next several years. What happens in genomics and public health will be determined as much by what policy makers do as by what genomic researchers and other experts discover. But not one of the panelists in this workshop is a policy maker who will be involved in making many of the decisions on issues such as medical coverage, access to care, confidentiality, FDA regulation, discrimination, training of public

health officials, public information campaigns, and genomic-related research.

The development of the integration of genomics and public health presents a rare opportunity to involve policy makers from both the federal and state levels. It is important to make sure that policy decisions are based upon data and real science. Rushing to judgment, including judgment about providing funding for research, is not appropriate. Policy makers should not repeat some of the problems associated with bioterrorism funding, that is, providing public health departments with money for genomics, but taking away much-needed funds from other important public health activities.

Policy makers must be involved from the beginning in all discussions and debates. We heard previously that public health professionals need training in genomics. So, too, do members of Congress, members of state legislatures, and other policy makers so that they can be better prepared to deal with the myriad complex and difficult issues facing the integration of genomics and public health. Like all potentially controversial advances in public health, this issue will need real champions in the policy-making arena.

There can be no doubt that policy makers will influence this field as much as any other type of player. They must be invited to the table as soon as possible, because public health champions today are very hard to come by.

Judith Feder, Ph.D.

At the same time that genomics has an enormous potential for expanding what is known about disease and about what can be done for people to improve our health as a population and individually, it also has the potential to increase inequities in our society and in access to health care, in part because of our voluntary insurance system. Testing provides information that, in this voluntary insurance market, can cause harm. Given the way our system operates, increased costs threaten cuts in benefits and coverage, thereby decreasing access to care.

Employer-sponsored health insurance is the way most Americans obtain health insurance. Although employers cannot explicitly discriminate against an individual in terms of health insurance based on an individual's disease, they can discriminate in terms of whom they employ. They can make employment conditions untenable for certain kinds of people, and they can manage company health insurance in ways that make it difficult for people who have health conditions to obtain the care they need.

The more pressure there is and the more legitimacy there is to testing and to technology in general, the more likely it is that our health care costs

are going to rise. Employers are already increasing the amounts individuals must pay out-of-pocket for health insurance. They are reexamining their formularies to determine the kinds of prescription medications they will or will not offer, thereby making it difficult for individuals with certain conditions or medication needs to find adequate insurance.

Even greater problems arise with insurance obtained outside employer-sponsored plans. Insurers want to make a profit: maximizing the premiums paid while minimizing the benefits distributed. In the small-employer market, there are real risks to insurers knowing what one's health status is because either one pays more, insurance is unavailable, or insurance is available but not for any body part that might remotely be affected by the gene or any other preexisting conditions. There is shrinking availability of insurance, so employers cut benefits. Individuals who are likely or believed likely to be susceptible to illnesses that are expensive to treat have difficulty obtaining coverage. Furthermore, such discrimination is not necessarily based on hard science.

Medicaid, which covers some but not all poor people, is a "squeezed" program with variation from state to state in the services it provides and criteria for eligibility. As costs rise, many states are trying to determine how to cut back their benefits. Therefore, even if Medicaid covers genetic tests, recipients will not benefit unless they can also obtain treatment under the Medicaid program.

Of course the 45 million to 50 million uninsured will not have access to anything. The more health care costs rise, the more we are going to see a shrinking in the affordability of health insurance, resulting in an increase in the numbers of people without insurance.

In summary, there is a problem because there is not full access to health care. Without full access for everybody, including the poor, disparities will increase. Many believe that insurance coverage for everyone is affordable without additional investments, that it is a matter of finding the will to provide such coverage. Providing such coverage would require a perspective change from one in which each person fends for himself to one that recognizes that everyone is in this together.

LESSONS LEARNED, PLACES TO GO

James G. Hodge, Jr., J.D., L.L.M.

The challenges identified during the workshop are significant and include those that are conceptual, legal, ethical, political, cultural, economic, organizational, and clinical. The presentations looked at these challenges through varying disciplinary approaches, including internal

medicine, biochemistry, psychiatry, genetic counseling, public health science, public health practice, biotechnology, law, ethics, economics, philosophy, psychology, and sociology. The varying tools used for interacting and intervening at the intersection of public health and genetics include the principles of science, research, practice-oriented methods, education, counseling, law and ethics, economics, technology, and informatics. All of these come together at the intersection of public health and genetics.

Interconnected factors must also be considered. Human genomics is significantly interconnected with proteomics, non-human genomics, and ecogenetics. There are also interconnected factors related to genomic information in general: nutrition and metabolism, the varying diseases and behaviors that people contribute to their potential susceptibility to a genetic condition, environmental exposures, and medications. Each of these factors must be systematically examined and understood in order to devise plans for connecting public health and genetics.

Clinical medicine, public health practice, and pharmaceuticals are also relevant. A failure in any particular area or a lack of resources or lack of opportunity affects the other areas. Finally, within public health itself, interconnected factors include core services, surveillance and research methods, vaccination policy, testing, screening, epidemiological investigations, and education. Education is only as good as the surveillance accomplished. Research is only as effective as the information obtained through our epidemiological investigations. The interplay of factors is important.

There are a series of critical observations and goals that pervade our collective disciplines that justify our tools and interventions. What is at present known about the science of genetics and genomics and proteomics and ecogenetics is quite impressive. We have made tremendous strides. However, what knowledge is needed to use genetics effectively to protect the public's health remains uncertain.

What is currently perceived as a good idea is identification of a single "biomarker," an identified genetic susceptibility that may work or may benefit a particular individual. But that is not what is needed in terms of the future for public health. Multiple factors and multiple interactions must be examined. Understanding must come in terms of whole populations, not just one individual. What a few know concerning the potential for genetics in public health is what, in the future, others must know, especially those people who can benefit from the advances being made.

Critical observation tells us that money can often influence objectives and interventions, but allocating resources to inappropriate or inefficient programs must be avoided. Resources must be allocated as equitably as possible. Genetic testing that is available to some because of wealth or

insurance benefits should be available to all. Finally, the concerns of many individuals (e.g., protection of sensitive identifiable genetic information) must be addressed responsibly.

With these multiple challenges, tools, interventions, observations, and goals, what must be done to develop meaningful plans and to translate possibilities into realities? We must assess our present knowledge, resources, and capacity.

This workshop has provided key lessons in five major areas: genetic science; genetics and public health; genetics, information, and behaviors; public health infrastructure; and ethical, legal, and social issues.

The genetic science lesson is that the genetics revolution has produced a wealth of new information. Scientific and technological advances in genetics, proteomics, comparative genomics, ecogenetics, toxicogenomics, bioinformatics, and computational biology have the potential to improve public health outcomes. How can the potential be marshaled? Causality is complicated; multifactor components underlie virtually all genetic conditions. Predicting the functional effect of various genetic sequences is critical, but again complicated. Additional research is essential to further identify and validate genetic variants.

What key lessons have been learned about genetics and public health? One thing is to suggest that the framework for genetic risk assessment for population health research definitely requires three elements: risk identification, risk characterization, and risk reduction. Community-based participatory research can contribute to widespread knowledge and awareness. Progress is being made to identify and prevent gene–environment interactions with correlating benefits. Continued research, funding, and education enhance the ability of public health authorities to incorporate genetics into public health. Existing public health approaches to genetic diseases (e.g., population screening, universal diagnosis) can at times be inappropriate or inefficient. The ability to address these issues in a cost-effective way will be critical.

In genetics information and behaviors, we have learned several key lessons. Primary care is critical to delivering genetic services to individuals and the population. These services are not, for the most part, going to be delivered through public health. The health care sector is an important partner in this endeavor. Furthermore, we lack the necessary information and research to make evidence-based decisions about the use of genetic tests. Cost-effectiveness analysis involving an assessment of opportunity costs can help determine whether a genetic intervention is either over- or underutilized. Lack of integration of genetic technologies into clinical and public health settings affects the cost-effectiveness of genomic medicine. Individual medical behaviors are the most important factors in public health improvement, and yet much remains to be learned about how to

influence personal behavior. Linked, multi-part interventions are needed to promote positive behavioral changes. Genomics will expand the opportunities and widen the disparities. As Dr. Foege indicated, there will be unbelievable opportunities and unbelievable inequities.

Our discussion of the public health infrastructure also brought forth some key lessons. Assuring the conditions in which people can be healthy is an objective of an ecological model for public health. Genetics underlies the essential services and functions of the public health system, it pervades everything done in public health, and it cannot be ignored. The heterogeneous public health system is, unfortunately, not organized to accomplish goals in genomics and public health; it is not tailored to providing essential services to the population in an equitable fashion. Biobanking offers significant benefits for understanding the contribution of genetic variation to health and disease, but the lack of harmonization and legal, ethical, and social complexities inhibit its full development. Public attitudes concerning genetic research are affected by public confidence, perceptions of utility, moral beliefs, and terminology.

Furthermore, the capacity for public health genomics is closely tied to the competencies of the members of the public health workforce and academia. Significant genetic data collections arising from technology do not necessarily offer direct benefits for public health practice. Finally, financing for the provision of genetic tests and services is challenged by payer concerns and mindsets, as well as limitations in existing tests.

There are important lessons about ethical, legal, and social issues for genomics and public health. Significant concerns exist regarding information privacy and discrimination. The protection of disease-specific groups and other vulnerable groups is not significantly addressed in laws. The HIPAA Privacy Rule, which applies to identifiable genetic data, allows public health authorities to collect such data for public health purposes. There are significant additional issues in genetic privacy, such as the duty to warn, that are increasingly being addressed through litigation. The recent statement by the Office of Human Research Protection (OHRP) exempting human subject research using coded data from the application of the Common Rule could lead to broader epidemiological research without adequate consent or oversight and could potentially undermine public trust. Laws can facilitate (and complicate) access rights of providers and patients to genetic test results. Fears of discrimination alone, regardless of realities, may sustain needs for affirmative antidiscrimination protections. Stratification invariably leads to distinguishing individuals from each other—the objective is to avoid invidious discrimination.

Well, where does one go from here? What should be explored in the future? One key issue is to unravel the advances in genetic science and research to identify clear objectives for public health. The application of

these advances must be enhanced for public health methodology and practice. Another major issue to explore is the assessment of infrastructure improvements that are essential to integrating genetics into public health. Additional issues include

- Funding and development of genetic, medical, and public health research to support and measure improvements in public health outcomes.
- Melding social and behavioral research and methods into public health genetics.
- Bridging health care and public health practitioners (and others) within the intersectoral public health system.
- Developing techniques for integrating genetics into public health practice that overcome challenges of limited funding, technology, and knowledge.
- Assuring access to public health genetics in ways that are equitable and sensitive to existing health disparities.
- Translating genetic information within and outside public health programs.
- Building public trust for public health genetic data collections through attention to culturally relevant factors and complex legal and ethical issues.
- Developing effective public education on public health genetics through specific objectives, targeted audiences, multiple channels, and sufficient exposures.
- Assuring that the public health workforce and its partners are capable of using genomics in real practice settings.
- Innovating to develop enhanced collections of longitudinal medical and genetic data to support multiple clinical and public health initiatives.
- Recognizing the effect of fiscal realities that suggest underwriting of existing genetic testing, pharmaceuticals, and services is limited.
- Reformating the legal regulatory framework to address issues in public health and genetics:
  - — Ensuring greater access to genetic tests.
  - — Mobilizing individuals to use genetic information for individual and communal health.
  - — Defining the conditions for third parties to use identifiable data.
- Engaging further review and study of these and related issues at the intersection of public health and genetics through roundtable discussions, full committee reports, or other long-term efforts.

There are several conclusions to be made from what has been presented during these past two days. First, the idea of benefits and risks pervades everything. What are the benefits and what are the risks? There

are no easy answers, but there is methodology available to begin to provide answers. Second, there is the promise of genetics, and there is the reality. Realistic ideas for the future are needed. Third, there is the debate about exceptionalism. Should things be done in an exceptional manner for genetics or can lessons be learned from other legal frameworks, other ethical norms, other public health sciences?

Finally, the current status of the genetic revolution has been compared to the germ theory ideas of the early 1900s. Right now is the time, because of heightened public health awareness in this country, to marshal this revolution for the benefit of the health of the public. The opportunity exists to achieve the desired end: measurable improvements in public health outcomes through the use of genomics.

3

Priorities

The international scientific community sequenced the human genome in 2001, thereby commencing the long and arduous task of understanding the relationships among variation in genes, environmental exposures, and human health. To date, most of the benefits of advances in genomics have been cast in individual terms, focusing primarily on clinical decision making, health care policy, and bioethics. There is, however, another important aspect of genomic science that has the potential to powerfully affect the health and well-being of populations. Known as "public health genomics," this emerging field assesses the impact of genes and their interaction with behavior, diet, and the environment on the population's health. The promise of public health genomics is to have practitioners and researchers accumulating data on relationships between genetic traits and diseases across populations, to use this information to develop strategies to promote health and prevent disease in populations, and to more precisely target and evaluate population-based interventions. Public health genomics is an exciting, multidisciplinary field that brings all the public health sciences to bear on the emerging challenge of interpreting the significance of genetic variation within populations and applying that knowledge in order to improve the health of the public.

Despite the vast promise of public health genomics, there is still much that must be understood before key strategies can be implemented. Our understanding of the science of genomics is incomplete, and a great deal of data gathering, statistical assessment, and research is necessary to assess the interrelationships among genes, the environment, behavior, and population health. Furthermore, there is a need to address potential health

disparities in the application of genomic knowledge and to ensure that all population subgroups have access to the benefits of genomics. No less important are the social, legal, and ethical problems that may accompany any significant application of public health genomics to the real world. Thus, while the potential for improving the public's health is enormous, the obstacles are currently equally substantial.

The workshop, "Implications of Genomics for Public Health," outlined many important issues and challenges to realizing the benefits of genetics and genomics for the public's health. Dr. Gilbert Omenn, the first keynote speaker, provided a vision of the future for genomics and public health. He described key challenges, available resources, and recommendations for policies and approaches. On the second day of the conference, the keynote speaker, Dr. Alexandra Shields, discussed the challenges of translating new knowledge into improved health in ways that benefit the entire population rather than increasing health disparities. Four panels, each of which was followed by a comment session, and a final workshop summation occupied the remainder of the agenda. The first panel provided an overview of the science of genomics, whereas the second panel addressed practice issues. On day 2 the opening panel examined the public health system, biobanks, education of the public, and public health workforce capacity. The final panel addressed genomic information and its application to population health, financing and access issues, and legal and regulatory issues. James Hodge, Jr., then provided a workshop overview of lessons learned and places to go.

After the conclusion of the workshop, committee members met to discuss each presentation and commentary and to identify and prioritize issues and approaches explored during the conference. The following presents the committee's deliberations and conclusions.[1]

The committee agreed that it is of primary importance to develop a coherent understanding of the scientific literature on genetics and its application to public health and health care. This requires the development of an approach to evaluating the scientific literature in order to set forth a framework for decision making about genetic evidence. Evidence can be used to motivate changes in practice, and therefore evidence is needed in the following areas:

[1]Time limitations precluded consideration of many important issues in the workshop discussion, for example, the importance of genomics to development, longevity, and physiological performance and capacity. Because this section of the report is necessarily based upon material presented in the workshop, issues not addressed in workshop presentations are not listed as priorities.

- Predispositions for the onset of disease, both discrete genetic conditions and complex, multifactorial diseases,
- Efficacy of treatments for people with diseases that have important genetic components,
- Behavioral and environmental interventions to reduce risk and improve health, and
- Cost-effectiveness of a broad range of clinical and environmental interventions.

It may be that an approach similar to that used by the U.S. Preventive Services Task Force and the Community Services Task Force could be used to evaluate evidence of effectiveness as well as cost-effectiveness. An approach to evaluating genetic tests proposed for use in general clinical settings would

- Focus initially on primary care;
- Choose clinical questions that have significant health consequences, are of relatively common frequency, have excellent analytic validity, and have effective interventions available;
- Develop analytic methods, including a specific literature search strategy, a way of assessing individual articles, a hierarchy of research designs, tools for assessing the quality of research, and specific links between evidence and graded conclusions; and
- Develop a coherent plan for communication and dissemination of findings.

Ideally, such evaluation would take place prior to the full use of interventions in the health care and public health systems.

Evaluation of the literature would also illuminate data gaps and the kinds of research that need to be conducted. Many types of research are needed—laboratory, basic research, population-based epidemiologic and behavioral studies, clinical trials, and effectiveness research based on use in clinical settings. In particular, a more clearly developed research agenda is needed to examine the relationship between the application of genomics and population health. For example, there are currently no studies that span the genome to proteome to metabolome, especially in populations. Currently research is either just genomics or just proteomics. Research is needed to enhance our understanding of gene–environment interactions, gene–gene interactions, and "omic" representations of biologic continuums of risk. In some ways this is the difference between thinking about genetics and thinking about genomics. Instead of thinking about and investigating one gene, the focus should be on the genome, then the proteome, and all

"omics." Research should include both large-scale and community-based participatory approaches.

We now know that the health of populations and individuals is determined by interactions among genes, socioeconomic circumstances, behavioral choices, environmental exposures, and medical care. Therefore, it is vitally important to conduct research on the interactions of these factors and their impacts on health. The results of such research would enable health care and public health practitioners to better support behavior change toward improved health outcomes.

Furthermore, there is a need to move from a focus on single-gene disorders to a new focus that addresses common complex diseases. Genetic heterogeneity must be considered in common complex diseases. A common disease phenotype may be caused by the action or interaction of a few to many genes, and in each case environmental factors may provide additional interactions. These interactions may lead to the same general clinical phenotype through many different mechanisms. The genomic approach is to stratify disease into different gene-based disorders as opposed to the public health approach directed at the common end point. It is now well known that allele frequencies for common polymorphisms in the genome can differ among ethnic groups, including disease-susceptibility alleles. Cultural practices and environmental factors may also vary among groups in ways that influence disease expression. Thus, the population burden of disease may also differ among these groups, even if underlying biological mechanisms of genetic susceptibility are the same. As a result of these two effects, preventive and intervention measures that also consider important cultural and behavioral characteristics of the population at risk may need to be tailored to specific groups.

Thus, the implications of genomics for public health require developing a new paradigm that stratifies the population into different risk groups based upon the effects of genes, gene–gene interaction, and gene–environment interactions involved in disease predisposition; these risk groups may or may not correspond to groupings based on ethnicity. This then leads to data gathering and bioinformatics[2] based upon the stratified populations, which in turn informs what the health care providers tell patients, what public health professionals tell the community, and the decision health care systems make in delivering care. In such a new paradigm, the messages are more complex and are stratified on the basis of groups. Combined with these opportunities is the need to be aware of and

[2]Bioinformatics is the collection, annotation, classification, storage, and analysis of high-dimensional biological information (e.g., genomic, transcriptomic, proteomic, metabolomic) using computers.

guard against an inappropriate use of subgrouping to increase or support existing disparities or to create new ones. A system should be created in which the population as a whole can use genomic information to improve health.

Moving from genetics to genomics, from single-gene diseases to complex diseases, and to a better understanding of gene–environment interaction requires change in the way we think about the health of individuals and the health of the population. For example, because of differences in frequencies of disease susceptibility alleles, there can be population differences in susceptibility to disease, while at the same time environmental factors may influence gene expression leading to diseases. Hypertension and G6PD deficiency in people of African ancestry is illustrative of this point; both genetic and environmental factors influence the disease. Parsing out the pieces has the potential to be a powerful aid to improving health. However, it is important to ensure that new knowledge about genomics and disease susceptibility in subgroups of the population is used to decrease health disparities, rather than allowing risk stratification to result in further discrimination and increasing health disparities such as those associated with racial groups. We need to create a system in which the population as a whole can use genomic information to improve health.

Change is also needed in the ways in which public health interventions and health information messages are delivered. Translational models must be developed and tested for delivering genomic information to public health practitioners, health care providers, and the public. It is necessary to learn how to tailor information and change behavior based on genetic information and to identify who is at risk, how to change risk, and how to target populations.

Additionally, current heuristic methods are no longer adequate to the task. Informatic support is needed for the clinician and public health practitioners who cannot draw upon a base of experience. In order to create the body of information, there must be databases that allow clinical experience to be captured and aggregated for new, more finely grained categories used for risk assessment, for example, analyzing what is genetic and what is environment, recognizing that both types of risk may present opportunities for intervention. For example, a child with PKU, a disorder that clearly results from genetic variation, is treated with a low phenylalanine diet, an environmental intervention, not gene transfer.

Educational needs in the area of public health genomics must be determined. What do clinicians need to know? What about public health researchers and practitioners? What do individuals in various risk categories need to know? Who needs to be educated about what and why? Effective mass media public education programs must be developed that

recognize the importance of language and negative attitudes. Effective public education requires

- Clear, specific objectives
- Targeted audiences
- Multiple channels
- Adequate exposure in a consistent way
- Behavioral research that incorporates the complexities of what we know about behavior change and the use of genetic information.

The best genomic information should be made available to the population to obtain the maximum population benefits in an equitable way. Mechanisms are needed to ensure that genetic information is used to reduce health disparities. Furthermore, it is important to determine what the legal system can do in terms of protecting against injustice and avoiding discrimination.

There are many lessons to be learned from existing large-scale database projects (biobanks). An important conclusion is that there needs to be more harmonization among these databases. Biobanks are a global public good, but there is a need for harmonization of systems, provision of safeguards that serve the public good but protect the community, and assurance that biobanks are organized, systematized, and searchable. Guidelines and tools for harmonization should be developed and should address the following questions:

- What is harmonization?
- What should biobanks look like?
- How should one provide adequate safeguards that facilitate operations but protect as necessary?

Finally there is the issue of the targeted use of drugs (pharmacogenomics). Such targeted use could facilitate analysis of current underuse, overuse, and misuse of drugs. Targeted and perhaps more limited use of drugs suggests new possibilities for cost savings and avoidance of drug–drug interactions and adverse drug reactions. It also raises the problem of generating adequate revenue to invest in expensive development of pharmacologic agents that are targeted at small populations.

In conclusion, the committee agreed with many of the speakers who pointed out that genomics holds the promise of providing great benefits for population health, yet also carries the shadow of vastly increasing health disparities if segments of the population are not able to access genomic technologies and services. As Dr. William Foege said, "The chal-

lenge to public health genomics is to overcome inequitable allocation of benefits, the tragedy that would befall us if we made the promise of genetics only for those who could afford it and not for all of society. Social evolution as a result of genomics will be what we want it to be, and now is the time to make our case."

Appendix A

Glossary

Acetaminophen: A crystalline compound, $C_8H_9NO_2$, used in medicine to relieve pain and reduce fever.[3]

ACMG: American College of Medical Genetics.

Allele: Any alternative form of a gene. Allelic variation in a gene arises through mutation of the DNA sequence defining the gene and may or may not be associated with trait variation (e.g., height, eye color). For example, if a particular DNA sequence is mutated from an A (adenine) to a G (guanine), then there are two alleles—an A allele and a G allele.

Allelic Heterogeneity: Different mutations of the same gene that produce similar phenotypes.

ASTHO: Association of State and Territorial Health Officers.

Biobank: A collection of biological samples and sample information organized in a systematic way for research purposes. Biobanks containing DNA samples have been set up in multiple countries to help identify genetic risk factors for disease and to understand the prevalence of these genetic mutations.

Bioinformatics: The collection, annotation, classification, storage, and analysis of high-dimensional biological information (e.g., genomic, transcriptomic, proteomic, metabolomic) using computers.

Biomarker: A biochemical indicator (e.g., cholesterol level) of an underlying disease risk factor or process.

Biometrician: One who specializes in the statistical analysis of biological observations and phenomena.[3]

Candidate Gene: A gene whose protein product is involved in the metabolic or physiological pathways associated with a particular disease.

Chemopreventive Agents: Chemical agents, drugs, or food supplements used to prevent disease.[3]

Clinical Utility: The degree to which a test alters medical management in a way that results in a net health benefit to the patients and is a function of the efficacy of an available treatment and the acceptance of the test by patients and clinicians.

Comparative Genomics: A field of research in which the genome sequences of different species such as humans, mice, and the fruit fly are compared to identify regions of similarity and difference.[4]

Competencies in Genomics: Professional standards of knowledge and ability to use genomics terms and concepts appropriately in practice. The CDC competencies in genomics are divided into three levels: those for all public health workers; those for all public health professional workers; and those in specialty or concentration-specific positions such as leaders/administrators, clinicians, epidemiologists, etc.

Continental Ancestry: Individuals whose ancestral origins are from a particular continent. Because the history of a mutation is dependent upon the geographic and demographic history of the people in which the mutation occurred, continental ancestry often provides a surrogate measure of the many mutations that occurred during the early part of human history and that now differ among the major ethnic groups.

DNA (Deoxyribonucleic Acid): DNA is the chemical substance associated with the biological heredity material passed down from parent to child. It contains adenine (A), guanine (G), cytosine (C), and thymine (T). It is present in the nucleus of almost all cells in an organism. The DNA molecule contains the coded information that cells need to produce proteins that govern all life processes.

Ecogenetics: The study of the interaction between the environments in our human ecology and the genetic variations within humans that influence the continuum between health and disease.

Epitasis: The masking of the phenotypic effect of alleles at one gene by alleles of another gene.[1] It is a term used to describe gene–gene interactions.

Ethnogenetics: The field focused on genetic variation in different populations. Ethnogenetics specifically looks at different populations with different genetic and/or environmental causes of the same phenotype.

Etiologic Heterogeneity: Differing causes of disease.

FDA: Food and Drug Administration.

Gene: DNA sequences that contain a code that can be translated into a particular protein.

Genetic Heterogeneity: A single phenotype that can be the result of mutations in several different genes

Genetic Knock-Out: Refers to experimental organisms where a particular gene has been deleted or manipulated so it no longer functions.

Genogram: A diagram outlining the history of the behavior patterns (such as divorce, abortion, or suicide) of a family's members over several generations in order to recognize and understand past influences on current behavior patterns; also a similar diagram detailing the medical history of the members of a family as a means of assessing a family member's risk of developing disease.[3]

Genome: The DNA sequence of all an organism's chromosomes.

Genomics: The study of the entire human genome. Genomics explores not only the actions of single genes, but also the interactions of multiple genes with each other and with the environment.

Genotype: People inherit one allele for a gene from each parent such that they have two copies of each gene. The pair of alleles defines a person's genotype. For a gene that has two alleles in the population (e.g., an A allele and a G allele), there are three possible genotypes—AA, AG, and GG.

GRAD: Genomic Research in African Diaspora.

Haplotype: A haplotype is an extension of the concept of an allele that pertains to multiple mutations along a chromosome. Specifically, it is the combination of mutations inherited that defines a haplotype. Consider a segment of the genome with three sites that vary among people: For an individual with a GG genotype at the first site, TA at the second site, and CC at the third site, the haplotype for that individual is GTC and GAC. This is the combination of genetic variations inherited separately from the individual's mother and father.

Haplotype Blocks: A haplotype block is a set of closely linked genetic markers that show low haplotype diversity because of high linkage disequilibrium. Identifying haplotype blocks may enable scientists to measure only a single mutation, rather than an entire set of mutations, in a genomic region that could be very important for expensive disease association studies. Haplotype blocks along a chromosome may be separated by regions of high recombination.

HapMap: A partnership of scientists and funding agencies from Canada, China, Japan, Nigeria, the United Kingdom, and the United States to develop a public resource that will help researchers find genes associated with human disease and response to pharmaceuticals. HapMap's goal is to ultimately develop a haplotype map of the human genome and identify haplotype blocks.

Heterogeneous Disorder: A disorder composed of subtypes with a spectrum of variable inheritance ranging from polygenic to monogenic inheritance.[6]

Heterozygote: An organism that has two different versions of an allele, for instance, one for blue eyes and the other for brown eyes.[5]

Heterozygous: A genotype in which the two copies of the gene are different.

HGRD: Human Genetic Research Database.

HIPAA: Health Insurance Portability and Accountability Act of 1996.

Homozygous: A genotype in which the two copies of the gene that determine a particular trait are the same.[4]

Informatics: The sciences concerned with gathering, manipulating, storing, retrieving, and classifying recorded information.[3]

IRB: Internal Review Board.

ISONG: The International Society of Nurses in Genetics.

Junk DNA/Non-Coding Region: A region of the genome where the DNA has no known function (i.e., it does not code for a protein, regulatory sequence, or other functional elements). These regions usually consist of repeating DNA sequences. The majority of the human genome has no known function; only 2 percent to 5 percent of the DNA sequence codes for genes.

Linkage Analysis: Traditionally, linkage analysis is the statistical analysis of the pattern of disease segregation and allele segregation in families to identify regions of the genome that may contain a gene causing the disease. There have been many extensions of this basic idea to try to identify genes for both common and rare diseases using genetic variations measured throughout the genome.

Linkage Disequilibrium: Occurs when the alleles at two different sites along a chromosomal region are correlated in their frequencies. Linkage disequilibrium can occur because a new mutation happens on a particular allelic background. Linkage disequilibrium can be detected by investigating whether observed frequencies of haplotypes in a population are equal to the expected frequencies when the alleles are not correlated.

Locus: The position of a gene on a chromosome. This term is a classical genetic concept used to understand gene order, gene distance, and gene function before gene and genomic DNA sequences were known.

Locus Heterogeneity: Mutations in different genes that produce the same phenotype. This term is synonymous with genetic heterogeneity.

Mendelian Disorders/Single-Gene Disorders: A disorder that is caused by mutations in a single gene (such as hemophilia), as opposed to polygenic disorders (such as hypertension) which involve the influence or interaction of several genes.[4]

Mendelian Inheritance: Named for Gregor Mendel, it is the pattern of inheritance of genes and chromosomes from parent to offspring. Mendel's theory of inheritance was biologically confirmed when meiosis was discovered. Meiosis is the process by which individuals create egg or sperm to carry half of their genetic material (i.e., one of each type of chromosome) to the next generation.

MeSH: The National Library of Medicine's controlled vocabulary thesaurus. It consists of sets of terms naming descriptors in hierarchical structure that permits searching at various levels of specificity.

Metabolic Profile/Metabolome: The quantitative assessment of all the low molecular weight molecules present in cells in a particular physiological or developmental state.

Microarray: In the most general sense, a microarray is an array of assays designed at the microscopic level that can be placed on a single solid base (e.g., a glass slide). Different microarray designs or platforms have been developed to type thousands of DNA mutations, gene expression transcripts, or proteins in a single individual.

Microarray Experiments/Gene Expression Array: A new way of measuring the expression of large numbers of genes simultaneously in a single individual or organism. Gene expression patterns (also known as profiles or signatures) are being used for everything from molecularly classifying tumors, to understanding gene regulatory networks, to identifying potential side effects of new drugs being developed.

Molecular Profile: A biomolecular (e.g., gene expression, protein, metabolite, chemical) pattern that is unique and associated with some specific biological context such as a tissue type, chemical exposure, or disease state. Synonym is Molecular Signature.

Molecular Signature: A biomolecular (e.g., gene expression, protein, metabolite, chemical) pattern that is unique and associated with some specific biological context such as a tissue type, chemical exposure, or disease state. Synonym is Molecular Profile.

mRNA: Messenger RNA, or a single-stranded molecule of ribonucleic acid that is transcribed from the DNA and then translated into protein.

Multifactorial Disorder: A disorder resulting from the contributions and interactions among multiple genetic and environmental factors. Most

common chronic diseases such as heart disease, hypertension, and diabetes are multifactorial disorders.

Multifactorial Inheritance: Multifactorial diseases aggregate in families but do not segregate in families as a single-gene disorder would segregate according to Mendelian inheritance patterns.

Multigenic Disorder: A disorder resulting from the combined influence of multiple genes.

Mutation: A mutation is a change in a DNA sequence. If the mutation occurs during the development of an egg or a sperm (i.e., gametes), then it becomes a heritable mutation. If the mutation occurs in any other body cell (i.e., part of the soma), then it is called a somatic mutation and it is not heritable. Somatic mutations are a cause of cancer. Mutations can be of many different types—substitutions, deletions, or insertions.

NCHPEG: National Coalition for Health Professional Education in Genetics.

NEDSS: National Electronic Data Surveillance System.

NHANES: National Health and Nutrition Examination Survey.

OHRP: Office of Human Research Protection.

Penetrance: The probability of developing disease (or some other outcome of interest) given that an individual has a particular genotype. The penetrance of a genotype is often estimated by examining the proportion of people with a particular genotype who develop the disease or outcome of interest.

Pharmacogenetics: The branch of genetics that studies the genetically determined variations in responses to drugs in humans or laboratory organisms.[3]

Phenome: The comprehensive representation of all phenotypes.[2]

Phenotype: A generic term used to describe attributes and characteristics of an organism—e.g., a biochemical phenotype, physiological phenotype, behavioral phenotype, or disease phenotype.

PHIN: Public Health Information Network.

Polygenic Inheritance: The inheritance pattern of a trait, such as height, that is governed by a large number of genes with variations that have small effects. Since each parent contributes half of their child's genotypic profile, polygenic inheritance predicts that the child will have a phenotype that is approximately the average value of the two parents.

Polymorphism/Polymorphic Variants: A mutation that is found at a frequency of greater than 1 percent in a population. All polymorphisms are mutations, but not all mutations are considered polymorphisms because they are not prevalent enough in a population. Single nucleotide polymorphisms (SNPs) are a class of polymorphisms being studied for their association with disease.

Population Based Cohort Study: A study where subjects are representative of the "at risk" population at large and are followed over time to determine the incidence of health outcomes. Often particular risk factors (e.g., genetic and environmental factors) are measured at the start of the study to determine if they predict who will and who will not develop disease.

Population Screening: The examination of a population of usually asymptomatic individuals to detect those with a high probability of having or developing a given disease.[3]

Prevalence: The proportion of a population that has a particular disease or health outcome at a particular point in time.

Proteome: The complete set of proteins found in a cell, tissue, or organism.

Proteomics: A branch of biology concerned with applying the techniques of molecular biology, biochemistry, and genetics to analyzing the structure, function, and interactions of the proteins in a particular cell, tissue, or organism.

PubMed: The U.S. National Institutes of Health (NIH) free digital archive of biomedical and life sciences journal literature.

RNA (Ribonucleic Acid): A chemical found in the nucleus and cytoplasm of cells; it transcribes the protein-coding instructions of DNA into a code that the protein-building ribosomes of a cell can understand. The chemical structure of RNA is similar to DNA—RNA also contains adenine (A), guanine (G), and cytosine (C), but instead of thymine (T), RNA contains uracil (U).[5]

SACGHS: Secretary's Advisory Committee on Genetics, Health, and Society.

SAGCT: Secretary's Advisory Committee on Genetic Testing.

SNPs (Single Nucleotide Polymorphisms): Currently, there is estimated to be about 6 million positions in the human genome where a mutation occurred at a single nucleotide (A, T, C, or G) and both its alleles are now greater than 1 percent prevalent in the population. These SNPs are important for studies of genetic or genomic associations with disease because the alleles are common in the population.

Toxicogenomics: A new scientific subdiscipline that combines the emerging technologies of genomics and bioinformatics to identify and characterize mechanisms of action of known and suspected toxicants.[2]

Transcriptome: The population of mRNA transcripts in the cell and their expression levels.[2]

UMLS (Unified Medical Language System): The National Library of Medicine project that develops and distributes multi-purpose, electronic "knowledge sources" And associated lexical programs for systems developers. Researchers find the UMLS products useful in investigating knowledge representation and retrieval questions.

Unaffected Carrier: An individual who carries a specific gene mutation allele but has not been diagnosed with the associated disease.

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Appendix B

Biosketches

Lawrence O. Gostin, J.D., L.L.D. (hon.) (*Chair*), is the John Carrol Research Professor of Law, Georgetown University; Professor of Public Health at Johns Hopkins University; and Director of the Center for Law and the Public's Health at Georgetown and Johns Hopkins. Previously, he served as Executive Director of the American Society of Law, Medicine & Ethics and as an Adjunct Professor at Harvard Law School and School of Public Health. He was also consulting legislative counsel to the U.S. Senate Labor and Human Resources Committee chaired by Senator Edward Kennedy.

Professor Gostin is on the editorial boards of several journals, and serves as law and ethics editor of the *Journal of the American Medical Association*. He has served on four Institute of Medicine (IOM) committees and is a member of the IOM Board on Health Promotion and Disease Prevention. Additionally, he has participated on the advisory committees of the World Health Organization, Centers for Disease Control and Prevention, National Institutes of Health, and UNAIDS. Professor Gostin was also a member of the President's Task Force on National Health Care Reform. From 1974 to 1985, Professor Gostin was head of the National Council of Civil Liberties, legal director of the National Association of Mental Health, and a member of the faculty at Oxford University. He received the Rosemary Delbridge Memorial Award from the National Consumer Council (U.K.) for the person "who has most influenced Parliament and government to act for the welfare of society." He also received the Key to Tohoko University for distinguished contributions to human rights in mental health after leading an International Commission of

Jurists delegation to Japan. He has successfully argued several cases before the European Court of Human Rights and has written the standard treatise on psychiatry and law in the United Kingdom.

Professor Gostin's latest books are *Public Health Law: Power, Duty, Restraint* (University of California Press, 2000); *Public Health Law and Ethics: A Reader* (University of California Press, 2002); *The Human Rights of Persons with Intellectual Disabilities: Different but Equal* (Oxford University Press, 2003); and *The AIDS Pandemic: Complacency, Injustice, and Unfulfilled Expectations* (University of North Carolina Press, 2004).

Melissa Austin, M.S., Ph.D., is Professor of Epidemiology at the School of Public Health and Community Medicine, the Director of the Institute for Public Health Genetics at the University of Washington, and a Joint Member at the Fred Hutchinson Cancer Research Center. She currently serves on the Advisory Council for the National Heart, Lung, and Blood Institute and was an established Investigator of the American Heart Association from 1994 to 1999.

Dr. Austin's research program focuses on the genetic epidemiology of chronic diseases and risk factors, including cardiovascular disease, diabetes, and familial forms of cancer.

Deborah Bowen, Ph.D., is an Associate Affiliate Professor of Psychology at the University of Washington, College of Arts and Sciences, and a Full Member in the Cancer Prevention Research Program of the Public Health Sciences Division at the Fred Hutchinson Cancer Research Center. The general focus of her research is on the implications of behavioral and social functioning at the level of the individual, small group, institution, or community for cancer prevention and control. More specifically, Dr. Bowen is interested in exploring the effects of community and of new technologies, including genetic testing and new communication technologies, on health outcomes and quality of life. She is active in the National Cancer Institute–funded Cancer Genetics Network.

Ellen Wright Clayton, M.D., J.D., is the Rosalind E. Franklin Professor of Genetics and Health Policy; Director of Genetics and Health Policy Center; Senior Fellow, Institute for Public Policy Studies; Professor of Law; and Professor of Pediatrics at Vanderbilt University. Dr. Clayton has been studying and teaching the ethical, legal, and social implications of developments in genetics for more than a quarter-century and has published two books and more than 75 peer-reviewed articles and book chapters. She has been an active participant in policy debates advising the National Human Genome Research Institute as well as numerous other federal and international bodies on an array of topics, ranging from issues in

children's health, including newborn screening, to the ethical conduct of research involving human subjects. In these roles, she has helped develop policy for numerous national and international organizations. She is a member of the Health Sciences Policy Board of the Institute of Medicine and recently served on the Committee on the Use of Third Party Toxicity Research with Human Research Participants of the Science, Technology, and Law Program.

Irving Gottesman, Ph.D., is the Bernstein Professor in Adult Psychiatry and Senior Fellow in the Department of Psychology at the University of Minnesota (UMN). Prior to his appointment at UMN, he served on the faculties of Harvard University, University of North Carolina, Washington University School of Medicine (Professor of Psychiatric Genetics), and University of Virginia.

Dr. Gottesman has written books on the genetic aspects of schizophrenia, which have been translated into Japanese and German. He was a Guggenheim Fellow at the University of Copenhagen and a MacArthur Foundation Fellow at the Center for Advanced Studies in the Behavioral Sciences (Stanford, California). He was elected Honorary Fellow of the Royal College of Psychiatrists in 1988 and received the 2001 Distinguished Scientific Contributions Award from the American Psychological Association. His interests include psychoses, personality disorders, genetic counseling for psychopathology, and assessment. He is Chair of the National Twin Register for the Institute of Medicine and also a member of the Board of the Medical Follow-up Agency.

Karen Greendale, M.A., C.G.C., is a board-certified Genetic Counselor and previous President of the National Society of Genetic Counselors. She directs the Genetics Program for the Bureau of Chronic Disease Services, New York State (NYS) Department of Health. She also directs the NYS Ovarian Cancer Education and Awareness Initiative and is involved in several projects relating to cancer survivors and survivorship. Her responsibilities include increasing awareness of the role of genetics in adult-onset chronic diseases such as various cancers, diabetes, cardiovascular disease, Alzheimer's disease, and the like. She has also been involved in numerous projects at the national level focused on integrating genomics into public health programs, including the Centers for Disease Prevention and Control's Genomics Competencies for the Public Health Workforce effort and two retreats for Chronic Disease Directors.

Sharon L. R. Kardia, Ph.D., is an Associate Professor of Epidemiology, Director of the Public Health Genetics Program, and Co-Director of the Michigan Center for Genomics and Public Health at the University of

Michigan, School of Public Health. Her main research interests are in the genetic epidemiology of cardiovascular disease and its risk factors. She is particularly interested in gene–environment and gene–gene interactions and in modeling complex relationships among genetic variation, environmental variation, and risk of common chronic diseases. She is also actively working on moving genetics into chronic disease programs in state departments of health.

David Nerenz, Ph.D., is a Senior Staff Investigator in the Center for Health Services Research at Henry Ford Health System in Detroit. Most of his current work is focused on the issue of racial and ethnic disparities in quality of care and on the ways in which health care organizations can reduce or eliminate disparities. He is also Director of Outcomes Research for the Department of Neurosurgery and the Neuroscience Institute at Henry Ford and is the site Principal Investigator for a national study of patterns and outcomes of care for patients with lung or colorectal cancer. Dr. Nerenz received his Ph.D. in Social Psychology from the University of Wisconsin–Madison in 1979. He has served on previous Institute of Medicine committees related to the health of Gulf War Veterans and HIV care.

Kenneth Offit, M.D., is the Chief of Clinical Genetics Service in the Department of Human Genetics at Memorial Sloan-Kettering Cancer Center. He is a medical oncologist with clinical and laboratory experience in cancer genetics. His research focuses on defining genetic factors that cause an increased susceptibility to cancer. Dr. Offit and colleagues identified the most common mutation associated with an increased risk of breast and ovarian cancer among individuals of Ashkenazi ancestry, and his ongoing research is aimed at defining new genetic risk factors and tailored interventions for families at hereditary risk for cancer. Dr. Offit served as a member of the National Cancer Insititute Cancer Genetics Working Group and is currently Chair of the Subcommittee on Cancer Genetics Education of the American Society of Clinical Oncology.

David L. Rimoin, M.D., Ph.D., is Professor of Pediatrics, Medicine and Genetics at the David Geffen School of Medicine at UCLA and the Steven Spielberg Chair and Director of the Medical Genetics Institute at Cedars-Sinai Medical Center. He received his M.D. from McGill University and his Ph.D. in human genetics from Johns Hopkins University. He has published over 350 papers in peer-reviewed journals and edited 11 books, including Rimoin and Emery's *Principles and Practice of Medical Genetics.* Dr. Rimoin has served as President of the American Society of Human Genetics and the American College of Medical Genetics Foundation, and was Founding President of the American College of Medical Genetics and

the American Board of Medical Genetics. Additionally, he served as Secretary/Treasurer of the American Federation for Clinical Research and President of the Western Society for Clinical Research and the Western Society of Pediatric Research. Dr. Rimoin is a member of the Institute of Medicine and served on the IOM Clinical Research Roundtable.

David L. Veenstra, Pharm.D., Ph.D., is an Assistant Professor in the Department of Clinical Pharmacy at the University of California, San Francisco. His primary research interests are the clinical, economic, and policy implications of pharmacogenomic-based drug therapies. His projects include studying the association between drug metabolizing enzymes and adverse drug reactions, estimating the cost-effectiveness of pharmacogenomic interventions, and evaluating the impact of pharmacogenomics on the health care system and pharmaceutical industry.

Dr. Veenstra also has significant experience in modeling chronic diseases such as diabetes, hyperlipidemia, hypertension, and hepatitis B and C. Recently, as part of an Academy of Managed Care Pharmacy (AMCP) educational program, Dr. Veenstra has been working with Pharmacy and Therapeutics committees to assist them in evaluating cost-effectiveness models submitted to health care plans by manufacturers.

Deborah Klein Walker, Ed.D., is a Principal Associate at Abt Associates in the Health Services, Research and Evaluation practice area. Before joining Abt Associates in 2004, Dr. Walker was at the Massachusetts Department of Public Health for 15 years, where she most recently was the Associate Commissioner for Programs and Prevention responsible for programs in maternal and child health, health promotion, and disease prevention (including the tobacco control program); primary care and community health programs (including those for HIV/AIDS and substance abuse); minority health; data integration; and information systems. Prior to state service, Dr. Walker was an Associate Professor of Human Development in the Departments of Behavioral Sciences and Maternal and Child Health at the Harvard School of Public Health and a faculty member at the Harvard Graduate School of Education.

Dr. Walker is Past President of the Association of Maternal and Child Health Programs and a former board member of the American Public Health Association. She is currently an Adjunct Professor at the Boston University School of Public Health and an Adjunct Lecturer at the Harvard School of Public Health. Dr. Walker's research and policy interests include child and family policy, program implementation and evaluation, public health practice, disability policy, community health systems, health outcomes, and data systems.

Liaison to Board on Health Promotion and Disease Prevention

George J. Isham, M.D., is Medical Director and Chief Health Officer for HealthPartners. He is responsible for Quality and Utilization Management, chairs the Benefits Committee, and leads Partners for Better Health, a program and strategy for improving member health. Before his current position, Dr. Isham was Medical Director of MedCenters Health Plan in Minneapolis. In the late 1980s, he was Executive Director of University Health Care, an organization affiliated with the University of Wisconsin–Madison. Dr. Isham received his Master of Science degree in Preventive Medicine/Administrative Medicine at the University of Wisconsin–Madison, and his Doctor of Medicine degree from the University of Illinois. He served his internship and residency in Internal Medicine at the University of Wisconsin Hospital and Clinics in Madison. His practice experience as a primary care physician included eight years at the Freeport Clinic in Freeport, Illinois, and three and half years as Clinical Assistant Professor in Medicine at the University of Wisconsin. HealthPartners is a consumer-governed Minnesota health plan formed through the 1992 affiliation of Group Health, Inc., and MedCenters Health Plan. It is a large managed health care organization representing nearly 800,000 members. Group Health, founded in 1957, is a network of staff medical and dental centers located throughout the Twin Cities. MedCenters, founded in 1972, is a network of contracted physicians serving members through affiliated medical and dental centers.

Staff

Lyla M. Hernandez, Study Director
Makisha Wiley, Senior Program Assistant
Rose Marie Martinez, Sc.D., Director, Board on Health Promotion and Disease Prevention

Appendix C

Workshop Agenda

Conference on Implications of Genomics for Public Health
National Academy of Sciences Main Building Auditorium

October 7–8, 2004

October 7, 2004

9:00 AM Welcome and Introduction
Lawrence Gostin, J.D., L.L.D., Chair

9:15 AM **Keynote.** Genomics and Public Health: A Vision for the Future
Gilbert Omenn, M.D., Ph.D.
University of Michigan Medical School

Panel Presentations—Each speaker will have 20 minutes for presentation.

9:45 AM The Science of Genomics and Its Application to Common Diseases
Aravinda Chakravarti, Ph.D.
Johns Hopkins University School of Medicine

10:05 AM Bridging Genomics and Population Health
Sharon Kardia, Ph.D., Member

10:25 AM Gene/Environment Interactions
David Eaton, Ph.D.
University of Washington School of Public Health and Community Medicine

10:45 AM **Comment—**Each person will have 10 minutes to comment.
Melissa Austin, M.S., Ph.D., Member
Sharon Kardia, Ph.D., Member
David Rimoin, M.D., Ph.D., Member

11:15 AM Question and Answer

11:45 AM LUNCH

Panel Presentations—Each speaker will have 20 minutes for presentation.

1:00 PM Clinical Use of Genomic Information
Alfred Berg, M.D., M.P.H.
University of Washington School of Medicine

1:20 PM Cost-Effectiveness Analysis in Decision Making
Scott Ramsey, M.D., Ph.D.
Fred Hutchinson Cancer Research Center

1:40 PM How Do People Use Information—A Continuum of Interventions
Ellen Gritz, Ph.D.
University of Texas M.D. Anderson Cancer Center
Susan Peterson, M.P.H., Ph.D.
University of Texas M.D. Anderson Cancer Center

2:00 PM How to Effect Change in the Population: The Gene/Environment/Behavioral Interaction
William Foege, M.D., M.P.H.
Emory University Rollins School of Public Health

2:30 PM BREAK

3:00 PM **Comment**—Each person will have 10 minutes to comment.
Deborah Bowen, Ph.D., Member
Kenneth Offit, M.D., Member
Nelson Freimer, M.D., UCLA Neuropsychiatric Institute

4:00 PM Question and Answer

5:00 PM Adjourn

October 8, 2004

8:30 AM Welcome
Lawrence Gostin, J.D., L.L.D., Chair

8:45 AM **Keynote:** Stratification, Justice, and Opportunity
Alexandra Shields, Ph.D.
Harvard University

Panel Presentations—Each speaker will have 20 minutes for presentation.

9:15 AM The Public Health System
J. Michael McGinnis, M.D., M.P.P.
The Robert Wood Johnson Foundation

9:35 AM International Lessons: Biobanks
Bartha Knoppers, Ph.D.
University of Montreal Center for Public Law Research

9:55 AM Education of the Public
Vicki Freimuth, Ph.D.
University of Georgia Grady College of Journalism and Mass Communication

10:15 AM Capacity
Kristine Gebbie, R.N., Dr.P.H.
Columbia University School of Nursing

10:35 AM BREAK

11:00 AM	**Comment**—Each person will have 10 minutes to comment. *Jean Chabut, M.P.H., Michigan Department of Community Health* *Sue Friedman, D.V.M., Facing Our Risk of Cancer Empowered (FORCE)* *Judith Benkendorf, M.S., C.G.C., Georgetown University Medical Center*
11:30 AM	Question and Answer
12:00 PM	LUNCH
	Panel Presentations—Each speaker will have 20 minutes for presentation.
1:00 PM	Genomic Information and Its Application to Population Health *Michael Liebman, Ph.D.* *Windber Research Institute*
1:20 PM	Financing and Access *Marc Williams, M.D.* *Gundersen Lutheran Medical Center*
1:40 PM	Legal and Regulatory *Ellen Wright Clayton, M.D., J.D., Member*
2:00 PM	**Comment—**Each person will have 10 minutes to comment. *Ruth Katz, J.D., M.P.H., George Washington University School of Public Health and Health Services* *Judith Feder, Ph.D., Georgetown Public Policy Institute*
2:30 PM	BREAK
3:00 PM	Lessons Learned, Places to Go *James G. Hodge, Jr., J.D., L.L.M.* *Johns Hopkins University Bloomberg School of Public Health*
4:00 PM	Question and Answer
5:00 PM	Adjourn