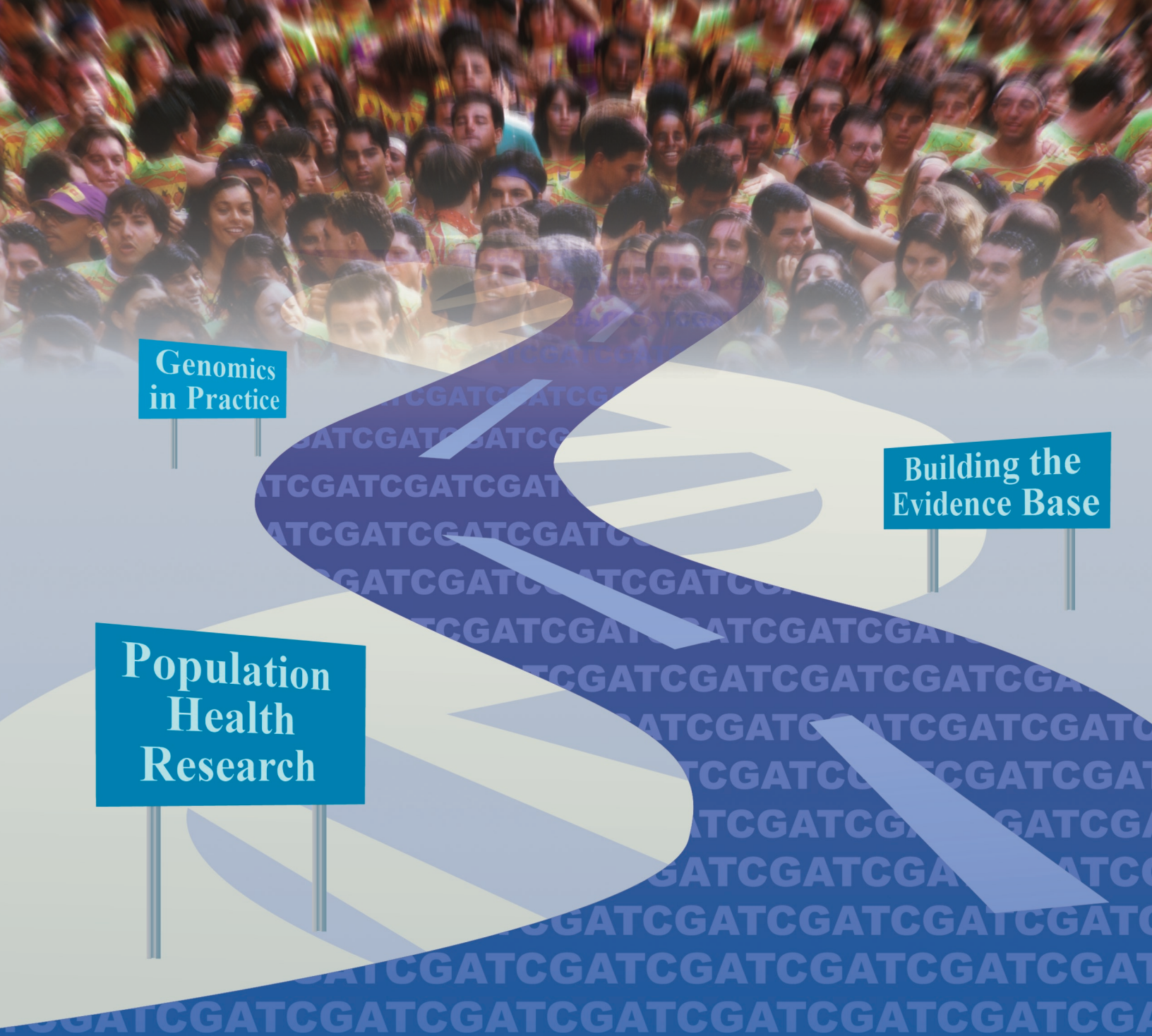


Genomics and Population Health:

United States 2003

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA
CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Produced by the Office of Genomics and Disease Prevention,
Centers for Disease Control and Prevention (CDC)

Edited by:
Marta Gwinn, MD, MPH
Sara Bedrosian, BA, BFA
Denae Ottman, MPH, RD, CHES
Muin J. Khoury, MD, PhD

Office of Genomics and Disease Prevention, CDC

For additional copies of Genomics and Population Health: United States 2003,
visit our website at http://www.cdc.gov/genomics/activities/ogdp/2003.htm.

Acknowledgements:

We are grateful to the following individuals for their support and assistance in making this report possible: Thelma Brown, Alex Charles, Sara Cote, Lori Durand, Sherilyn Jordan, Cynthia Moore, and Leah Simpson.

Publication, March 2004

Suggested Citation:
Centers for Disease Control and Prevention, Office of Genomics and Disease Prevention.
Genomics and Population Health: United States 2003.
Atlanta, GA; 2004. Also available at http://www.cdc.gov/genomics.

Table of Contents

Foreword

Muin J. Khoury

Public Health Professional
A person educated in public health or a related discipline who is employed to improve health through a population focus.

(Who Will Keep the Public Healthy? Educating Public Health Professionals in the 21st Century, IOM, 2003, p. 30)

Welcome to the first CDC report on genomics and population health! In this periodic report, we hope to present a timely and practical collection of vignettes of the status of genomics and population health in the United States. This information is intended for **public health professionals** who are interested in integrating genomics into health promotion, disease prevention and health care. The report includes information on what we know, what we don't know and what is currently relevant in this rapidly evolving field. At the outset, we realize that many terms and concepts may be new and we therefore include a brief introduction to the "lingo" developed by the University of North Carolina at Chapel Hill. For your convenience, additional links to relevant Web sites and other resources are also available throughout the report.

With the completion of the Human Genome Project in 2003, the stage has been set for an accelerated pace of discovery of thousands of genetic variants. Many variants will be studied for association with diseases of major public health importance, including adult chronic diseases, childhood conditions, infectious, environmental and occupational diseases. Applications of genetic information in diagnosis and prevention of various diseases must be driven by evidence on gene functions in normal and disease states as well as by the value of such information to improve health outcomes. In spite of the potential promise and excitement about human gene discoveries, there are still immense gaps in the knowledge needed for a successful translation of new research results into population health benefits. This "translation gap" calls for an important public health leadership role in applied research, policy development and integration of genomics into the practice of 21st century medicine.

In this first report, we present some examples to show how public health is beginning to address three major gaps along the genomics "translation highway":

1. Conducting genomics and population health research,
2. Developing evidence on the value of genomic information, and
3. Integrating genomic information in practice and programs.

1. Conducting genomics and population health research.

Most human disease results from interaction between inherited genetic variations and numerous environmental factors (e.g., diet, infections, lifestyle, chemicals and social factors). With the thousands of genetic variants discovered, there is a real urgency to characterize what genetic variation means for health, to assess the prevalence of genetic variants in different populations, and to examine their contribution to the population burden of disease, death and disability. In this first report, we highlight two current CDC efforts in this area. The first example (Chapter 1) is a project to evaluate the prevalence of 57 genes and their variants in a nationally representative sample of the United States population. We provide an overview of the criteria used to select these genes for study and a description of the planned project. The second example (Chapter 2) discusses the potential for examining the role of human genomics in the setting of acute public health investigations, a mainstay of public health efforts to characterize and prevent disease occurrence in communities with acute health problems or a disproportionate burden of disease.

2. Developing evidence on the value of genomic information.

To use genetic information successfully in population-level programs and individual management of patients, we need solid scientific evidence to help guide policy development and guideline recommendations. In this report, we review the public health implications of the evolving asthma genomics research, including pharmacogenomics, the new targeting of drug therapies to specific genotypes (Chapter 3), as well as the evolving evidence and guidelines about genetic testing for breast and ovarian cancer (Chapter 4). We also discuss the example of MCADD to describe an emerging area of newborn screening using the new technology of tandem mass spectrometry, which is increasingly adopted in state public health programs (Chapter 5). We also highlight a CDC initiative to develop and evaluate family history tools for augmenting chronic disease prevention efforts (Chapter 6). We ask critical questions about the role of "genetic profiling" tests that are being promoted for preventing coronary heart disease and determine whether or not such tests are ready for prime time (Chapter 7), and review ethical, legal and social issues (Chapter 8).

3. Integrating genomic information in practice and programs.

Because health professionals are most concerned with practice and programs, this section of our report is the longest. To integrate genomic information into practice and programs, we need a competent workforce, a robust health system, and an informed public. We need careful policy development and planning that recognizes the complexity of genomics issues while building on approaches that have been successful in evaluating other health related technologies. We provide an update on efforts to ensure the quality of genetic testing (Chapter 10). We also provide timely and relevant practice information for two specific conditions: hereditary

hemochromatosis (Chapter 11) and cystic fibrosis (Chapter 9). We cover training issues (Chapter 12), genomic tools for public health (Chapter 13), issues related to state genetic planning (Chapter 14), and provide Internet-based resources (Chapter 15).

We hope that the topics chosen for this report reflect emerging common interests and concerns. We have tried to present population-based data when available, describe potential applications to public health and prevention practice, and offer value-added interpretation. The report is based on a collaboration of many individuals and programs at CDC and other partners. We are indeed very thankful for their efforts.

We would like to invite readers to give us feedback on this first report, to help us improve future editions. Please use the comments card found in this report or visit our Web site: (http://www.cdc.gov/genomics/activities/ogdp/2003.htm). Current information on the application of genomics in public health is still sparse and contains many gaps; however, we hope that increasing experience at the state and community levels will help to fill these gaps over time. We hope that the data and information contained in these reports will prove useful in guiding public health research, policy and practice in order to help reap the benefits of the Human Genome Project for citizens in the 21st century.

Genomics and Population Health 2003:

January

3rd Annual Program Implementation Meeting: Improving the Efficacy and Effectiveness of Tandem Mass Spectrometry Screening for Newborns, Berkeley, California

February

Ten articles from CDC Family History workshop published in supplement to the *American Journal of Preventive Medicine*

NHGRI: ENCODE (ENCyclopedia of DNA Elements) launches an interactive public research consortium for identifying all functional sequences of the human genome

17th National Conference on Chronic Disease Prevention and Control
Session: The Family History Tool, St. Louis, Missouri

March

Family History as a Tool for Public Health and Preventive Medicine:
A Public Health Perspective, CDC Web site

April

50th Anniversary of the Double Helix

Human genome sequence completed

January February March April May June

May

Partnership for Prevention publishes *Harnessing Genetics to Prevent Disease and Improve Health*

Genomics and the Future of Public Health Symposium, CDC, Atlanta, Georgia

Communication: Key to Appropriate Genetic Test Referral, Result Reporting, and Interpretation,
Mt. Sinai School of Medicine, CDC

June

Inaugural meeting of DHHS Secretary's Advisory Committee on Genetics, Health and Society

Roche announces the new AmpliChip CYP450, which identifies small variations in two genes affecting drug response

A Year at a Glance

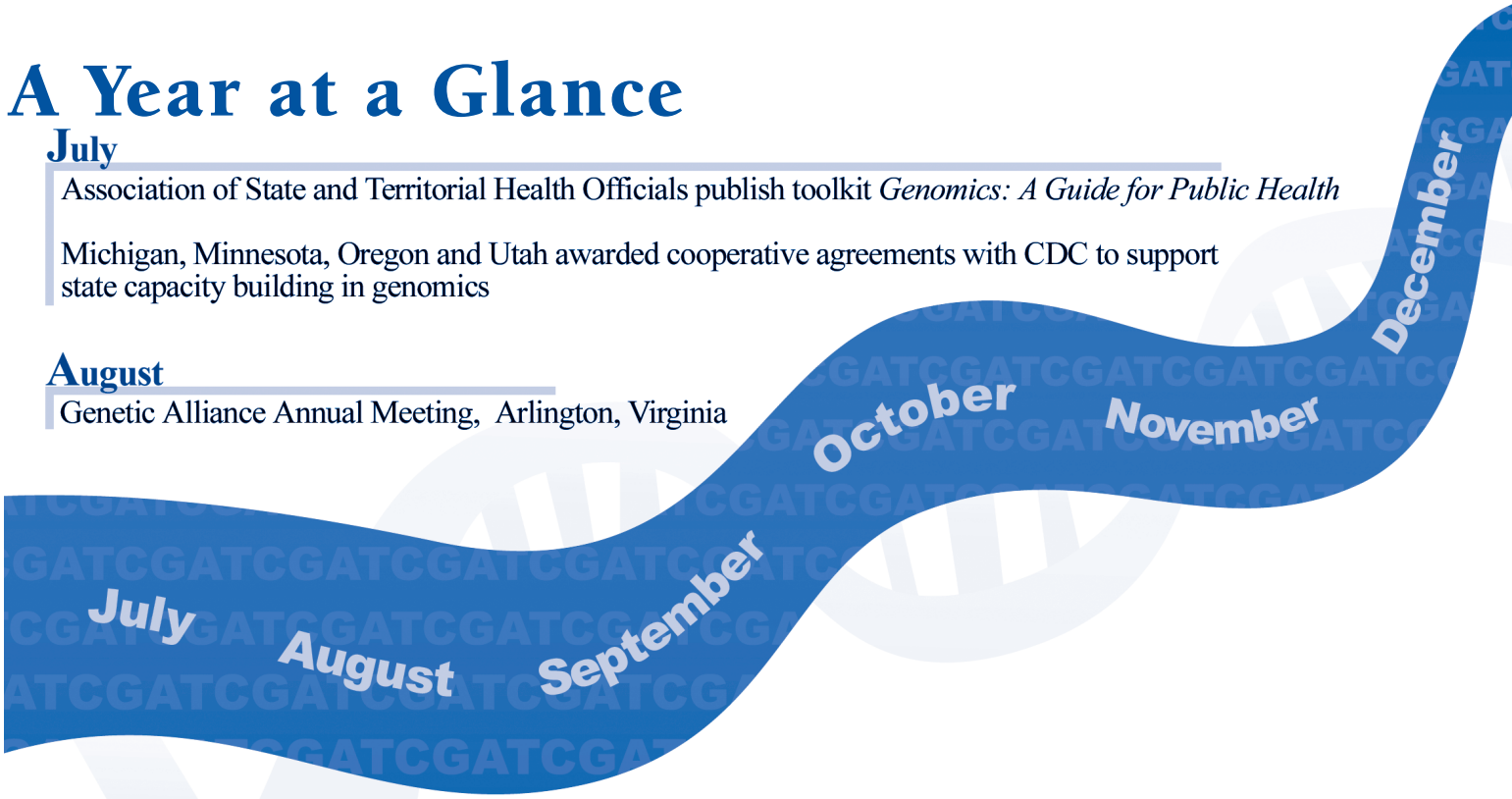
July

Association of State and Territorial Health Officials publish toolkit *Genomics: A Guide for Public Health*

Michigan, Minnesota, Oregon and Utah awarded cooperative agreements with CDC to support state capacity building in genomics

August

Genetic Alliance Annual Meeting, Arlington, Virginia



September

Three research centers funded to evaluate Family History Tool for health promotion and disease prevention

CDC 2003 Cancer Prevention Conference includes sessions on genetics and family history, Atlanta, Georgia

University of Washington, Centers for Genomics and Public Health, Asthma Working Group Summary Meeting, Seattle, Washington

October

The State of CDC, Fiscal Year 2003 summarizes CDC's accomplishments for the past fiscal year and includes a brief discussion of genomics

Genetic Information Nondiscrimination Act of 2003 passed by U.S. Senate, 95-0

Office of In Vitro Diagnostic Devices (OIVD), FDA, advises Roche that the "AmpliChip cannot be commercially distributed without an appropriate premarket determination from FDA"

November

Newborn Screening for Cystic Fibrosis Meeting, CDC and Cystic Fibrosis Foundation, Atlanta, Georgia

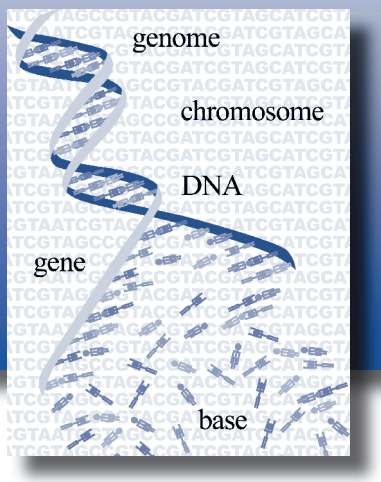
December

FDA approves first DNA-based lab tests for genetic clotting risk

The International HapMap Consortium outlines rationale behind effort to create a map of human genetic variation in *Nature*

Human Genome Epidemiology: A Scientific Foundation for Using Genetic Information to Improve Health and Prevent Disease, edited by Muin J. Khoury, Julian Little, and Wylie Burke

Help With the Lingo… What Do the Terms Mean?



Elizabeth Mahanna

Genetics vs. genomics

The two terms are sometimes used interchangeably. However, genetics usually refers to the study of single genes, while genomics refers to the study of all the genes in a person or organism. The human genome is a person's complete set of DNA.

"Sequencing the genome" is another buzz phrase that has gotten a lot of press

Perhaps you heard the announcement back in April 2003 that scientists at the Human Genome Project "sequenced the entire human genome." **Sequencing** refers to a detailed description of the order of chemical building blocks of DNA. Human DNA is made up of billions of these building blocks, called bases.

Backtracking for a moment… what is the relationship between DNA, bases, genes, and chromosomes?

The chemical **DNA** (deoxyribonucleic acid) is in all the cells of our body. It contains chemical building blocks called **bases**. There are only four bases (A, T, G and C) but they repeat in an ever-changing order throughout our genes. **Genes** are pieces of DNA that contain instructions for making cells or for what cells do. Each gene contains instructions for building one or more proteins, but a gene can contain millions of bases, so deciphering how it works or what a mutation is can be very difficult. A **mutation** is a change in the order of the bases in a gene.

Amazingly, genes make up only about 2% of the human genome—the rest are regions that do not make instructions as genes do. It is currently thought that we have between 30,000 and 40,000 genes (only twice as many as a fruit fly). Each gene contains instructions for building proteins, and the **genome** can be thought of as the complete book of instructions. The genome is not one extremely long piece of DNA, but rather it is divided into separate pieces, called **chromosomes**. Each chromosome has many genes—between 231 (Y chromosome) and 2968 (chromosome 1). We have 46 chromosomes in 23 pairs. One chromosome in each pair we inherit from our father, and one in each pair we inherit from our mother. We have two nearly-identical copies of every gene, with the exception of those on

the "sex" chromosomes, named X and Y. Females have two X chromosomes and males have an X and a Y.

It's the proteins

Actually, it's not the genes that carry out instructions for the body's cells—it's the proteins. Each gene "codes for" or makes a protein or proteins. The proteins do the work in the body. Through these proteins, our genes control how we process foods, detoxify poisons, respond to infections, and the like. Humans can make at least 100,000 different kinds of proteins. Ever heard the word "proteomics"? It's the science of figuring out these proteins.

We are 99.9% the same

Scientists have found that, of the 3 billion or so bases in the human genome, 99.9% are exactly the same from person to person. About 3 million (or 0.1%) are different, and that's what makes us unique. Three million may seem like a big number, but it's not much compared to 3 billion. Scientists now think that there are more genetic differences between people of the same race than between people of different races.

Disease is a result of the interaction between genes and environment

This is true for almost all diseases. The word "environment" encompasses many things. It includes what you eat, your lifestyle and habits (smoking, alcohol use, exercise, etc.), and what chemicals you may have been exposed to (including medications). It also includes your physical environment such as climate or sun exposure and psychological factors such as stress. Environment pretty much includes everything that is not genetic.

Changes or mutations in genes, for the most part, do not cause disease. They influence a person's vulnerability to things in the environment. If we inherit "mutated" genes from our parents, we do not inherit disease—we inherit an increased susceptibility risk for certain diseases. We've all heard of the people that exercised all their life, watched their cholesterol and ate healthy meals—and dropped dead of a heart attack at age 40. We've also heard of the people who smoke, drink, have an unhealthy diet, and live to be 100. Most people fall somewhere between those two extremes.

Most common diseases, such as cancer, heart disease, and diabetes, result from a complicated interaction between several genes and the environment. A few rare diseases (such as Huntington's or Tay-Sachs disease) are disorders that arise from a single gene and do not appear to have an environmental component. These diseases account for a very small proportion of human disease. Other single-gene disorders are greatly affected by environment, such as hereditary hemochromatosis or PKU.

Many people tend to classify a disease as either genetic or environmental. For example, Uncle Harold smoked all his life and died of lung cancer. Smoking obviously caused his lung cancer. However, only 10-15% of smokers will develop lung cancer. So there must be something else going on—most likely variations in people's genes that either predispose them to getting cancer or protect them from it.

Modified from the University of North Carolina at Chapel Hill, School of Public Health, Web site: http://www.sph.unc.edu/nciph/phgenetics/index.htm. This Web site was made possible by a grant from HRSA.

Chapter 1

National Health and Nutrition Examination Survey (NHANES) III DNA Bank: Gene Variants Important to Public Health

Mary Lou Lindegren for the NHANES CDC-Wide Working Group

NHANES III DNA Bank

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative survey of the United States population, conducted by the National Center for Health Statistics (NCHS).[1] Detailed interviews, clinical, laboratory and radiological examinations are conducted as part of the survey. NCHS has collected these data with an assurance of confidentiality.

During the second phase of NHANES III (1991-1994),[2] white blood cells were frozen and cell lines were immortalized with Epstein-Barr virus, creating a DNA bank.[3] The bank is maintained by the National Center for Environmental Health, CDC, and contains specimens from more than 7000 participants. In 2002, NCHS requested proposals for the use of these specimens.[4, 5]

Collaborative CDC-Wide Project

A CDC-wide working group of epidemiologists and laboratorians, representing most Centers and Institutes at CDC, was convened to develop a collaborative proposal for determining the prevalence of selected genotypes of public health importance using the NHANES III DNA Bank.

Selecting Genetic Variants Important to Public Health

The criteria used to select genes for the proposal included:

- known or hypothesized association with diseases of public health importance,
- role in pathways affecting multiple diseases,
- identified functional variants,
- relatively common variants (prevalence >2%),
- previously described gene-environment or gene-gene interactions,
- relevant phenotypic data available in NHANES datasets, and
- no current use for clinical risk assessment or intervention.

Several challenges that made this process difficult were:

- gaps in published information,
- many available studies demonstrated problems with methodology, including selection bias, small sample size, and lack of attention to potential interaction, and
- non-replication of many published gene-disease associations.

The final proposal included 87 variants of 57 genes known to be important in at least six major pathways:

- nutrient metabolism (e.g., folate and homocysteine; lipids; glucose; alcohol; vitamin D),
- immune and inflammatory responses (e.g., cytokines, cytokine receptors),
- activation and detoxification pathways (e.g., drugs, carcinogens, environmental contaminants),
- DNA repair pathways (e.g., ionizing radiation, environmental toxins),
- hemostasis and renin/angiotension pathways, and
- developmental pathways.

Genotyping will be performed in collaboration with the National Cancer Institute (NCI) at the NCI Core Genotyping Facility.

Potential Value for Public Health

Prevalence data from the NHANES database will be the basis for future analysis of gene-disease associations and gene-environment interactions. Gene-environment interactions are considered to be the fundamental biological processes that both maintain health and bring about disease. As our understanding of these interactions grows, establishing the prevalence of **gene variants** known to interact with specific environmental factors will be a key factor in assessing the potential impact of environmental interventions. Genotypic information will add another dimension to the analysis of clinical, physical, and lifestyle information collected by NHANES. Additional analysis of **genotype-phenotype** relations will be proposed once the prevalence data have been evaluated.

Prevalence
The number of people with a trait or condition at a specific point in time.

Gene Variant
A variation in the sequence most commonly observed for a particular gene.

Genotype
The genetic make-up of an individual.

Phenotype
The observable traits or characteristics of an individual.

Two Other CDC Projects Using NHANES III DNA Samples

Prevalence of Gene Variants that Code for Enzymes Involved in Nicotine and Carcinogen Metabolism in the United States Population and their Association with Body Burden of Cotinine

Karen Steinberg, et al.

This proposal involves correlating over 40 **Single Nucleotide Polymorphisms** or **SNPs** (pronounced "snips") in 14 genes involved in drug-nicotine metabolism and smoking behavior with serum cotinine measurements already performed, and with self-reported smoking variables.

Frequency of Common Genotypes of Folate-Related Genes and their Effect on the Relation between Intake and Blood Levels of Folate and Homocysteine

Lorenzo Botto, et al.

This proposal will evaluate the individual and joint effects (interactions) of selected common polymorphisms of three genes in the folate metabolism pathway and the consumption of folic acid on homocysteine and folate levels.

Single Nucleotide Polymorphism – SNP
Common, but minute, variations that occur in human DNA at a frequency of one in every 1,000 bases.

NHANES CDC-Wide Working Group
http://www.cdc.gov/genomics/NHANES.htm

ATSDR	Agency for Toxic Substances and Disease Registry
NCBDDD	National Center on Birth Defects and Developmental Disabilities
NCHSTP	National Center for HIV, STD, and TB Prevention
NCID	National Center for Infectious Diseases
NCEH	National Center for Environmental Health
NCCDPHP	National Center for Chronic Disease Prevention and Health Promotion
NIOSH	National Institute for Occupational Safety and Health
NIP	National Immunization Program
NCHS	National Center for Health Statistics
OGDP	Office of Genomics and Disease Prevention
PHPPO	Public Health Practice Program Office

References

1. National Center for Health Statistics. National Health and Nutrition Examination Survey. [online survey]. Available at: http://www.cdc.gov/nchs/nhanes.htm. Accessed Feb 16, 2004.

2. National Center for Health Statistics. Plan and operation of the Third National Health and Nutrition Examination survey, 1988-94. *Vital Health Stat* 1994;1:1-62.

3. National Center for Health Statistics. NHANES III Stored Biologic Specimens. Web site. Available at: http://www.cdc.gov/nchs/about/major/nhanes/coverpage.htm. Accessed Feb 16, 2004.

4. National Center for Health Statistics. NHANES III DNA Specimens. Guidelines for Proposals. Web site. Available at: http://www.cdc.gov/nchs/about/major/nhanes/dnafnlgm2.htm. Accessed Feb 16, 2004.

5. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey III (NHANES) DNA Specimens: Guidelines for Proposals to Use Samples and Proposed Cost Schedule. 2002:67:51585-51589. Also available at: http://www.access.gpo.gov/su_docs/fedreg/frcont02.html and http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=2002_register&docid=02-20038-filed. Accessed Feb 18, 2004.

Chapter 2

Genomics and Acute Public Health Investigations

Jairam Lingappa and Mary Lou Lindegren

What is an Acute Public Health Investigation (APHI)?

An Acute Public Health Investigation (APHI) is a timely assessment of adverse health events followed by rapid application of prevention and control measures. APHIs use epidemiological and laboratory methods, and have long been recognized as the responsibility of the nation's public health system. State and local health departments, as well as the health ministries of other nations, often invite CDC to assist in field investigations to determine the cause and extent of a particular acute public health problem. These investigations typically evaluate demographic, behavioral and exposure-related risk factors. APHIs accomplished through federal, state and local public health partnerships have earned the public health system both national and global recognition.

Incorporating Human Genomics into APHIs

The translation of genomic information for public health research and practice presents a unique opportunity for enhancing APHIs. As our knowledge of the role of human genomics in human susceptibility and disease causation increases, so does its potential to sharpen our response to acute public health events. Health investigations where human genomics may be important include:

- disease clusters (e.g., infectious disease outbreaks, cancer or birth defect clusters),
- exposure clusters (e.g., environmental, occupational and bioterrorism), and
- adverse reactions to therapeutics (e.g., vaccines, antibiotic prophylaxis and blood products).

The decision to collect human genomic information during an Acute Public Health Investigation must be informed both by scientific potential and by available resources. Investigations that could incorporate human genomics need to be evaluated using scientific criteria (e.g., what is known about human genomic factors and the disease, etc.) Resources also must be evaluated, as there may be challenges involved in sample collection, specimen and data banking, genomic testing, and possible delays (due to protocol review or increased demands on participants and investigators).

Incorporating human genomics into APHIs has great potential to benefit public health, including opportunities to learn more about diseases that occur largely in epidemic settings (e.g., cholera, SARS), or as a result of mass exposure to rare threats (e.g., toxic releases, anthrax), or where interventions could be more effectively targeted or genomic tools more efficiently utilized. In addition, as detailed exposure data is often collected during an APHI, the incorporation of human genomics would allow for the assessment of gene-environment interactions. Finally, banked specimens from AHPIs may provide a key resource for addressing long term research questions about human genomic factors in relation to disease causation and prevention interventions.

Research approaches that could lead to enhanced prevention, detection and control of future adverse health events include the assessment of:

- genomic profiles (e.g., relation to susceptibility, resistance, severity, prognosis, interactions with other risk factors and response to therapeutics),
- exposure profiles (e.g., the use of mRNA transcripts to estimate exposure levels or characterize exposure), and
- outcome variation (e.g., the use of protein expression to characterize outcomes).

This information may aid in identifying causes of adverse health events and directing public health and clinical interventions, such as vaccination, exposure reduction, behavioral intervention, and therapeutics.

APHI Working Group

CDC has formed a multidisciplinary APHI Working Group in collaboration with the Council of State and Territorial Epidemiologists (CSTE) to develop a plan and tools for incorporating genomics into APHIs. The Working Group will engage state public health departments and other partners to address several core areas:

- science – selection of genes and gene pathways for study;
- technology – collection, storage, processing and banking of biologic specimens, technologies for human genomic testing, database issues and **bioinformatics**;
- epidemiology and statistics – study design, implementation, and analysis;
- ethical, legal, and social implications (ELSI) – informed consent, Institutional Review Board (IRB) issues, confidentiality, and security.

Bioinformatics
The science of managing and analyzing biological data using advanced computing techniques; especially important in analyzing genomic research data.

The Working Group is planning a workshop in 2004, and is inviting external consultants who will provide additional expertise and guidance for developing a research agenda for including human genomics in APHIs. Workshop participants will offer input on priority research areas such as:

- assessing criteria for prioritizing investigations that should incorporate human genomics,
- identifying information gaps and needs,
- developing standard tools and protocols for the field and laboratory work as well as the informed consent process,
- making tools available to epidemiologists and public health officials involved in the acute public health investigation,
- creating educational materials for the public health workforce both within CDC and with the states involved in APHIs, and
- developing pilot studies and just-in-time protocols.

Conclusion

The genomics revolution can refine our ability to conduct effective investigations of acute public health events. Enhancing our understanding of disease pathogenesis and susceptibility improves future public health prevention and control efforts.

Chapter 3

Asthma Genomics: Implications for Public Health

Tabitha Harrison, Karen Edwards, and Wylie Burke

What Causes Asthma?

Asthma is a chronic lung condition characterized by airway inflammation, airway hyper-reactivity and reversible airway obstruction. The disease is found disproportionately in children and minorities, and prevalence has increased significantly since the early 1980s. No single factor is responsible for the development of asthma. Environmental exposures, such as house dust mites, fungal spores, cockroaches, tobacco smoke, and animal dander have been identified as contributors. In addition, as early as the 1920s, studies demonstrated the existence of a familial predisposition to asthma. There is strong evidence for both genetic and environmental contributors to the development of asthma.

Public Health Implications of Asthma Genomics Research

In 2003, the Asthma Working Group, created by the University of Washington Center for Genomics and Public Health, organized an evaluation of the implications of asthma genomics research for public health. Based on an initial literature review and discussion, the UW Asthma Working Group identified four areas of potential action in which genomic research or information might contribute to public health efforts to reduce asthma morbidity and mortality:

- population-based prevention,
- targeted prevention based on risk status,
- diagnosis, and
- management.

The Working Group also defined five key perspectives to use when evaluating potential interventions:

- patient and family,
- community,
- researcher,
- health care professional, and
- public health practitioner.

The plan for expert consultation sought feedback on these potential areas of intervention and important considerations from each of the identified perspectives. A sixth perspective—that of the commercial developer—was added based on comments made during the consultation.

The first round of consultation made use of asthma expertise available in the Seattle community and in Washington State. Subsequent rounds of consultation sought advice from:

- experts at the University of Michigan Center for Genomics and Public Health and the University of North Carolina Center for Genomics and Public Health,
- national experts identified through consultation with local and federal advisors, and
- experts attending the American Thoracic Society meeting (Seattle, May 2003) and the National Conference on Asthma 2003 (Washington DC, June 2003).

Experts were interviewed individually or in small groups; most experts also identified additional relevant medical literature. Over the course of the consultation and literature review, some common themes emerged. These included the potential role of **genomic profiling** as a means for identifying individuals with increased asthma risk; the implications of commercial incentives for technology development; the relevance of current data on behavioral interventions, treatment adherence and clinical outcomes for potential genome-based interventions; and the significance of current data related to differences in asthma prevalence across demographic groups for public health research and actions.

Genomic Profiling
Concurrent detection of multiple gene variants associated with predisposition to a particular disease.

Pharmacogenomics and Predictive Testing

Pharmacogenomics
Refers to the use of genomic techniques to enhance drug development and define drug responses.

Consultants consistently identified **pharmacogenomics** as the area of genomic research most likely to change asthma care in the near future. Genetic factors have been estimated to account for 60% to 80% of the variability in asthmatics patients' response to medications.[1] Genomic strategies will aid in the identification of new drug targets, and may lead to drugs designed for use in specific subsets of

asthmatic patients, defined by genotype. In addition, pharmacogenomic research will produce genetic tests designed to predict drug responses and adverse side effects.

In the long term, genomic research may also produce genetic tests that will aid in disease classification, predict prognosis, or identify unaffected children who are at increased risk to develop asthma. One possible application of the latter capability would be newborn testing, to identify infants who might benefit from environmental modifications or immunotherapy for prevention. While such research holds promise for innovative treatments and effective prevention, it will not succeed without careful attention to the interaction between genetic and non-genetic contributors to asthma.

Public Health Actions—Asthma Genomics Research

Actions on the part of public health can help to ensure that genomic research supports public health goals to reduce asthma morbidity and mortality. These include:

- On-going critical evaluation of research on genetic contributors to asthma, to guard against overly simplistic interpretation of data addressing genetic hypotheses. Headlines proclaim the discovery of "the gene for disease X", without much attention to the complex etiology of diseases such as asthma.[2] Researchers and practitioners concerned about the public health implications of asthma research need to be vigilant against the over-interpretation of genetic data, or an overly ready assumption of genetic causes for observed differences.

- Funding and advocacy, to ensure that evidence gaps are addressed with appropriate research strategies. In particular, public health input will help to ensure adequate selection and definition of study populations, meaningful measures of environmental exposure, and inclusion of appropriate clinical outcomes.

- Participation in design of recruitment and data management strategies for population-based genomic research. CDC and state public health agencies could play an important role in crafting public messages and recruitment strategies to ensure adequate participation in population-based studies, and in developing policies for data collection and management that reduce fears about inappropriate uses of genetic information.

- Support for evidence-based practice in pharmacogenomics and genetic testing, including rigorous assessment of the utility and cost-effectiveness

of drugs requiring prior testing to determine candidacy for treatment, and of genetic tests proposed as a means to tailor drug regimens or predict future disease.[3]

- Advocacy to ensure access to genomics-based therapies for the medically underserved, when they are found to be cost-effective.

- Utilization of the convening power of public health, to foster multidisciplinary collaboration in research and broad stakeholder participation in the development of research and clinical practice policies.

In order to accomplish these goals, public health will need an infrastructure for technical support, consultation, and education. The most efficient approach is likely to involve an incremental development of expertise, starting with a small, centralized, multidisciplinary group that works in partnership with designated state liaison persons and academic centers conducting research in public health genetics.

References

1. Drazen JM, Silverman EK, Lee TH. Heterogeneity of therapeutic responses to asthma; *Br Med Bull* 2000;56: 1054-70.

2. Khoury MJ, Thrasher JF, Burke W, Gettig EA, Fridinger F, Jackson R. Challenges in communication about genetics: a public health approach. *Genet Med* 2000;2:198-201.

3. Burke W. Genetic testing. *N Engl JMed* 2002;347:1867-75.

Chapter 4

Public Health Assessment of *BRCA1* and *BRCA2* Testing for Breast and Ovarian Cancer

Monica R. McClain, Glenn E. Palomaki, Linda A. Bradley, and Ralph J. Coates

Breast and Ovarian Cancer: An Important Public Health Problem

Breast cancer is the most common form of cancer in United States women (approximately 216,000 new cases will be diagnosed in 2004), and the second most common cause of cancer deaths (approximately 40,000 deaths per year).[1] Ovarian cancer is less common (about 25,000 new cases each year), but about three-quarters of cases are diagnosed at a late stage, when it is often fatal. Each year, an estimated 809,000 person-years of life are lost due to breast cancer, and 232,000 person-years are lost due to ovarian cancer.[2]

Genetic Tests for Breast and Ovarian Cancer Susceptibility

Most breast and ovarian cancers occur after menopause, and the risk increases with age. Because most symptoms and clinical signs of breast cancer are relatively specific and well understood, an early diagnosis is possible through established mammography screening programs. Ovarian cancer signs and symptoms are not apparent in the early stages and routine screening is not recommended for the general population. Diagnosis of breast or ovarian cancer is by biopsy and pathologic examination.

Two genes, *BRCA1* and *BRCA2* (*BR*east *CA*ncer genes), are associated with predisposition to hereditary breast or ovarian cancer. Mutations in these genes are identified in 1-2% of women with breast cancer and 5-10% of women with ovarian cancer.[3] A prominent characteristic of these inherited cancers is early age at onset. Women identified with a *BRCA1* or *BRCA2* mutation have a substantially increased risk of developing breast and/or ovarian cancer during their lifetime. These risks are compared with those in the general population in the following table:

Table 1. Risks of Developing Breast and Ovarian Cancer by Age 70 in the General Population Compared with Women with a *BRCA1* or *BRCA2* Mutation

Cancer Type	General Population Risk By Age 70[4] (%)	*BRCA1* or *BRCA2* Mutation Risk By Age 70[3](%)
Breast Cancer	9.7	35 – 85
Ovarian Cancer	~ 1	9 – 66

The two *BRCA* genes have been patented. As a result, one laboratory performs most clinical testing for *BRCA* mutations in the U.S. and the test itself is trademarked under the name BRACAnalysis™. Comprehensive *BRCA* analysis is one form of the test that examines the full sequence of the *BRCA1* and *BRCA2* genes to look for mutations that indicate a predisposition to hereditary breast and ovarian cancer.

A Public Health Perspective

Genetic testing for *BRCA1* and *BRCA2* mutations is a complex process and is not recommended for women in the general population. At present, *BRCA1* and *BRCA2* mutation testing may be appropriate for only a small proportion of women (less than one percent). These women can make an informed decision about testing in collaboration with their health care providers. An informed decision requires that the potential benefits and potential risks or limitations of testing are considered.

The Role of Family History in *BRCA1* and *BRCA2* Testing

The first step in considering *BRCA1* and *BRCA2* mutation testing for adult women is to ask about the woman's family history of breast and ovarian cancer because:

- most breast and ovarian cancers are not inherited, but occur sporadically;
- *BRCA1* and *BRCA2* mutations are uncommon (about 1 in 400 women carry a mutation);
- the cost of full genetic testing (Comprehensive BRACAnalysis) is nearly $3000;
- women with a strong family history are more likely to have a mutation.

Screening women by asking their family history is relatively inexpensive and identifies families in which the chance of finding a *BRCA1* or *BRCA2* mutation is at least 10%. It does, however, have disadvantages:

- there is no standard definition of a positive family history for breast/ovarian cancer;
- about half of the women who carry a *BRCA1* or *BRCA2* mutation will not have a positive family history;[3]
- in most families with a positive history of breast and ovarian cancer, *BRCA1* and *BRCA2* mutations are not involved;[3,5]
- some types of mutations in the *BRCA1* or *BRCA2* genes are not detectable by the methodology used for Comprehensive BRACAnalysis.

The Role of Genetic Counseling in *BRCA1* and *BRCA2* Testing

Organizations commonly recommend that when a woman considering *BRCA1* and *BRCA2* mutation testing has a family history suggestive of inherited breast and ovarian cancer, she should consult with a genetic counselor or other provider with experience in cancer genetics.[6,7] The decision to undergo genetic testing is complicated and involves understanding the nature and risks of breast and ovarian cancers and the risks, benefits and alternatives to genetic testing. Women will need to consider these issues along with their preferences and values.[8]

The process of genetic counseling is designed to assist in:

- understanding the test and its limitations,
- understanding medical facts,
- understanding the hereditary contribution to the disorder, and
- choosing the course of action that is appropriate, based on level of risk, family goals, and ethical and religious beliefs.

Resources are available to assist health care providers and patients in locating genetic counseling services in their area (e.g., http://www.nsgc.org).

BRCA1 and *BRCA2* Mutation Testing

If the woman seeking genetic testing has not had breast or ovarian cancer, organizations that support genetic testing recommend that a family member with cancer be tested first.[6] If a mutation is not found, testing of other family members is not warranted. If a mutation is detected, subsequent testing of family members is simpler (and cheaper) because testing is focused on the identified mutation.

Family members found to have the identified mutation are at increased risk for developing breast or ovarian cancer. Family members who do not have the identified mutation have the same risk for developing breast or ovarian cancer as members of the general population with similar demographic and environmental characteristics.

If mutation testing cannot be performed on an affected family member, further genetic testing of family members may not be warranted because the test results might not be informative. For example, finding no mutations in a woman who does not have cancer does not distinguish between the possibilities that:

1. she did not inherit a *BRCA1* or *BRCA2* mutation that caused cancer in other family members, or

2. the increased risk of cancer in her family is not caused by a detectable *BRCA1* or *BRCA2* mutation.

If a woman is found to have *BRCA1* or *BRCA2* mutation, she may benefit because she knows she is at higher risk and she may choose some medical options discussed in the following section. Finding a mutation prompts several additional considerations:

- Carrying a mutation may present psychological and social dilemmas, and introduce the potential for employment and/or insurance discrimination.

- Males can also carry a *BRCA*1 or *BRCA*2 mutation. In males, mutations in *BRCA*1 and *BRCA*2 have been associated with an increased risk of male breast cancer (especially *BRCA*2 mutations) and prostate cancer.

- Approximately 13% of Comprehensive BRACAnalysis tests report a variant of "uncertain clinical significance".[9] This means that it is unknown whether or not these variants are associated with increased cancer risk, so that the woman will not know if her test result signifies an increased risk of cancer.

Surveillance and Risk-Reducing Strategies for Breast and Ovarian Cancer

Organizations that recommend testing and genetic counseling also recommend surveillance for women who choose not to have risk reducing surgeries.

Breast Cancer Surveillance by Mammography and/or Magnetic Resonance Imaging (MRI):

- Increased surveillance for early breast cancer detection is acceptable to at least half of women with a *BRCA1* or *BRCA2* mutation.[3]

- In women with *BRCA1* or *BRCA2* mutations, surveillance will identify about two-thirds of the breast cancers.[3]

- How effective breast cancer surveillance is in reducing mortality in women with a *BRCA1* or *BRCA2* mutation is not known.

- The false positive rate of breast cancer surveillance in women with a BRCA1 or *BRCA2* mutation is not known.

Ovarian Cancer Surveillance by Serum Tumor Markers and/or Ultrasonography:

- Increased surveillance for ovarian cancer detection is less acceptable than breast cancer surveillance in women with a *BRCA1* or *BRCA2* mutation.[3] This is likely because the effectiveness of these tests in detecting cancer and reducing mortality is uncertain.[3]

- About 4% of women who undergo surveillance for ovarian cancer will have a false positive result—that is, they will also have exploratory surgery that does not detect ovarian cancer.[3]

Risk-Reducing Surgeries

Risk-reducing surgeries are the most effective means of preventing breast and/or ovarian cancer. While women with *BRCA1*or *BRCA2* mutations who choose preventive mastectomy (surgical removal of breast tissue) may reduce their risk of breast cancer by at least 90%, acceptance of this option is 15% or less in the U.S.[3] Oophorectomy (surgical removal of the ovaries) may reduce the risk of breast cancer by about half and the risk of ovarian cancer by nearly 100%.[3] Oophorectomy has higher acceptance (13-50%, depending on the study) among BRCA mutation carriers, particularly those over age 40 (64-78%).[3]

Chemoprevention

Chemoprevention of breast cancer is another option, but is less acceptable to women regardless of mutation status, possibly due to side effects such as blood clots.[10] In one study, only 5% of all women accepted treatment by tamoxifen.[11] There is also some uncertainty about the effectiveness of tamoxifen in reducing the risk of breast cancer in women who carry *BRCA1* or *BRCA2* mutations.[12,13]

Lifestyle Changes

Although excess body weight and physical inactivity may be responsible for about one fourth to one third of breast cancers in women in the general population,[14] the effects of lifestyle modifications (e.g., diet, exercise, not smoking) in *BRCA1* and *BRCA2* mutation-positive women have not been directly studied. Patients at increased risk may welcome the opportunity to be in control of these aspects of their lives and may enjoy improved health.

Evaluation of *BRCA1* and *BRCA2* Testing in Practice

Although at least four organizations have issued guidelines on the use of *BRCA1* and *BRCA2* mutation testing for breast and ovarian cancer susceptibility in the U.S.,[3] no one set of guidelines has been universally accepted and implemented in clinical practice. This is due in part to the small amount of information available to assess how well the test identifies women who may benefit from testing and how effective and acceptable the interventions are. Other reasons may include the complexity of implementing and interpreting family history questionnaires. See *Chapter 10, Ensuring the Quality of Genetic Testing in the United States*, for more information.

Understanding the public health impact of genetic tests also requires the collection of data to investigate performance in practice, as well as quality, utilization and access. Collaboration between public health agencies, clinical care providers, professional organizations, and industry will be needed to collect this information. Related projects supported by CDC include:

- an evidence-based ACCE Review on *BRCA1* and *BRCA2* mutation testing in women with a family history of breast/ovarian cancer (ACCE is a model process for evaluating data on genetic tests; see http://www.cdc.gov/genomics/activities/fbr.htm),

- a study by the U.S. Preventive Services Task Force to examine the clinical utility of *BRCA1* and *BRCA2* mutation testing, funded by the Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, CDC, and

- a study to determine the impact on knowledge, attitudes and actions of a direct-to-consumer advertising campaign about *BRCA1* and *BRCA2* mutation testing that targeted women and their health care providers in two pilot cities, Atlanta, GA and Denver, CO.

Effectiveness of *BRCA1* and *BRCA2* Testing for Prevention

- Overall, *BRCA1* and *BRCA2* mutations are responsible for only a few percent of breast and ovarian cancers, but effective risk-reducing strategies are available.

- Access to these risk-reducing strategies may be limited by lack of insurance or inadequate coverage, failure of health care providers to appropriately refer, or availability of services in certain areas.

- Limited information is available about implementation issues surrounding the use of a routine family history plus *BRCA1* and *BRCA2* mutation testing strategy. Limited information is also available about the economic consequences.

- Acceptance of mutation testing is also limited by other issues, such as adverse health consequences of some prevention strategies and social stigmatization.

Conclusion

Genetic testing for *BRCA1* and *BRCA2* mutations may be appropriate for individuals with specific family histories of breast and/or ovarian cancer. There are many issues that must be considered throughout the testing process in order for an individual to make an informed decision regarding testing.

References

1. American Cancer Society. Cancer Facts and Figures. Web site. Available at: http://www.cancer.org/downloads/MED/Page4.pdf. Accessed Mar 29, 2004.
2. Brown ML, Lipscomb J, and Snyder C. The burden of illness of cancer: economic cost and quality of life. *Annu Rev Public Health* 2001; 22:91-113.
3. McClain MR, Palomaki GE, Haddow JE. Breast and ovarian cancer. *ACCE Review*. Web site. Available at: http://www.cdc.gov/genomics/activities/fbr.htm. Accessed Mar 31, 2004.
4. Feuer EJ, Wun LM. DEVCAN: Probability of Developing or Dying of Cancer Software [computer program]. Version 5.0. Bethesda (MD): National Cancer Institute; 1999.
5. Pinsky LE. Why should primary care physicians know about breast cancer genetics? *West J Med* 2001;175:168-73.
6. New York State Dept. of Health and American College of Medical Genetics. Genetic susceptibility to breast and ovarian cancer: assessment, counseling and testing guidelines. 1999. Web site. Available at: http://www.health.state.ny.us/nysdoh/cancer/obcancer/contents.htm. Accessed Mar 30, 2004.
7. American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. *J Clin Oncol* 2003;21:2307-406.
8. Sheridan SL, Harris RP, Woolf SH, for the Shared Decisionmaking Workgroup. Shared decisionmaking about screening and chemoprevention: a suggested approach from the U.S. Preventive Services Task Force. Article originally in *Am J Prev Med* 2004;26(1): 56-66. Agency for Healthcare Research and Quality, Rockville, MD. Also available at: http://www.ahrq.gov/clinic/3rduspstf/shared/sharedba.htm. Accessed Mar 30, 2004.
9. Frank TS, Deffenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. *J Clin Oncol* 2002; 20:1480-90.
10. U.S. Preventive Services Task Force. Chemoprevention of breast cancer: recommendations and rationale. July 2002. Agency for Healthcare Research and Quality, Rockville, MD. Web site. Available at http://www.ahrq.gov/clinic/3rduspstf/breastchemo/breastchemorr.htm. Accessed Mar 30, 2004.

11. Port ER, Montgomery LL, Heerdt AS, and Borgen PI. Patient reluctance toward tamoxifen use for breast cancer primary prevention. *Ann Surg Oncol*. 2001; 8:580-5.

12. Narod SA, Brunet JS, Ghadirian P, Robson M, Heimdal K, Neuhausen SL, et al. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Hereditary Breast Cancer Clinical Study Group. *Lancet* 2000;356:1876-81.

13. King MC, Wieand S, Hale K, Lee M, Walsh T, Owens K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. *JAMA* 2001;286:2251-6.

14. International Agency for Research on Cancer. Weight control and physical activity. IARC Handbooks of Cancer Prevention, Vol. 6. IARC Press, Lyon, 2002.

Chapter 5

Newborn Screening for MCAD Deficiency

Mary Dott, Roberta C. M. Wines, Barbara Adam, and Scott Grosse

What is MCADD?

Medium chain acyl-CoA dehydrogenase deficiency (MCADD), a fatty acid oxidation disorder, is an **autosomal recessive** enzyme deficiency. This condition prevents the normal use of fat as an alternative source of energy during times of fasting or increased metabolic demands. People with MCADD cannot burn fat for energy when their bodies run out of glucose, and as a result they may be affected by low blood sugar, altered central nervous system function, coma, or sudden death.[1, 2] If treatment is initiated before the onset of metabolic crisis, however, morbidity and mortality can be prevented.[1] With an early diagnosis, MCADD can be managed successfully by eating regularly and avoiding fasting.[2]

Autosomal Recessive
Inheritance of two copies of a mutant gene, one from each parent, on one of the 22 autosomes (chromosomes other than X or Y).

Why Test Newborns for MCADD?

Plasma concentrations of MCADD markers in the blood decline significantly after the first few days of life.[3] Because MCADD can be identified more easily during the newborn period, and pre-symptomatic treatment is reported to prevent morbidity and mortality, advocacy groups such as the March of Dimes[2] have recommended universal newborn screening for MCADD.

Tandem Mass Spectrometry Screening Test

Tandem mass spectrometry (MS/MS) is currently used to screen for MCADD as well as for other metabolic diseases.[4] This method detects elevated levels of certain intermediate metabolites of medium-chain fatty acids that are associated with MCADD. Octanoylcarnitine (C8) is the primary MCADD marker; additional markers include hexanoylcarnitine (C6), decanoylcarnitine (C10), and decenoylcarnitine (C10:1).[3,5]

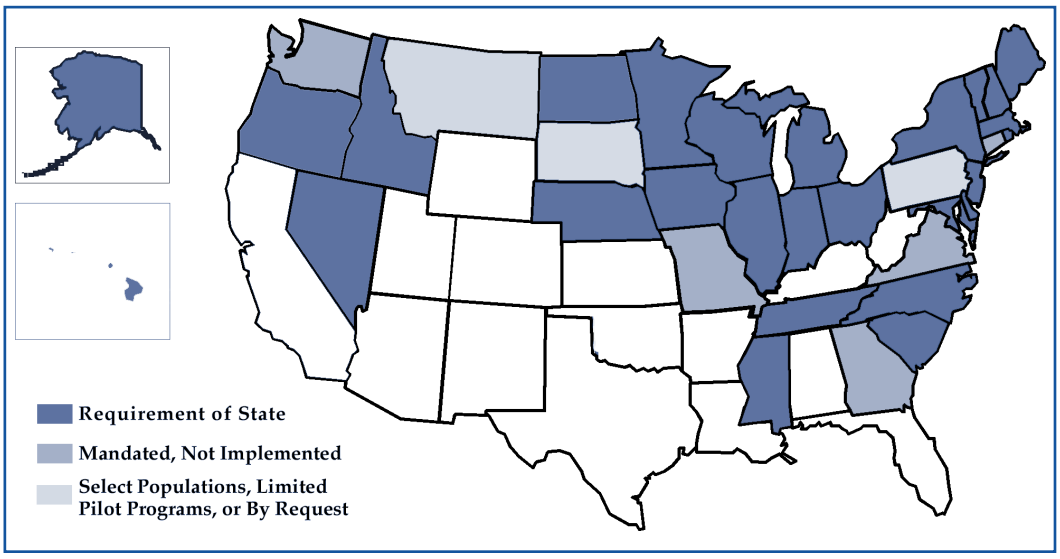
The high specificity and sensitivity of MS/MS to identify MCADD have been verified by reported results of newborn screening tests and retrospective MS/MS analyses of specimens from individuals who have been diagnosed clinically. Combined results[5-10] from 1.9 million newborn screening tests contained approximately equal numbers of true-positive (n=112) and false-positive (n=110) MS/MS test results and no known false-negative results.

Retrospective MS/MS analyses[6,11-12] of 56 specimens from unscreened, clinically diagnosed MCADD patients produced only one false-negative result, obtained from a stored newborn screening blood spot sample that had been collected from a newborn in metabolic crisis.

Adding MCADD Screening to Existing Newborn Screening Programs

Professional groups, including the American Society of Human Genetics (ASHG) and American College of Medical Genetics (ACMG),[13] have decided that the use of MS/MS in newborn screening programs might benefit patients. Many states[14] (Figure 1) have added screening for MCADD to their newborn screening programs and other states are currently considering adding screening for this disorder. The process by which states evaluate diseases as candidates for their screening programs varies. Massachusetts has documented the importance of an advisory committee in deciding to screen for MCADD.[15]

Figure 1. State Newborn Screening Programs Performing MS/MS Testing for MCADD, as of January 2004[14]



Is Universal Screening for MCADD Justified?

Reviews of MCADD as a candidate for newborn screening found that it fulfills either most[16] or all[17] of the criteria conventionally used to justify universal screening. MCADD is the most common fatty acid oxidation disorder. Newborn screening programs report prevalence between 1 in 12,500 and 1 in 25,000;[5-10] this is similar to the frequency of phenylketonuria (PKU) in the same populations.

The natural history of MCADD is still not well understood.[18] It is unknown what proportion of people identified with MCADD through MS/MS screening would

become symptomatic without this screening and subsequent interventions. Identifying affected people who would otherwise remain asymptomatic could subject them to unnecessary medical therapies, psychological stress, and difficulty in obtaining health insurance. Population-based studies to demonstrate the usefulness of MCADD screening have been recommended.[18] CDC and the Health Resources and Services Administration (HRSA) are funding follow-up studies of identified children to increase understanding of the impact of newborn screening for MCADD and other disorders identified by MS/MS.

The potential impact of early identification and intervention for MCADD on mortality is not well understood. Estimated mortality among children clinically diagnosed with MCADD ranges from 8% to 25%.[1,19-21] One study estimated mortality in an unscreened cohort of children with MCADD.[4] This study found eight children with MCADD among 100,600 British children whose stored newborn blood spots were analyzed using MS/MS; one (12.5%) of the eight children with MCADD died. Larger studies of this type or prospective data from screening programs could provide more precise mortality estimates.

The potential impact of newborn screening for MCADD on morbidity is unknown. Long-term neurological impairment has been reported in 16% to 33% of survivors of metabolic crises, about half of whom are seriously impaired.[1,19-21] No cases of neurological impairment in children with MCADD identified by screening programs have been reported.[22-24] Systematic long-term assessment of neurological outcomes is needed; although preliminary data from an assessment of infants born in New England and Pennsylvania indicate normal cognitive development.[24]

Cost-Effectiveness of Newborn MCADD Screening

The two published studies that analyzed cost-effectiveness of adding MS/MS to newborn screening concluded that it is probably cost-effective, either for MCADD alone[9] or because of the added benefits from early detection of disorders in addition to MCADD.[25] A study published in 2003 concluded that, for jurisdictions already using MS/MS to screen for PKU, it would be cost-effective to screen for MCADD as well.[26]

The cost-effectiveness of screening (from the perspective of the screener) using MS/MS depends on the technology chosen and on assumptions about the numbers of lives saved and cases of disability prevented. According to the Wisconsin Public Health Laboratory,[9] the laboratory cost of MS/MS screening for MCADD is about $4 per infant. The additional costs of confirmatory testing and specialist services for children with MCADD are estimated to add $1.25 per infant

Quality-Adjusted Life Years (QALYs)
Outcome of a treatment measured as the number of years of life saved, adjusted for quality.

screened. The Wisconsin study estimated a cost-effectiveness ratio of $42,000 per **quality-adjusted life years (QALYs)** in the base-case analysis, and $6,000 in the best-estimates analysis. The authors concluded that the true cost-effectiveness ratio is probably below the normal cutoff of $50,000 per QALY most commonly used to justify healthcare interventions.

Challenges for Implementing MCADD Screening

The addition of new disorders to newborn screening programs presents many challenges. For MCADD, these may include implementing new technology in the laboratory and assuring appropriate follow-up to confirm the diagnosis of MCADD and begin effective interventions promptly. Legal and ethical issues are also present at every stage of developing and conducting newborn screening programs.

Laboratory Implementation Issues: The use of MS/MS has proven to be a reliable method to screen for MCADD. Because plasma concentrations of MCADD markers decline significantly after the first few days of life,[3] it is important to establish age-appropriate cutoff levels for newborn screening tests. CDC's Newborn Screening Quality Assurance Program[27] conducts proficiency testing surveys that have allowed U.S. newborn screening laboratories to meet Clinical Laboratory Improvement Amendments (CLIA) quality assurance (QA) requirements.[28] The surveys include specimens enriched with three MCADD markers—C8, C6, and C10 (no synthetic standard is available for C10:1).

Follow-Up Implementation Issues: Short- and long-term follow-up protocols are essential components of newborn screening programs.[29] Several states have developed pilot short- and long-term follow-up studies. For example, Oregon and Iowa are part of a cooperative agreement with CDC to develop a long-term follow-up protocol for MS/MS screening.

Legal and Ethical Issues: MS/MS technology used for MCADD screening is able to detect more disorders than those mandated by newborn screening policy, although for many of these disorders, information about the clinical validity or utility of testing is not available. This presents an ethical dilemma that states have approached in various ways. In some states, parents are given the option to consent to receive results of non-mandated tests; other states do not make non-mandated test results available.

Conclusion

Laboratory testing is only one element of an effective newborn screening program. Clinical follow-up is essential for optimizing outcomes for children and their families. Some states are conducting research that will help fill knowledge gaps related to MS/MS screening for MCADD and other disorders. For example, the

California Department of Health Services instituted a pilot program that lets parents volunteer to have their child undergo supplemental testing for MCADD and other disorders detectable by MS/MS technology. This project aims to generate epidemiological data that will be used to inform policy decisions about which disorders to add to the list of routine screening tests, as well as to evaluate protocols and develop guidelines for follow-up.

Resources

General

National Newborn Screening and Genetics Resource Center (NNSGRC)
1912 W. Anderson Lane, Ste. 210
Austin, TX 78757
Phone: (512) 454-6419
http://genes-r-us.uthscsa.edu/index.htm

March of Dimes (MOD)
1275 Mamaroneck Avenue
White Plains, NY 10605
http://www.modimes.org/

Morbidity and Mortality Weekly Report (MMWR)
April 13, 2001; Vol. 50; No. RR-3
Using Tandem Mass Spectrometry for Metabolic Disease Screening Among Newborns: A Report of a Work Group
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5003a1.htm

Newborn Screening Quality Assurance
In Genetics and Public Health in the 21st Century, Khoury MJ et al., editors. Oxford University Press, 2000.
http://www.cdc.gov/genomics/info/books/21stcent3.htm

Tandem Mass Spectrometry

Newborn Screening Quality Assurance Program (NSQAP)
http://www.cdc.gov/nceh/dls/newborn_screening.htm

Policy/Legal Issues

National Conference of State Legislators (NCSL)
Denver Office:
7700 East First Place
Denver, CO 80230
Tel: 303-364-7700
Fax: 303-364-7800

Washington Office:
444 North Capitol Street, N.W., Suite 515
Washington, D.C. 20001
Tel: 202-624-5400
Fax: 202-737-1069
For information re: genetics laws and legislative activity go to:
http://www.ncsl.org/programs/health/screen.htm

Ethics

Hastings Center
Route 9-D / 21 Malcolm Gordon Road
Garrison, NY 10524-5555
Phone: (845) 424-4040
For information re: ethics and newborn screening project go to:
http://www.thehastingscenter.org/research/prog2/healthcarepolicy_4.htm

References

1. Wilson CJ, Champion MP, Collins JE, Clayton PT, Leonard JV. Outcome of medium chain acyl-CoA dehydrogenase deficiency after diagnosis. *Arch Dis Child* May 1999;80: 459-62.

2. March of Dimes Newborn Screening Recommendations. March of Dimes. Available at: http://www.marchofdimes.com/professionals/580_4043.asp. Accessed Apr 11, 2003.

3. Chace DH, Kalas TA, and Naylor EW. The application of tandem mass spectrometry to neonatal screening for inherited disorders of intermediary metabolism. *Annu Rev Genomics Hum Gene*t 2002;3:17-45.

4. CDC. Using tandem mass spectrometry for metabolic disease screening among newborns. A report of a working group. *MMWR* 2001;50(RR-3):1-23.

5. Pourfarzam M, Morris A, Appleton M, Craft A, Bartlett K. Neonatal screening for medium-chain acyl-CoA dehydrogenase deficiency. *Lancet* 2001;358:1063-4.

6. Carpenter K, Wiley V, Sim KG, Heath D, Wilcken B. Evaluation of newborn screening for medium chain acyl-CoA dehydrogenase deficiency in 275,000 babies. *Arch Dis Child Fetal Neonatal Ed* 2001; 85(2):F105-9.

7. Andresen BS, Dobrowolski SF, O'Reilly L, Muenzer J, McCandless SE, Frazier DM, et al. Medium-chain acyl-CoA dehydrogenase (MCAD) mutations identified by MS/MS-based prospective screening of newborns differ from those observed in patients with clinical symptoms: identification and characterization of a new, prevalent mutation that results in mild MCAD deficiency. *Am J Hum Genet* 2001; 68:1408-18.

8. Zytkovicz TH, Fitzgerald EF, Marsden D, Larson CA, Shih VE, Johnson DM, et al. Tandem mass spectrometric analysis for amino, organic, and fatty acid disorders in newborn dried blood spots. *Clin Chem* 2001;47:1945-55.

9. Insinga RP, Laessig RH, Hoffman GL. Newborn screening with tandem mass spectrometry: examining its cost-effectiveness in the Wisconsin Newborn Screening Panel. [erratum appears in *J Pediatr* 2003 Jan;142(1):56]. *J Pediatr* 2002;141:524-31.

10. Schulze A, Lindner M, Kohlmuller D, Olgemoller K, Mayatepek E, Hoffmann GF. Expanded newborn screening for inborn errors of metabolism by electrospray ionization-tandem mass spectrometry: results, outcome, and implications. *Pediatrics* 2003;111:1399-406.

11. Chace DH, Hillman SL, Van Hove JL, Naylor EW. Rapid diagnosis of MCAD deficiency: quantitatively analysis of octanoylcarnitine and other acylcarnitines in newborn blood spots by tandem mass spectrometry. *Clin Chem* 1997;43:2106-13.

12. Vreken P, van Lint AE, Bootsma AH, Overmars H, Wanders RJ, van Gennip AH. Quantitative plasma acylcarnitine analysis using electrospray tandem mass spectrometry for the diagnosis of organic acidaemias and fatty acid oxidation defects. *J Inherit Metab Dis* 1999;22:302-6.

13. Tandem mass spectrometry in newborn screening. American College of Medical Genetics/American Society of Human Genetics Test and Technology Transfer Committee Working Group. *Genet Med* 2000;2:267-9.

14. National Newborn Screening and Genetics Resource Center. U.S. National Screening Status Report-MS/MS. Web site. Available at: http://genes-r-us.uthscsa.edu/resources/newborn/msmstests.htm. Accessed Jan 7, 2004.

15. Atkinson K, Zuckerman B, Sharfstein JM, Levin D, Blatt RJ, Koh HK. A public health response to emerging technology: expansion of the Massachusetts newborn screening program. *Public Health Rep* 2001;116:122-31.

16. Seymour CA, Thomason MJ, Chalmers RA, Addison GM, Bain MD, Cockburn F, et al. Newborn screening for inborn errors of metabolism: a systematic review. *Health Technol Assess* 1997;1:i-iv,1-95.

17. Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leaonard JV, et al. Neonatal screening for inborn errors of metabolism: cost, yield and outcome. *Health Technol Assess* 1997;1:i-iv,1-202.

18. Wang SS, Fernhoff PM, Hannon WH, Khoury MJ. Medium chain acyl-CoA dehydrogenase deficiency human genome epidemiology review. *Genet Med* 1999;1: 332-9.

19. Iafolla AK, Thompson RJ Jr, Roe CR. Medium-chain acyl-coenzyme A dehydrogenase deficiency: clinical course in 120 affected children. *J Pediatr* 1994;124:409-15.

20. Wilcken B, Hammond J, Silink M. Morbidity and mortality in medium chain acyl coenzyme A dehydrogenase deficiency. *Arch Dis Child* 1994;70:410-2.

21. Pollitt RJ, Leonard JV. Prospective surveillance study of medium chain acyl-CoA dehydrogenase deficiency in the U.K. *Arch Dis Child* 1998;79:116-9.

22. Zytkovicz TH, Fitzgerald EF, Marsden D, Larson CA, Shih VE, Johnson DM, et al. Tandem mass spectrometric analysis for amino, organic, and fatty acid disorders in newborn dried blood spots: a two-year summary from the New England Newborn Screening Program. *Clin Chem* 2001;47:1945-55.

23. Wilcken B, Carpenter K, Wiley V. Comment. *Lancet* 2002;359:627-8.

24. Waisbren SE, Albers S, Amato S, Ampola M, Brewster TG, Demmer L, et al. Effect of expanded newborn screening for biochemical genetic disorders on child outcomes and parental stress. *JAMA* 2003;290:2564-72.

25. Schoen EJ, Baker JC, Colby CJ, To TT. Cost-benefit analysis of universal tandem mass spectrometry for newborn screening. *Pediatrics* 2002;110:781-6.

26. Venditti LN, Venditti CP, Berry GT, Kaplan PB, Kaye EM, Glick H, et al. Newborn screening by tandem mass spectrometry for medium-chain Acyl-CoA dehydrogenase deficiency: a cost-effectiveness analysis. *Pediatrics* 2003;112:1005-15.

27. Meredith-Malloy N, editor. Newborn Screening Quality Assurance Program: 2002 Tandem Mass Spectrometry Annual Summary Report. Atlanta: Centers for Disease Control and Prevention, 2003;2:1-27.

28. American Academy of Pediatrics/Newborn Screening Task Force. Serving the family from birth to medical home. *Pediatrics* 2000;106(suppl):383-427.

29. Pass KA, Lane PA, Fernhoff PM, Hinton CF, Panny SR, Parks JS, et al. U.S. newborn screening system guidelines II: follow-up of children, diagnosis, management, and evaluation. Statement of the Council of Regional Networks for Genetic Services (CORN). *J Pediatr* 2000;137:S1-46.

Chapter 6

The Family History Public Health Initiative

Paula Yoon and Maren Scheuner

Family History Is Valuable for Prevention

People who have close relatives with certain chronic diseases, like heart disease, diabetes, and cancer, are more likely to develop those diseases themselves. Studies suggest that having a first-degree relative with one of these diseases can at least double a person's risk of developing disease; this risk generally increases with an increasing number of affected relatives, especially if their disease was diagnosed at an early age.[1] Physicians usually collect information about a patient's family history, but often do not discuss, revisit or update it over time. Thus, they may miss opportunities to offer specific prevention recommendations for diseases that run in the patient's family.[2]

What is a First-Degree Relative?

First-degree relatives include immediate blood relatives, such as parents, siblings, or children. Second-degree relatives include aunts, uncles, nieces, nephews, and grandparents. First-degree relatives have approximately half their genes in common. From a genetic standpoint, you are closer to first-degree relatives because you share more of the same genetic material.

Knowledge of increased risk for chronic diseases due to family history can influence the clinical management and prevention of a disease. Prevention strategies include:

- targeted lifestyle changes such as diet, exercise, and stopping smoking,
- screening at earlier ages, more frequently, and with more intensive methods than might be used for average risk individuals,
- use of chemoprevention such as aspirin, and
- referral to a specialist for assessment of genetic risk factors.

Screening and prevention guidelines are available for many chronic disorders,[3-6] and data are accumulating regarding the effectiveness of these strategies for high-risk individuals.[7-9]

Disease Risk Due to Gene-Environment Interactions

Most common diseases result from the complex interactions of multiple genes with multiple environmental factors. These factors can include long-term exposures to pollution or sunlight, behaviors such as smoking or inactivity, and cultural factors such as diet. Despite progress in sequencing the human genome, considerable research is needed to understand the genes that predispose to chronic diseases.

Among the genes that are being studied are genes that code for carcinogen metabolizing enzymes (e.g., *NAT2* and *GSTM1*) and genes that regulate nutrient metabolism (e.g., *MTHFR*). Much work still needs to be done in order to understand how genes interact with each other and the environment to cause disease. In the meantime, family medical history represents a "genomic tool" that can capture the interactions of genetic susceptibility, shared environment, and common behaviors in relation to disease risk.

Role of Genetic Testing

Single-Gene Variant
A trait that is determined by a single gene.

Single-gene variants handed down in families may result in rare diseases such as Huntington's disease. Some of these variants (e.g., of *BRCA1* and *APC*) also result in common diseases, like breast and colorectal cancer. For more information, see *Chapter 4, Public Health Assessment of BRCA1 and BRCA2 Testing for Breast and Ovarian Cancer*. Fortunately, these variants are rare in the population, but when a harmful genetic variant is suspected in a high risk family, genetic testing may be possible.

Confirming a suspected genetic risk can relieve anxiety related to not knowing and may suggest specific preventive interventions. Genetic testing can also reassure relatives when familial susceptibility can be ruled out. A genetic specialist can determine when genetic testing might be considered and can counsel the patient on the risks and benefits of the testing process. A family history assessment is the first step towards identifying high risk families who may benefit from a genetic work-up.

Family History and the Family Tree

Family history information that is needed to assess disease risk includes the number, gender, and closeness of affected relatives, their ages at disease onset, and any associated health conditions. Organizing this information into a detailed family tree or pedigree graphically illustrates clusters and inheritance of traits within families. Instructions for recording a family history and drawing a pedigree can be found on many Web sites, including that of the National Society of Genetic Counselors (http://www.nsgc.org/consumer/familytree/index.asp).

The CDC Family History Initiative

The CDC Office of Genomics and Disease Prevention (OGDP) is collaborating with several CDC programs and the National Institutes of Health (NIH) in a family history public health initiative. The purpose of this initiative is to evaluate the use of family history for assessing risk for common diseases, as well as its role in influencing early detection and prevention strategies.

The initiative began in early 2002 with a review of the existing literature and a paper that introduced the concept of using family history for disease prevention.[1] At a workshop in May 2002, experts reviewed family history as a risk factor for several chronic diseases including cardiovascular disease, diabetes, asthma, and several cancers. Workshop participants discussed the accuracy and reliability of family medical history and attempted to gauge how useful knowledge of family history might be for motivating people to change their behavior. A series of scientific papers based on the workshop presentations was published in February 2003 as a theme issue in the *American Journal of Preventive Medicine*.[10]

Interested workshop participants joined with others to form the Family History Workgroup in order to explore, develop and test family history tools for disease prevention. This multidisciplinary group includes representatives from CDC programs, the NIH, other federal agencies, state public health programs, academia, and the health care community.

Selecting Diseases to Include in a Family History Tool

The Family History Workgroup first established the following criteria for deciding which diseases should be included in a family history tool:

- substantial public health burden,
- clear case definition,
- high awareness of disease status among relatives,
- accurately reported by relatives,
- family history is an established risk factor,
- prevalence of family history can be estimated in the population,
- effective interventions for primary and secondary prevention, and
- different recommendations for groups at different levels of familial risk.

The workgroup next reviewed other family history tools being used or developed for primary care and compiled a list of approximately 45 diseases that were included in these tools. After applying the inclusion criteria, the workgroup narrowed the list to 15 diseases.

Prototype Family History Tool

For public health purposes, family history tools should be simple, easily applied, and adaptable to different settings. Most of the existing family history tools that the workgroup reviewed were found to be too lengthy and difficult to interpret. The workgroup decided in May 2003 to develop a prototype family history tool that would include only a few diseases, making it easier to pilot test and evaluate in population-based settings. The diseases included in the prototype include:

- heart disease,
- stroke,
- diabetes, and
- colorectal, breast and ovarian cancer.

The prototype family history tool consists of a three-step process of data collection, risk classification, and recommendations for intervention, as shown in Figure 1.

Data Collection

The family history tool prototype is called Family Healthware. It is computer-based and self-administered and can be completed in a provider's office or at home before a medical consultation. The work group decided to create an electronic version of the tool that can process complex familial risk algorithms and provide feedback to patients and physicians. When completed, the tool will be made available as a CD-ROM and as a download from the Internet. Other formats, such as paper-based or touch-screen versions, are also being considered.

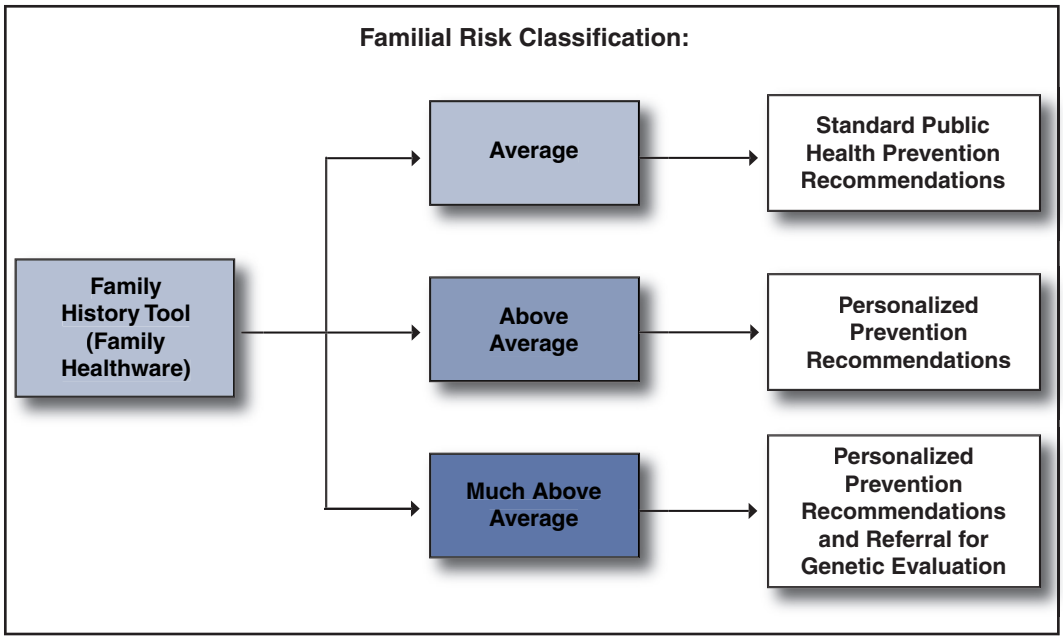
Family Healthware will collect:

- personal information, including age, gender, and race/ethnicity,
- numbers of relatives in each category (mother, father, children, siblings, grandparents, aunts, and uncles),
- personal history of heart disease, diabetes, stroke, colorectal cancer, breast cancer, and ovarian cancer, indicating whether age at diagnosis was below or above a disease-specific age threshold (e.g., age 60 for heart disease),
- history of the same six diseases for relatives and age at diagnosis in each category, and
- personal risk factors, such as body mass index (determined by height and weight), diet, exercise, use of tobacco products and alcohol, and screening behaviors such as mammogram and cholesterol screening.

Classification

Family Healthware will include software algorithms that interpret the data and provide a brief synopsis of disease risk and suggestions for follow-up. The goal is to keep data collection simple while gathering enough information to classify people into risk levels. The underlying scheme being considered includes three risk levels—average, above average, and much above average—that are determined mainly by the number and closeness of affected relatives and their ages at disease onset.[11] The risk classification would be used to guide and inform prevention activities.

Figure 1, Example: Proposed scheme for using family history to guide and inform prevention



Intervention

Family Healthware is being developed for use in primary care settings and for public health purposes. Primary care providers can play a major role in prevention by reviewing their patients' family histories and making recommendations for early detection or intervention strategies and counseling on lifestyle. Patients will be able to maintain and update their family history records at home and can discuss the implications with their providers during annual visits. The general public will also be able to retrieve the tool from the Internet and complete the assessment at home.

Family Healthware will produce an individualized assessment page that indicates the level of familial risk for each disease, and may include prevention messages about recommended behavior changes and screening.

An electronic resource manual that complements the tool is being developed for health care providers. The resource manual is organized into disease-specific chapters and includes an explanation of risk levels, including possible genetic conditions underlying "much above average" risk, and suggestions for assessment of additional risk factors. The resource manual will also include recommended preventive interventions for each level of risk (if available), and additional resources for health care providers and patients. These recommendations will be evidence-based, appropriately referenced, and supported by links to other Web sites, such the National Cancer Institute, the American Cancer Society, the National Heart, Lung and Blood Institute, the American Heart Association, Online Mendelian Inheritance in Man, and GeneClinics/GeneTests.

Evaluation Studies

Extensive pilot testing and evaluation studies are being planned to examine the validity and utility of the Family Healthware prototype. At the end of FY 2003, CDC awarded funding to three research centers—the University of Michigan School of Medicine, Evanston Northwestern Healthcare Research Institute, and Case Western Reserve University School of Medicine—for a collaborative study set in primary care clinics. The study will assess whether family history risk assessment, classification, and personalized prevention messages influence health behaviors and the use of preventive medical services. Additional studies will be developed to evaluate the tool in other public health and preventive medicine settings.

References

1. Yoon P, Scheuner MT, Peterson-Oehlke K, Gwinn M, Faucett A, Khoury MJ. Can family history be used as a tool for public health and preventive medicine? *Genet Med* 2002;4:304-10. Also available at: http://www.cdc.gov/genomics/info/reports/research/famhist_yoon.htm. Accessed Feb 16, 2004.
2. Acheson LS, Wiesner GL, Zyzanski SJ, Goodwin MA, Stange KC. Family history-taking in community family practice: implications for genetic screening. *Genet Med* 2000; 2:180-5.
3. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.
4. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393-403.
5. Straus SE, Majumdar SR, McAlister FA. New evidence for stroke prevention. *JAMA* 2002;288:1388-95.

6. Smith RA, Cokkinides V, von Eschenbach AC, Levin B, Cohen C, Runowicz CD, et al. American Cancer Society guidelines for the early detection of cancer. *CA Cancer J Clin* 2002;52:8-22.

7. Järvinen HJ, Aarnio M, Mustonen H, Aktan-Collan K, Aaltonen LA, Peltomaki P, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterol* 2000;118:829-34.

8. Narod SA, Risch H, Moslehi R, Dorum A, Neuhausen S, Olsson H, et al. Oral contraceptives and the risk of hereditary ovarian cancer. *N Engl J Med* 1998;339:424-8.

9. Narod SA, Brunet J, Ghadirian P, Robson M, Heimdal K, Neuhasusen S, et al, for the Hereditary Breast Cancer Study Group. Tamoxifen and the risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: A case-control study. *Lancet* 2000;356:1876-81.

10. CDC. Family History as a Tool for Public Health and Preventive Medicine Workshop, May 1-2, 2002. Atlanta, Georgia. Web site. Available at: http://www.cdc.gov/genomics/info/conference/famhist.htm. Accessed Feb 16, 2004.

11. Scheuner MT, Wang SJ, Raffel LJ, Larabell SK, Rotter JI. Family history: a comprehensive genetic risk assessment method for the chronic conditions of adulthood. *Am J Med Genet* 1997;71:315-24.

Chapter 7

Genetic Testing and the Prevention of Coronary Heart Disease: A Case Study

Marta Gwinn and Ann Malarcher

A 50 year-old man, Mr. C, calls the Department of Public Health with a question:

"Will a **genomic profile** *test help me know what I should do to prevent coronary heart disease?"*

Mr. C says that his father had a heart attack when he was 59 years old. He knows that he needs to take care of his health and just had a complete physical, including an electrocardiogram and a treadmill test. Everything checked out fine, but because his cholesterol was "a little high," his doctor recommended a reduced-fat diet and prescribed a lipid-lowering drug. Mr. C's wife then asked her doctor, an alternative medicine practitioner, for another opinion. He suggested that Mr. C should look into the new DNA tests that provide an individualized "genomic profile" and personalized recommendations for nutritional supplements to prevent coronary heart disease. Mr. C visited several Web sites that offer such tests, but wasn't sure whether he should get one. He called the health department because he was looking for an objective opinion, unbiased by provider preferences or commercial interests.

Genomic Profiling
Concurrent detection of multiple gene variants that have been associated with predisposition to a particular disease.

Is Genomic Profiling for Coronary Heart Disease (CHD) Ready for Prime Time?

Diseases of the heart are the leading cause of death in the United States, accounting for almost one third of all deaths. Most of these are due to CHD, including deaths from myocardial infarction and CHD-related heart failure. After declining substantially during the 20th century, CHD and stroke incidence and mortality may be leveling off, suggesting the need not only for redoubled efforts but also for modified strategies to promote healthy lifestyles and improve early detection and intervention.[1]

Mr. C turned 50 in 2003, the year that also marked the 50th anniversary of the discovery of DNA and completion of the Human Genome Project. Sequencing the genome ahead of schedule has further heightened expectations that health benefits will follow quickly. In particular, the idea that genetic tests could offer

people individualized estimates of risk and interventions based on their genotypes has captured the imagination of scientists and the public. This enthusiasm for personalized medicine has fueled a rush to develop and market new genomic tests, often without establishing that the tests are valid or useful.
Several commercial enterprises have sprung up to offer DNA-based tests for susceptibility to complex diseases, with names such as Obesity Susceptibility Profile, Nutritionscreen, Oxidative Stress Profile and CardioGenomic Profile.* These tests are advertised on Web sites that offer extensive information targeted to consumers, as well as information for health care providers. These "genomic profiles" typically consist of tests for combinations of gene variants; the specific combinations are considered proprietary and are usually not disclosed in online or printed product information.

A critical evaluation of genomic profiling for guiding individualized health promotion and disease prevention concluded that this approach is "not ready for prime time" because of lack of evidence in two key areas: [2]

1. **Clinical Validity:** Many initial reports associating one or more genetic variants with coronary heart disease are not confirmed—and are sometimes contradicted—by subsequent research studies. Systematic approaches to reviewing the evidence are still in early stages of development.

2. **Clinical Utility:** Does genomic profiling provide any information that would change individual prevention or management recommendations? Do these recommendations result in positive behavior change and reduced morbidity and mortality?

Medical Family History as Genomic Profiling

An established approach to "genomic profiling" that should not be overlooked is the medical family history. The tendency for coronary heart disease (CHD) to cluster in families was first recognized over one hundred years ago. A positive family history can capture the effects and interactions of shared genetic and environmental factors, whether measured or unmeasured, that lead to disease expression in a family: *"it is quite possible that even with our ability to measure hundreds and thousands of genes and environments we may find that family history is the best, low-cost way to identify the at-risk subgroups in the population."* [3] In this respect, family history is as relevant to public health programs as it is to clinical practice.[4, 5]

*Use of trade names is for example only and does not imply endorsement of DHHS. For examples, see Genovations: Predictive Genomics for Personalized Medicine, http://www.genovations.com; Sciona, http://www.sciona.com; GeneLink: Genetic Biosciences for Improving the Quality of Life, http://www.bankdna.com.

Family History is Still the Best Genomic Tool

In 2002, a meeting on genomics and chronic disease, conducted by the Chronic Disease Directors, a national organization affiliated with the Association of State and Territorial Health Officials, called for investigating the utility of targeting interventions to persons at risk for chronic diseases because of their family history.[6] The meeting report called for extending the use of family history beyond high-risk families to the much larger group of families at moderate risk for chronic disease due to shared genetic background and environment. This interest spurred the development of the Family History Initiative. See *Chapter 6, The Family History Public Health Initiative*, for more information.

Guidelines for CHD Prevention

Public health agencies and medical care systems are promoting the use of evidence-based guidelines that incorporate family history information to manage risk factors and treat heart disease. The following reports provide examples:

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)
Family history of premature cardiovascular disease (men under age 55 or women under age 65) is identified as a major risk factor for CVD.
http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)
Family history should serve as a factor for making treatment decisions relative to setting and reaching LDL-cholesterol goals.
http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm.

American Heart Association Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update
The guide calls for identifying high-risk patients for whom screening and intervention in first-degree relatives (including children) would be an important aspect of primary prevention.
http://circ.ahajournals.org/cgi/content/full/106/3/388

Conclusion

Mr. C already knows that because of his father's history, he needs to focus on actions to reduce his risk of CHD. Taking a more detailed family history of CHD and stroke could help Mr. C and his doctor discuss additional ways to reduce his risk. Mr. C didn't mention whether his father is the only relative with CHD or discuss his cholesterol level, except to say it was "a little high." Although inherited high-risk syndromes like familial hypercholesterolemia account for only a small proportion of CHD, failure to detect them

can have serious consequences for affected individuals and families.[7] A documented medical family history is valuable for distinguishing both moderate- and high-risk individuals and families.

References

1. CDC. Preventing Heart Disease and Stroke. Web site. Available at: http://www.cdc.gov/nccdphp/bb_heartdisease/index.htm. Accessed Feb 16, 2004.
2. Haga SB, Khoury MJ, Burke W. Genomic profiling to promote a healthy lifestyle: not ready for prime time. *Nature Genet* 2003;34:347-50.
3. Kardia SLR, Modell SM, Peyser PA. Family-centered approaches to understanding and preventing coronary heart disease. *Am J Prev Med* 2003;24:143-51.
4. Hunt SC, Gwinn M, Adams TD. Family history assessment: strategies for prevention of cardiovascular disease. *Am J Prev Med* 2003;24:136-42. Also available at: http://www.cdc.gov/genomics/info/reports/research/famhist_assess.htm. Accessed Feb 16, 2004.
5. CDC. Family History for Preventive Medicine and Public Health. Web site. Available at: http://www.cdc.gov/genomics/activities/famhx.htm. Accessed Feb 16, 2004.
6. Chronic Disease Summit. A report from the Association of State and Territorial Chronic Disease Directors. March 2002. Web site. Available at: http://www.chronicdisease.org/Genomics_Summit_Report.pdf. Accessed Feb 16, 2004.
7. Malarcher AM, Giles WH, Khoury MJ. Helping high-risk families: medical and public health approaches. *Genet Med* 2002;4:239-40. Also available at: http://www.cdc.gov/genomics/oldWeb01_16_04/info/reports/program/highriskfamily.htm. Accessed Feb 16, 2004.

Chapter 8

Genomics and Public Health: Ethical, Legal, and Social Issues

Toby Citrin and Stephen M. Modell

Introduction

This article is divided into sections discussing key ethical, legal and social implications of genomic science for public health. It includes resources that may help public health professionals develop an approach for resolving these issues as they take shape now and in the future. Ethical, legal and social are somewhat arbitrary categories because these issues are almost always intertwined. For example, the potential misuse of genetic information for purposes of discrimination and stigmatization raises ethical concerns, points out the need for protective legislation, and describes a significant social problem. Ethical, legal and social issues may be either real or only perceived, but the distinction between reality and perception often does not matter to consumers and policy makers. Examining these issues from a public health perspective can be helpful in either instance.

Ethical, Legal and Social Issues (ELSI)

During the last decade and a half, the National Human Genome Research Institute (NHGRI) has supported an extensive program of scholarly work on the ethical, legal, and social implications of genetics research, known collectively as ELSI. ELSI inquiry examines the values underlying the use of new genetic technology, ideally before it is in use.

Public Health Ethical, Legal and Social Issues (PHELSI)

Since 1999, genetic research has increasingly focused on the discovery of human genetic variations linked to susceptibility to common illnesses, rather than on the rare, **single-gene disorders** that have been the traditional focus of clinical genetics. Efforts to understand and prevent these more widespread conditions, which often involve complex gene-environment interactions, fall under the purview of public health. We have used the term PHELSI to refer to ethical, legal and social implications that arise when genomics is used for the advancement of public health.

Single-Gene Disorder
Refers to a disorder that is determined by a single gene.

Is PHELSI Different From ELSI?

The ethical, legal and social implications of using genetic technology in medicine have been the subject of a rich and growing literature.[1] Most of this scholarship has applied principles of bioethics to the use of genetics in medical research and practice, and emphasizes the individual and the patient-physician relationship.

At the same time, there has been a renaissance in the literature on public health ethics in the past decade. Public health actions are intended for the public good, defined either in terms of groups of individuals or the population as a whole.[2] The public health perspective is at the center of the distinction between PHELSI and ELSI.

Public Health Ethics

While scholars have considered the ethical principles underlying public health practices for many years, more recent scholarship has made a distinction between bioethics and principles more specifically relevant for public health. Lachmann writes about the "conflicts between the priorities of public health and the emphasis of medical ethics on the duty of the doctor to the individual patient".[3] Lane et al. describe the historical identification of bioethics with the rights of the individual, limiting its value to address current issues of public health—especially issues relating to health disparities among different demographic groups.[4]

Rothstein has identified an "ongoing need to reassess [public health's] scientific, ethical, legal, and social underpinnings",[5] and Cole has pointed out that most public health programs require an explicit fundamental justification which can be based upon principles of morality.[6] Other scholars have recently formulated frameworks for the application of ethics in public health,[7,8] and have identified literature uniquely appropriate for considering ethical issues in public health.[9] The American Public Health Association has promulgated a Public Health Code of Ethics.[10]

As genomics is increasingly studied and practiced in the public health context, it is useful to analyze the ensuing ethical, legal and social issues using a public health framework that emphasizes:

- the use of science to further the health of the population, rather than the health of particular individuals,
- the welfare of the collective as well as the autonomy of the individual,
- issues of discrimination and health disparities,
- the historical relationship between public health and distributive justice (the societal obligation to be fair when providing health resources to different groups), and
- balancing the prevention of disease against the curing of illness.[11]

Scrutiny of the Tuskegee syphilis study and the discriminatory sickle cell screening programs of the 1970s has led public health officials to emphasize the avoidance of social harms to particular groups (e.g., African Americans); in addition to the desire to avoid harm, public health ethics are also concerned about treating all groups with fairness. The principle of social justice seen through the lens of public health ethics requires that differences in race/ethnicity, socioeconomic status, and inherited family background should not skew how the benefits of genomic research are distributed.[4,12] Public health policy offers a variety of safeguards against potential inequities, from public education to collective action.

Ethical Issues in Public Health Genomics

As genomic research points out new ways to identify persons at risk, using this knowledge presents new ethical challenges. Most of the literature on ethical issues related to public health genetic screening deals with mandatory newborn screening programs for single-gene disorders (e.g., phenylketonuria and sickle cell disease). Tests for these disorders have high predictive value, and treatment can either eliminate or reduce the severity of symptoms. Tandem mass spectrometry, in contrast, has delivered an expanded list of potential newborn screening tests, for which predictive value and usefulness are less certain.[13] See *Chapter 5, Newborn Screening for MCAD Deficiency*, for more information.

Increasingly, screening programs are being suggested for the identification of individuals at risk for chronic disease (e.g., cystic fibrosis, hemochromatosis, coronary heart disease, and cancer), suggesting a different balance of ethical considerations.[14] An even more divisive ethical area is prenatal screening for conditions without definitive or effective treatment, e.g., beta-thalassemia (Cooley's anemia), Tay-Sachs disease, or serious or fatal **trisomies**. Some have argued that the focus of public health efforts should be on "phenotypic prevention" (the prevention of disease manifestation) rather than "genotypic prevention" (avoiding the birth of individuals with a given genotype).[15] Others have pointed out the benefits of prenatal screening as a public health intervention, given that it provides couples with risk-related information. The informed couple can use this information in their decision-making, and make specialized plans in the case of a decision to deliver an infant with a genetic condition.[16]

Trisomy
The presence of an extra chromosome, resulting in a total of three chromosomes of that particular type instead of the usual pair.

The use of family history to identify individuals at risk for disease has been a traditional tool of medical diagnosis and is now being tested as a potentially useful public health tool for identifying at-risk populations.[17] See *Chapter 6, The Family History Public Health Initiative*, for more information. Similarly, information on averted deaths (e.g., from arrhythmia in long QT syndrome) and on cause of death from death records has been proposed as a basis for identifying family members at risk for the same disease.[18] The use of family history and death records, however, raises the issue of privacy rights of persons alive or dead.[19]

Another area of increasing public health interest is the use of existing biological samples gathered for one purpose, e.g., blood spots from newborn screening programs, or blood collected for the National Health and Nutrition Examination Survey (NHANES), (see *Chapter 1, National Health and Nutrition Examination Survey*), for other applications, such as epidemiologic research and identifying individuals with similar risk profiles who could benefit from screening.[20, 21]

Each of these current and potential public health activities raises issues of informed consent, confidentiality of genetic information, potential stigmatization and discrimination, and the balancing of individual autonomy against the public health goal of collective action. Appropriate analysis of these issues requires care in order to maintain a clear distinction between activities undertaken for research and those to be implemented in public health practice.[22, 23]

Legal Issues in Public Health Genomics

Each of the ethical issues identified above can also be considered from a legal perspective. In general, laws and policies to guide the use of genomic technology lag far behind its actual application in medical and public health practice. While legal scholars have developed useful models of legislation, summaries of relevant state legislation maintained by the National Conference of State Legislatures disclose diverse policies, variable responses among states to the need for legislation, and lack of consensus on whether federal, state or mixed legislation is most appropriate.[24] Variance also exists within and among states in the spread of protections offered by state public health records privacy laws, further complicated by Health Insurance Portability and Accountability Act (HIPAA) privacy rules on unauthorized disclosures of health information.[25]

A growing area of concern is commercialization arising from the private ownership of genomic technology, and the increasing conflict between financial incentives driving the marketing of biomedical technology and the public health goal of maximizing the public's health through cost-effective interventions.[26, 27]

Social Issues in Public Health Genomics

The incorporation of genomics in public health practice has significant implications for social policy. As we consider the implications of each new genomic intervention in public health, it is essential that we also consider the cumulative impact of genomics on the nature of our society. Two related areas of social concern are fears of a rebirth of eugenics and the potential of genetics to widen health disparities between different demographic groups.

Historians have pointed out the intersections between public health and eugenics during the early 20th century and the danger that new genetic technologies might

be misused to serve goals other than that of preventing disease. Pernick warns that "Past similarities between eugenics and public health serve as an alarm clock for all the health sciences, not as a lullaby for genetics",[28] and Duster has expressed concern that given the discriminatory context of American society, the application of new genetic technologies could lead to a return of eugenics through the "back door".[29] Conversely, Kitcher has described the positive potential of "utopian genetics" to serve public health goals, given adequate public education and equal access to genetic technology.[30]

The "double-edged sword" of genetics pointed out by many commentators can result in either the widening or the narrowing of health disparities among the population. An increasing amount of genetics research is focused on chronic diseases, and highlights group disparities in disease frequency. Disparities in access to the benefits of genomic research, or the distortion of research findings to stigmatize racial and ethnic minorities, could further widen health inequities.[31] If the new tools of genetics are made available to all who could benefit, however, the prevalence of many chronic diseases could be reduced in the American population.

Engagement and Education to Address PHELSI

How can we realize the positive potential of genomics as a tool of public health while avoiding social harms? The literature suggests that the related strategies of public engagement and public education are crucial.

The active engagement of an informed public is essential to ensuring that these new, powerful scientific tools are used in the public interest to achieve improvements in total population health. A large and growing body of literature has developed to define and support a resurgence of civic participation in policy making.[32, 33] The NIH-funded project *Communities of Color and Genetics Policy* has demonstrated a successful process for engaging minorities in policy development to address concerns of special relevance to African-American and Latino citizens.[34] In addition to participation in community policy making, the representation of diverse groups on newborn and chronic disease advisory committees and among key genetics decision-makers should be a major priority of public health.

The most important factor for determining whether genetics will enhance or impede public health goals is the extent to which the public is adequately informed about genetics. Unfortunately, a large share of public knowledge about genetics has been derived from mass media, highlighting presumed genetic breakthroughs, and fostering a sense of genetic determinism. The interplay of genes and environment in most diseases is not widely understood.[35]

Public health leadership should promote citizen education in several ways:

- *Information to the Media:*
  Public health professionals in practice and academia should become providers of accurate information on genetics to the media, in order to counterbalance the more sensational reporting that too often occurs. The public health viewpoint can add depth and social concern to the sources often tapped by the media for information: biomedical researchers and corporate biotech and pharmaceutical firms.

- *Education:*
  Public health practitioners have a role in responding to teaching requests from social and civic organizations, and in providing "information-on-demand" resources relating to genetics.[36, 37] In addition, academically-based public health professionals have the responsibility of assuring that future public health practitioners are knowledgeable about public health genetics and PHELSI issues.[7, 38] A fundamental, long-term educational strategy also includes K-12 education. Since most formal education in genetics is acquired by the end of high school, it is essential that this basic education be accurate and stress the ethical, legal and social implications of genetics as well as the science.[39] If our youth learn about genetics as one of several factors influencing health and disease, and as a growing technology that can be put to beneficial or harmful uses, they will have the intellectual background to interpret and judge other sources of information on genetics that they encounter as adults.

A Genetic Agenda for Public Health

Our brief review of the literature on PHELSI suggests several key roles for public health professionals in public health agencies, academic institutions, or other organizations whose work involves improving community health. In addition to learning about and using genetic tools that can be incorporated in public health practice, public health professionals must address the ethical, legal and social issues that arise. They can carry out this role in their practice and by encouraging public engagement, promoting public education, and becoming effective providers of balanced information. By assuming these responsibilities, public health professionals will help assure that genetic technologies are applied in ways that are ethically, socially, and legally just, and consonant with the values of a diverse society.[2]

References

For an expanded list of references for this chapter, please visit our Web site at http://www.cdc.gov/genomics/activities/ogdp/2003.htm

1. Annas GJ, Elias S, eds. *Gene Mapping: Using Law and Ethics as Guides*. New York: Oxford Univ. Press; 1992.
2. Institute of Medicine, Board on Health Promotion and Disease Prevention. Committee on Assuring the Health of the Public in the 21st Century. The future of the public's health in the 21st century. Washington, DC: National Academies Press; 2003:28-33. Also available at: http://www.iom.edu/report.asp?id=4304. Accessed Feb 16, 2004.
3. Lachmann PJ. Public health and bioethics. *J Med Philos* 1998;23:297-302.
4. Lane SD, Rubinstein RA, Cibula D, et al. Towards a public health approach to bioethics. In: Cantwell A-M, Friedlander E, Trainor ML, eds., Ethics and Anthropology: Facing Future Issues in Human Biology, Globalism, and Cultural Property. *Ann NY Acad Sci* 2000;925:25-36.
5. Rothstein MA. Rethinking the meaning of public health. *J Law Med Ethics* 2002;30: 144-9.
6. Cole P. The moral bases for public health interventions. *Epidemiology* 1995;6:78-83.
7. Callahan D, Jennings B. Ethics and public health: forging a strong relationship. *Am J Pub Hlth* 2002;92:169-76.
8. Kass NE. An ethics framework for public health. *Am J Public Health* 2001;91:1776-82.
9. Beauchamp DE, Steinbock B, eds. New Ethics for the Public's Health. New York: Oxford Univ. Press; 1999.
10. American Public Health Association. Public Health Code of Ethics. Washington, D.C;2001. Web site. Available at: http://www.apha.org/codeofethics. Accessed Jan 11, 2004.
11. Michigan Center for Genomics and Public Health. Ethical, legal, and social issues in public health genetics. Ann Arbor, MI; 2002. Web site. Available at: www.sph.umich.edu/genomics/focus_areas/PHELSI.html. Accessed Jan 11, 2004.
12. Turnock BJ. *Public Health: What It Is and How It Works*. Gaithersburg, MD: Aspen Publishers; 1997.
13. Atkinson K, Zuckerman B, Sharfstein JM, Levin D, Blatt RJ, Koh HK. A public health response to emerging technology: expansion of the Massachusetts newborn screening program. *Pub Health Rep* 2001;116:122-31.
14. Burke W, Coughlin SS, Lee NC, Weed DL, Khoury MJ. Application of population screening principles to genetic screening for adult-onset conditions. *Genet Test* 2001;5:201-11.

15. Khoury MJ. Relationship between medical genetics and public health: changing the paradigm of disease prevention and the definition of a genetic disease. *Am J Med Genet* 1997;71:289-91.

16. Clayton EW. What should be the role of public health in newborn screening and prenatal diagnosis? *Am J Prev Med* 1999;16:111-5.

17. CDC. Family history as a tool for public health and preventive medicine: a public health perspective. Atlanta, GA; 2003. Web site. Available at: http://www.cdc.gov/genomics/info/perspectives/famhistr.htm. Accessed Dec18, 2003.

18. Liebman J. Some legal, social, and ethical issues related to the genetic testing revolution, as exemplified in the long QT syndrome. *J Electrocardiol* 2001;34 Suppl: 183-8.

19. Botkin JR. Protecting the privacy of family members in survey and pedigree research. *JAMA* 2001;285:207-11.

20. McQuillan GM, Porter KS, Agelli M, Kington R. Consent for genetic research in a general population: the NHANES experience. *Genet Med* 2003;5:35-42.

21. Pelias MK, Markward NJ. Newborn screening, informed consent, and future use of archived tissue samples. *Genet Test* 2001;5:179-85.

22. Press N, Clayton EW. Genetics and public health: informed consent beyond the clinical encounter. In: Khoury M, Burke W, Thomson E, eds., *Genetics and Public Health in the 21st Century*. New York: Oxford Univ. Press;2000:505-26.

23. Holtzman NA, Andrews LB. Ethical and legal issues in genetic epidemiology. *Epidemiol Rev* 1997;19:163-74.

24. National Conference of State Legislatures. Genetic Technologies Project. Denver, CO;2003. Web site. Available at: http://www.ncsl.org/programs/health/Genetics/gtp-o.htm. Accessed Jan 11, 2004.

25. Gostin LO. National health information privacy regulations under the Health Insurance Portability and Accountability Act. *JAMA* 2001;285:3015-21.

26, Gollust SE, Hull SC, Wilfond BS. Limitations of direct-to-consumer advertising for clinical genetic testing. *JAMA* 2002;288:1762-7.

27. Caufield T. Genetics services and market forces. *Nat Rev Genet* 2002;3:734.

28. Pernick MS. Eugenics and public health in American history. *Am J Public Health* 1997;87:1767-72.

29. Duster T. *Backdoor to Eugenics*. New York: Routledge; 1990.

30. Kitcher P. *The Lives to Come*. New York: Simon & Schuster; 1996.

31. Lee SS, Mountain J, Koenig BA. The meanings of "race" in the new genomics: implications for health disparities research. *Yale J Health Policy Law Ethics* 2001;1:33-75.

32. Yankelovich D. *The Magic of Dialogue*. New York: Simon & Schuster; 1999.

33. Garland MJ. Experts and the public: a needed partnership for genetic policy. *Public Underst Sci* 1999;8:241-54.

34. Citrin T. Communities of color and genetics policy project: policy reports and recommendations. Ann Arbor, MI:University of Michigan;2001. Web site. Available at: http://www.sph.umich.edu/genpolicy. Accessed Jan 11, 2004.

35. Khoury MJ, Thrasher JF, Burke W. Challenges in communicating genetics: a public health approach. *Genet Med* 2000;2:198-202.

36. EvansGroup. Washington state genetics education plan. Seattle, WA; 1997. Web site. Available at: http://mchneighborhood.ichp.edu/wagenetics/media/wagenetic.pdf. Accessed Jan 11, 2004.

37. Kaye CI, Proud VK. Genetics education: guidelines and resources for the public health. In: Freeman SB, Hinton CF, and Elsas, II, LJ, eds., Genetic Services: Developing Guidelines for the Public's Health. Atlanta, GA: Council of Regional Networks for Genetics Services (CORN); 1996.

38. Modell SM, Citrin T. Ethics instruction in an issues-oriented course on public health genetics. *Hlth Educ Behav* 2002;29:43-60.

39. McInerney JD. The Human Genome Project and biology education. *BioScience* 1995;45:786-91.

Chapter 9

Carrier Testing for Cystic Fibrosis: Transition from Research to Clinical Practice

Linda A. Bradley and Ira Lubin

About Cystic Fibrosis

Autosomal Recessive
Inheritance of two copies of a mutant gene, one from each parent, on one of the 22 autosomes (chromosomes other than X or Y).

Cystic fibrosis (CF) is one of the most common **autosomal recessive** genetic diseases in North America, occurring most frequently in Caucasian Americans of European descent, and less frequently in other racial and ethnic groups, such as African Americans and Asian Americans. CF is characterized by chronic lung disease, problems with digestion, and male infertility. Pancreatic problems occur in 85% of affected individuals, but lung function is the critical factor in prognosis and survival.

CFTR: The CF Gene

The *CFTR* gene was identified on Chromosome 7 in 1989, and controls the production of *cystic fibrosis transmembrane conductance regulator* (*CFTR*) protein. This protein controls the flow of salt and water in and out of cells, particularly those that line the lungs and digestive system. Abnormal *CFTR* protein results in reduced flow of water and build-up of thick secretions, and leads to the characteristic symptoms of CF.

Over 1,000 disease-associated changes, or mutations, have been identified in the *CFTR* gene, but most are rare. One mutation, Δ*F508*, is by far the most commonly found among Caucasians of European descent. In this group, about 1 in 25 persons is a carrier—that is, has one *CFTR* gene with a mutation and one normal *CFTR* gene. Carriers are asymptomatic and not at risk for CF. Individuals with CF have mutations in both *CFTR* genes—one from each parent—and are deficient in functional *CFTR* protein.

Cystic Fibrosis Carrier Testing

Following the release of a practice guideline on prenatal/preconception cystic fibrosis carrier testing in October of 2001, the number of pregnant women choosing to have this testing is increasing rapidly. One laboratory reported an increase from 1,000 tests per month in 2001 to 14,000 tests per month in mid-2003.[1] It is possible that as many as a million women (about 25% of all U.S. births) could be opting for testing within the next year. Understanding the history, successes and problems of this first population-based testing effort can provide

vital information about what is needed for a successful transition of a genetic test from research to clinical and public health practice in the United States.

History of CF Testing in the United States: Transition from Research to Clinical Practice

When the *CFTR* gene was discovered in 1989, widespread testing for CF mutations became a possibility. Experts cautioned, however, that screening in the general population should await improvement in the sensitivity of the test as well as the results of pilot testing.[2] In 1997, an NIH Consensus Conference reviewed existing knowledge about CF and the results of CF carrier testing pilot studies.[3] The Consensus Panel recommended that CF carrier testing should be offered to:

- couples seeking prenatal care or planning a pregnancy,
- adults with a family history of CF, and
- partners of persons with CF.

The Consensus Panel also emphasized that this testing should be phased in, to allow time for development of laboratory resources and educational materials for patients and their health care providers.

Subsequent workshops considered issues related to implementation of CF testing in routine practice.[4,5] A joint committee of the American College of Medical Genetics (ACMG), the American College of Obstetricians and Gynecologists (ACOG), and the National Human Genome Research Institute (NHGRI) was designated to coordinate the development of guidelines for provider and patient education, informed consent, and laboratory testing and reporting.

In spite of concerns about appropriate use and performance of CF testing, some consensus emerged in the following years. By 2001, some geneticists and obstetricians had begun offering this testing option to selected groups.[6,7] Widespread introduction of screening really began, however, when the ACMG published *Laboratory Standards and Guidelines for Population-Based Cystic Fibrosis Carrier Screening*[8] and ACOG distributed to its membership *Preconception and Prenatal Carrier Screening for Cystic Fibrosis: Clinical and Laboratory Guidelines* (see Resources).

The joint ACOG/ACMG guidelines recommend that CF testing should be:

- offered to people with a family history of CF and to reproductive partners of persons with CF,

- offered to couples where one or both partners are Caucasian and are planning a pregnancy or seeking prenatal care, and

- available with appropriate information about limitations to couples in other racial or ethnic groups who are at lower risk and for whom testing is less effective (e.g., Hispanics, African Americans, Asian Americans).

These and more recent[9] guidelines are intended to assist health care providers and laboratories in implementing clinical recommendations. They describe laboratory standards, ways to convey expectations and limitations of testing, and prenatal diagnosis options for identified carrier couples.

Key Facts About CF Carrier Testing

- CF occurs in about 1 in 2,500 Caucasian newborns of European descent.
- Laboratory errors in *CFTR* testing occur at a rate similar to other clinical laboratory tests (U.S. estimate is about 1-2% of test results). Performance may improve with experience and the use of confirmatory testing.[10]
- About 88% of *CFTR* mutations in non-Hispanic Caucasians can be identified by testing for 25 common mutations. In this high-risk group, about 78% of carrier couples can potentially be identified.[11]
- The 25-mutation testing panel identifies a smaller proportion of *CFTR* mutations in other U.S. populations:

Population	Identified using 25 mutation testing panel (%)	
	Carriers	Carrier couples*
Hispanic Caucasian	52	27
African American	42	18
Asian American	24	6

*Estimates assume that both members of the couple are from the same racial/ethnic group, and that both members carry a *CFTR* mutation.

Evaluation of Prenatal CF Screening

To support the transition of molecular technology from research to use in clinical and public health practice, CDC funded a model process to evaluate genetic tests by assembling, analyzing, and reporting available data on safety and effectiveness. The report, *Population-Based Prenatal Screening for Cystic Fibrosis via Carrier Testing*, summarizes what we currently know about using the *CFTR* test for prenatal/preconception carrier testing, and was written for health care professionals, payers, and policy makers (http://www.cdc.gov/genomics/activities/FBR/CF/CFIntro.htm).

2003: Learning from Implementation and Practice

In 2003, a large U.S. genetic testing laboratory and the ACMG focused scientific and media attention on potential problems related to CF carrier testing.[12] For example, it was reported that as many as 20 couples may have had prenatal diagnostic testing (i.e., amniocentesis) that was "unnecessary" based on current guidelines—that is, the couples' risk of having a child with CF was not high enough to warrant a recommendation that those couples consider prenatal diagnosis.[13-16]

There was widespread debate about whether such a problem is more likely to result from (a) misinterpretation of complex testing results by providers, (b) variability in laboratory compliance with existing clinical guidelines, (c) poor communication between laboratories and providers, or (d) clarity and content of reports of DNA test results.[14-16] It should be noted, however, that the extent of this, and other anecdotally-reported implementation issues, remains unclear. Among the tens of thousands of women screened, it is not known what problems are being encountered, nor how frequently. Very little reliable data are currently available on the numbers and characteristics of women using this testing, and even less on outcomes of testing.

Public Health Importance of Lessons Learned

In response to these concerns, the CDC and Mt. Sinai School of Medicine hosted a conference on *Communication: Key to Appropriate Genetic Test Referral, Result Reporting and Interpretation* that focused on CF carrier testing as a model, and the Genetics and Public Policy Center at Johns Hopkins University convened a panel discussion on the use and regulation of CF testing.[17] These events provided an opportunity for interaction between clinicians, laboratory professionals, policy makers, payers, the public health community, and consumers. Some topics included:

Challenges in educating health care providers and consumers:

- Informed health care providers, consumers, payers, policy makers, and others are crucial for ensuring that integration of genetic tests into routine care yields the greatest benefit and results in minimal harm.

- Validated educational materials about genetic tests for health care providers and consumers need to be readily available and usable, in order to ensure that both the provider and the patient understand the benefits and limitations of testing.

- In order to ensure appropriate use of new tests and facilitate smooth integration into routine practice, best practice guidelines must be widely disseminated to laboratories and health care providers, including

specialists and general practice physicians, mid-level practitioners (e.g., midwives, physician assistants, nurse practitioners), nurses and health educators.

Communication between health care providers and laboratories:

- Testing involves many steps: selecting the appropriate genetic test, the process of information and consent, obtaining and forwarding the correct specimen and patient information to a qualified laboratory, performing and reporting the test, and communicating results both to the provider and to the patient.

- Laboratories report difficulty in obtaining key patient information (e.g., reason for testing, family history, race/ethnicity) that is needed to select the appropriate test, and to interpret results correctly.

- Health care providers report variability among laboratories in test ordering and reporting practices and in how patient information is collected and used. They describe a need for test requisitions and reports that are simple and clear, and that use standardized terminology.

Compatibility of clinical and laboratory guidance with U.S. healthcare delivery models:

- Physician offices and clinics may lack resources to support some aspects of CF testing, such as educating patients, documenting consent, and providing access to key resources and expertise (e.g., genetic counseling, diagnostic testing) when appropriate.

- Key patient information must be collected and transmitted to the laboratory; this process may become complicated when, for example, patients leave the doctor's office to have blood drawn.

- Preconception/prenatal CF carrier testing has provided insight into other potential complications related to our health care delivery system. For example, offering testing is recommended for partners of women who have been identified as CF carriers. The partner's sample may be sent to a different laboratory, however, because a different physician has ordered the test or because the partner has different insurance coverage. This raises questions about appropriate linkage and interpretation of the couple's test results, as well as the potential difficulty of monitoring the effectiveness of CF carrier testing in practice—questions that can only be answered by testing surveillance and data collection.

Post-implementation data collection to assess the public health impact of testing:
The number of CF carrier tests performed is increasing rapidly, but good data on utilization, quality, acceptability, and access are lacking. Problems encountered in the transition from research to clinical practice need to be documented and quantified, and the data used to reevaluate the screening process and make timely changes in recommendations and guidelines as needed.

- Population-based data on prevalence of genetic variants in affected and healthy populations are needed to select mutations to be included in genetic testing panels, and to re-evaluate such panels as new data become available. The 25-mutation CF panel is currently under review.

- Test request and reporting formats should facilitate communication between clinicians and laboratories and support proper interpretation of genetic tests.

- U.S. healthcare delivery models that link the patient to medical professionals, laboratory testing, counseling services, and payment options should be examined to assure appropriate services are accessible and cost effective.

- When a genetic test makes the transition from research to practice, appropriate data collection must continue to monitor its quality, acceptability, accessibility, utilization, usefulness, and fit with healthcare delivery models.

In recognition of the significance of the issues raised, additional CDC initiatives are being developed, including efforts to support effective pre-implementation evaluation of tests, facilitate partnerships between laboratories and health care providers, and ensure appropriate ordering, reporting, and use of genetic tests.

Resources

2001 Guidelines and Educational Brochures

Preconception and Prenatal Carrier Screening for Cystic Fibrosis: Clinical and Laboratory Guidelines - October, 2001 ($15, $9 ACOG members)
ACOG Bookstore Professional Resources: http://sales.acog.com/acb/stores/1/

Cystic Fibrosis Carrier Testing: The Decision is Yours
(http://www.acog.org/from_home/wellness/cf001.htm)

Cystic Fibrosis Testing: What Happens If Both My Partner and I Are Carriers?
(http://www.acog.org/from_home/wellness/cf002.htm)

References

1. Vastag B. Cystic fibrosis gene testing a challenge: experts say widespread use is creating unnecessary risks. (Reprinted) *JAMA* 2003;289:2923-4.
2. Statement of the American Society of Human Genetics on Cystic Fibrosis Carrier Screening. *Am J Hum Genet* 1992;51:1443-4.
3. NIH Consensus Statement. *Genetic Testing for Cystic Fibrosis* April, 1997. Vol. 15, No. 4. Available at: http://consensus.nih.gov/cons/106/106_intro.htm. Accessed Mar 4, 2004.
4. Mennuti MT, Thomson E, Press N. Screening for cystic fibrosis carrier state. *Obstet Gynecol* 1999;93:456-61.
5. Haddow JE, Bradley LA, Palomaki GE, Doherty RA, Bernhardt BA, Brock DJ, et al. Issues in implementing prenatal screening for cystic fibrosis: results of a working conference. *Genet Med* 1999;1:129-35.
6. Strom CM, Huan D, Buller A, Redman J, Crossley B, Anderson B, et al. Cystic fibrosis screening using the college panel: platform comparison and lessons learned from the first 20,000 samples. *Genet Med* 2002;4:289-96.
7. Rohlfs EM, Shou A, Sugarman EA, Heim RA, Pace RG, Knowles MR, et al. The I148T *CFTR* allele occurs on multiple haplotypes: a complex allele is associated with cystic fibrosis. *Genet Med* 2002;4:319-23.
8. Grody WW, Cutting GR, Klinger KW, Richards CS, Watson MS, Desnick RJ, et al. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. *Genet Med* 2001;3:149-54.
9. Richards CS, Bradley LA, Amos J, Allitto B, Grody WW, Maddalena A, et al. Standards and guidelines for *CFTR* mutation testing. *Genet Med* 2002;4:379-91.

10. Palomaki GE, Bradley LA, Richards CS, Haddow JE. Analytic validity of cystic fibrosis testing: a preliminary estimate. *Genet Med* 2003;5:15-20.

11. Palomaki GE, Haddow JE, Bradley LA, FitzSimmons SC. Updated assessment of cystic fibrosis mutation frequencies in non-Hispanic Caucasians. *Genet Med* 2002;4:90-4.

12. Watson MS, Desnick RJ, Grody WW, Mennuti MT, Popovich BW, Richards CS. Cystic fibrosis carrier screening: issues in implementation (Editorial). *Genet Med* 2002;4: 407-9.

13. Franklin CR, LeGrave D, York M, Entwistle TD, Strom CM. Reporting the CFTR intron 8 5T allele in general population screening: muddying the waters. [abstract]. Annual Clinical Genetics Meeting Program & Abstracts, March 13-16, 2003, San Diego, CA; sponsored and accredited by the American College of Medical Genetics:68.

14. Genetic screening: concerns over cystic fibrosis test examined. *Los Angeles Times*. 2003 May 13.

15. Cystic fibrosis screening creates confusion and risks. *USA Today*. 2003 May 1.

16. Hamilton J. Genetic tests for cystic fibrosis raise concerns. *National Public Radio*. 2003 April 4;Morning Edition. Transcript available at: http://discover.npr.org/features/feature.jhtml?wfId=1219425. Accessed Feb 12, 2004.

17. Genetics and Public Policy Center. Cystic Fibrosis Forum: Canary in the Coal Mine? Expert Panel Examines Use and Regulation of Cystic Fibrosis Genetic Testing. Washington, DC, May 14, 2003. Web site. Available at: http://www.dnapolicy.org/cf/forum.jhtml. Accessed Mar 4, 2004.

Chapter 10

Ensuring the Quality of Genetic Testing in the United States

Bin Chen and Linda A. Bradley

Why is the Quality of Genetic Testing Important to Public Health?

Genetic tests for about 1,000 health conditions have been developed, of which more than 600 are currently available for clinical testing.[1] Many genetic tests identify DNA variants; others measure biochemical markers or analyze chromosomes. Most are used for diagnosis of rare single-gene disorders or chromosome abnormalities, and a few are used for newborn screening.[2]

A growing number of genetic tests may have population-based applications, including determining the risk of developing a disease or condition in the future (e.g., predictive testing for breast cancer or cardiovascular disease), and recognizing genetic variations that can influence response to medicines (**pharmacogenomics**). These genetic tests, therefore, have the potential for broad public health impact.

Pharmacogenomics
Refers to the use of genomic techniques to enhance drug development and define drug responses.

About GeneClinics and GeneTests

The GeneClinics and GeneTests Web site, a publicly funded medical genetics information resource, contains comprehensive reviews of common genetic disorders and information on available genetic tests. Either of these links will take you to the Web site: http://www.geneclinics.org or http://www.genetests.org.

Genetic Testing Issues

Important issues that have been raised regarding genetic testing include the need to:

- facilitate translation of research findings to quality testing in clinical and public health settings,
- prevent premature commercialization of tests before safety, efficacy, and cost-effectiveness can be established,
- provide information on proper use of genetic tests to health care providers, policy makers, and the public,

- maintain adequate oversight of genetic testing,
- monitor the use of genetic tests and ensure appropriate access to testing and related clinical services, and
- address complex social issues posed by genetic testing.

Who Considers These Issues in the United States?

In 1997, the National Institute of Health (NIH)—Department of Energy (DOE) Task Force on Genetic Testing issued a report on genetic testing in the United States that provided recommendations on how to ensure the development of safe and effective genetic tests.[3] In 1998, the Department of Health and Human Services (HHS) established the Secretary's Advisory Committee on Genetic Testing (SACGT) to provide advice on medical, scientific, ethical, legal, and social issues raised by the use of genetic tests. In consultation with the public, SACGT considered potential mechanisms and options for evaluating genetic tests, providing information about genetic testing to stakeholders, and enhancing testing oversight.[4]

In 2003, HHS established the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS), in order to address genetic issues in a broader scope and continue discussion on oversight of genetic testing. Other public and private entities that consider issues related to the safety and effectiveness of genetic tests include:

- federal and state government agencies,
- professional associations,
- laboratory accreditation organizations,
- health plans and healthcare payers,
- policy groups, and
- patient advocacy organizations.

What Oversight Currently Exists for Genetic Testing?

In the United States, laboratory testing devices and kits are subject to FDA oversight. When tests are packaged and sold as kits or testing systems to laboratories, the FDA requires data collection and evaluation as part of pre-market approval or clearance. Currently, however, almost all genetic tests are developed by laboratories in-house and are called **"home brew"** tests, and are not available as FDA-approved kits.

"Home Brew"
Almost all genetic tests are performed by laboratories that have developed these tests in-house.

At present, the Centers for Medicare and Medicaid Services (CMS) provide oversight for "home brew" testing by regulating clinical laboratories under the Clinical Laboratory Improvement Amendments (CLIA); http://www.cms.hhs.gov/clia. CLIA regulations require laboratories to be responsible for all phases of the testing process and focus on laboratory quality systems and in-house analytic validation—analytic validity defines the ability of a test to measure accurately and reliably what it purports to measure. Currently, clinical cytogenetics—the analysis of human chromosomes—is recognized as a specialty area under CLIA, but a broader specialty of genetics does not yet exist. As a result, there are no specific requirements at the federal level for laboratories performing molecular and other types of genetic testing.

Watch for …
The CDC, in partnership with CMS, has been working to introduce a genetic testing specialty under CLIA to establish specific requirements for laboratories performing genetic testing. A Notice of Proposed Rule Making for a genetic testing specialty under CLIA is expected in the near future.
http://www.phppo.cdc.gov/dls/genetics/policy.asp

"Home Brew" Genetic Tests and the FDA

To date, the FDA has not regulated "home brew" genetic tests offered by laboratories as clinical services, but regulation remains an option. The FDA does provide a standard of measurement for regulating certain testing reagents as analyte-specific reagents (ASRs). ASRs are used as components in laboratory-developed ("home brew") genetic tests and can be sold only to laboratories certified under CLIA to perform high-complexity testing.

It should be noted that FDA review is designed to evaluate a test's performance, including analytic validity, clinical validity, and some aspects of clinical utility. Clinical validity defines a test's ability to detect or predict a particular disorder. Clinical utility defines the risks and benefits associated with the introduction of a test into practice, including the impact of positive and negative test results on health outcomes, cost-effectiveness, and ethical, legal and social issues associated with test use. Many points considered in assessing the clinical utility of a test, however, are outside the usual purview of FDA and CLIA review.

FDA News - December 17, 2003…
FDA Approves Lab Tests for Genetic Clotting Risk - The FDA announced approval of the first DNA-based laboratory tests for an inherited disorder.
http://www.fda.gov/bbs/topics/NEWS/2003/NEW00998.html

How Do States Regulate Genetic Testing?

Some state agencies regulate laboratories performing genetic testing through licensure of personnel and/or facilities. For example, New York requires laboratories to submit validation data for approval prior to offering patient testing. South Dakota requires that genetic tests be performed in a laboratory that:

- is accredited by a program approved by HHS, such as the College of American Pathologists, and
- enrolls in a proficiency-testing program.

What Private Sector Organizations Are Concerned with Genetic Testing?

Private-sector organizations develop voluntary laboratory and clinical guidelines and standards that help to ensure appropriate performance and use of genetic tests.

Examples of such organizations include:

- American College of Medical Genetics (http://www.acmg.net),
- College of American Pathologists (CAP) (http://www.cap.org),
- American Academy of Pediatrics (http://www.pediatrics.org),
- American College of Obstetricians and Gynecologists (http://www.acog.org),
- American Society of Human Genetics (http://www.asgt.org),
- National Society of Genetic Counselors (http://www.nsgc.org),
- Association of Molecular Pathologists (http://www.ampweb.org), and
- NCCLS (http://www.nccls.org).

What is Needed to Ensure the Safety of Genetic Testing?

In order to ensure the safety and effectiveness of genetic testing in the United States, the following needs have been identified:

- development of a standardized approach for evidence-based review of new genetic tests to establish safety, efficacy, and cost-effectiveness prior to use in routine clinical care,
- ongoing assessment of laboratory practice in genetic testing and identification of needs for quality improvement, and
- clarification of the roles of regulatory and other government agencies, professional organizations, and advocacy groups in genetic test oversight and policy development.

How is CDC Addressing These Needs?

The CDC has initiated a number of activities to address these needs:

Assessing laboratory practice in genetic testing:

- Funding Mt. Sinai School of Medicine to survey the state of practice in clinical molecular and biochemical genetic laboratories. Results showed that genetic testing was available in a variety of laboratory settings, but indicated that specific improvements in quality assurance practices were needed to ensure high quality service.[5]

- Collaboration with Tulane University to assess the variability of result reporting for cystic fibrosis and factor V Leiden testing and evaluate the usefulness of different report formats to physicians in interpreting genetic test results. The findings demonstrated variability in report content, including a lack of some information deemed critical by professional guidelines and recommendations.[6]

- Contracting with Duke University School of Medicine and the University of California at Los Angeles to pilot-test approaches to developing positive controls for genetic tests and help ensure continuous availability of quality control materials for the development, validation, performance, and quality assurance of genetic tests.

More information can be found at: http://www.phppo.cdc.gov/dls/genetics/default.asp.

Evidence-based review and surveillance of genetic tests:

- Establishing a cooperative agreement with the Foundation for Blood Research to develop and test a model process for assembling, analyzing, and disseminating data on the safety and effectiveness of DNA-based genetic tests and testing algorithms. This model process is described by the acronym ACCE, which stands for: analytic validity, clinical validity, clinical utility and ethical, legal and social implications—the four components by which a test is evaluated. Over a 3-year period, five tests for different disorders were evaluated, with a goal of facilitating appropriate transition of genetic tests from investigational settings to use in clinical and public health practice. More information can be found at http://www.cdc.gov/genomics/activities/fbr.htm. See more information about an ACCE review in *Chapter 4, Public Health Assessment of BRCA1 and BRCA2 Testing for Breast and Ovarian Cancer*.

- Conducting a study on the impact of direct-to-consumer marketing. From September 2002 to February 2003, the major U.S. provider of genetic testing for breast and ovarian cancer susceptibility (*BRCA1/2* testing) conducted a direct-to-consumer advertising campaign that targeted women aged 25-54 and their health care providers in two pilot cities, Atlanta, GA and Denver, CO. The CDC study was intended to assess the impact of the advertising campaign on knowledge, attitudes and actions of health care providers and consumers related to breast and ovarian cancer risk and *BRCA* testing.

Suggested Reading On Genetic Test Evaluation:

Haddow JE and Palomaki GE. ACCE: A model process for evaluating data on emerging genetic tests. *Human Genome Epidemiology*. Khoury MJ, Little J, and Burke W, eds. Oxford University Press, Inc. New York, 2003;217-33.

Burke W, Atkins D, Gwinn M, Guttmacher A, Haddow J, Lau J, et al. Genetic test evaluation information needs of clinicians, policy makers and the public. *Am J Epidemiol* 2002;156:311-8.

More information on genetic testing can be found on the OGDP Web site: http://www.cdc.gov/genomics/gTesting.htm

References

1. GeneTests Web site. Available at: http://www.geneclinics.org. Accessed Feb 15, 2004.
2. Yoon PW, Chen B, Faucett A, Clyne M, Gwinn M, Lubin IM, et al. Public health impact of genetic tests at the end of the 20th century. *Genet Med* 2001;3:405-10.
3. Holtzman NA, Watson MS, eds. Promoting safe and effective genetic testing in the United States. Bethesda (MD): National Institutes of Health; 1997. Web site. Available at: http://www.genome.gov/10001733. Accessed Feb 15, 2004.
4. Secretary's Advisory Committee on Genetic Testing. Enhancing the oversight of genetic tests: recommendations of the SACGT. Bethesda (MD): National Institutes of Health; 2000. Web site. Available at: http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.htm. Accessed Feb 15, 2004.
5. McGovern MM, Benach, MO, Wallenstein S, Desnick RJ, Keenlyside R. Quality assurance in molecular genetic testing laboratories. *JAMA* 1999; 281:835-40.
6. Andersson HC, Krousel-Wood MA, Jackson K, Rice J, and Lubin, IM. Medical genetic test reporting in molecular cystic fibrosis and factor V Leiden in North American laboratories. *Genet Med* 2002:4:324-7.

Chapter 11

Hemochromatosis: Information and Resources for Health Care Providers

Michele Reyes, Diane Dunet, Heidi Michels Blanck, and Daurice Grossniklaus

What is Hemochromatosis?

Hemochromatosis is a disorder where too much iron accumulates in tissues and organs, resulting in iron overloading. If left undiagnosed and untreated, iron overloading can cause serious health problems, and can even be fatal.

In the United States, the majority of hemochromatosis cases are caused by variants in the *HFE* gene, namely *C282Y* and *H63D*. A recently-published review of HFE genotype frequencies reported that about 9% of the population carries one copy of the *C282Y* mutation and about 0.5% is *C282Y* **homozygous** (carries two copies of the *C282Y* mutation). The homozygous genotype is responsible for most cases of hemochromatosis,[1] but the proportion of people with this genotype who will develop the disorder (i.e., the **penetrance** of the genotype) is unknown.

Homozygous
Possessing two identical copies of a particular gene, one inherited from each parent.

Penetrance
Probability that manifestations of a gene change will be seen in an individual.

Hemochromatosis can be detected with simple blood tests and the treatment of choice, phlebotomy (bloodletting), is relatively easy and inexpensive. Early diagnosis and treatment of hemochromatosis provides a tremendous opportunity to reverse the course of the illness and to prevent the most serious health problems of advanced stage hemochromatosis, which are:

- cirrhosis of the liver,
- liver cancer,
- cardiomyopathy (heart muscle disorders), and
- heart failure.

More information about hereditary hemochromatosis can be found on the CDC Web site at: http://www.cdc.gov/genomics/info/perspectives/hemo.htm.

Why Is Hemochromatosis a Public Health Problem?

Research conducted by the CDC and others indicates that primary care physicians may lack the knowledge they need to be able to identify patients at risk for hemochromatosis.[2] These studies have also identified widespread misunderstanding among health care professionals about the appropriate diagnostic tests and treatments for hemochromatosis. Until the last decade,

diagnosis of hemochromatosis most commonly relied on diagnosing the triad of cirrhosis, diabetes mellitus, and skin bronzing, and was only confirmed through a liver biopsy that uncovered evidence of iron overload. These methods could only confirm later-stage hemochromatosis, even though early detection and treatment are essential to reducing serious illness and death from this disease.

When CDC surveyed 2,841 diagnosed hemochromatosis patients, over two-thirds (67%) had initially received various multiple diagnoses, including arthritis, liver disease, hormonal deficiencies, and diabetes.[2] These patients actually did have those conditions, but the underlying cause, iron overload, had been missed. Patients reported that they saw an average of 5 physicians before receiving a diagnosis of hemochromatosis, on average 9.5 years after the onset of symptoms. Reducing this time lag by increasing physicians' awareness of the early symptoms of hemochromatosis is clearly an important disease prevention opportunity.

Is Population Screening Recommended for Hemochromatosis?

Screening patients to detect and treat chronic diseases early has become an important part of medicine and public health.[3] The 1996 discovery of the HFE variants *C282Y* and *H63D* responsible for most cases of iron overloading held promise for prevention and earlier treatment of the serious health consequences of advanced stage hemochromatosis.[4] Hereditary hemochromatosis quickly moved into the public health spotlight as medical experts and patient support groups called for population screening.

When policy-makers evaluated population-based screening for hereditary hemochromatosis in the late 1990s, however, important knowledge gaps were identified.[5-7] For example, little is known about the clinical course of hemochromatosis, the likelihood of complications, or the prevalence of asymptomatic iron overload. In addition, reliable information about the prevalence and penetrance of the HFE variants is not available. To help fill in these knowledge gaps, the National Heart Lung and Blood Institute launched a 5-year study in 2001 of 100,000 adults in primary care settings.[8] The results of this study will help policy-makers to understand the benefits and risks of using primary care-based diagnostic screening for iron overload and hemochromatosis.

Genetic testing also raises issues related to ethical, legal, and social concerns. For more information, please see *Chapter 8, Genomics and Public Health: Ethical, Legal, and Social Issues*. Even when these issues are adequately addressed, decisions to institute population screening must also be supported with enough scientific evidence of public health effectiveness as well as with enough available resources to treat those patients identified through screening. For a population-based screening program to be effective, it must identify people who are at risk of developing the disease. For the program to be cost-effective as well, it should

identify only those people who are very likely to develop the disease and are thus most likely to benefit from intervention.[9] Benefits are proportional to the number of cases prevented; therefore, a screening program that fails to identify people who will develop the disease—or that identifies many people who would not have become ill, even in the absence of intervention—will have a less favorable cost-benefit ratio.

Although initial estimates of the percentage of at-risk individuals who would actually develop hemochromatosis were high, ranging from 40-70%,[10] more recent studies have reported clinical estimates ranging from <1-50%.[11-14] Inconsistencies regarding these estimates persist in the scientific literature. Further studies are warranted, including studies designed to find out more about the role of genetic and environmental factors.

At this time, therefore, public health policy-makers have concluded that additional information is needed before population-based screening for hereditary hemochromatosis can be recommended as a prevention strategy. Currently, enhanced case detection among individuals with hemochromatosis symptoms and family-based detection are the most practical strategies for early diagnosis and treatment of hemochromatosis.

CDC's Online Training on Hemochromatosis for Health Care Providers

Physicians and other health-care providers continually face the challenge of incorporating the rapidly expanding pool of genetics information and the accompanying new technologies into their everyday practices. Continuing medical education is required to stay abreast of this exponential growth in knowledge. The CDC's new online course entitled *Hemochromatosis: What Every Clinician and Other Health Care Professional Needs to Know* (http://www.cdc.gov/hemochromatosis/training/index.htm) provides training on:

- the genetics of hemochromatosis, and
- patient care for physicians and other healthcare providers.

The course was developed by the CDC, in collaboration with hemochromatosis experts throughout the United States. The goals of this educational campaign are to:

- promote health by increasing awareness and early detection of hemochromatosis, and to

- provide a strategy for health care providers for early intervention in the course of the disease.

The core curriculum for *Hemochromatosis: What Every Clinician and Other Health Care Professional Needs to Know* consists of six modules and a series of case studies. The Web-based self-instructional format was designed to appeal to busy practitioners with limited time for training. Course resources integrate research findings with clinical practice in an attractive, easy-to-use format. Module and course summaries, self quizzes, and a series of interactive case studies allow the learner to tailor the course to his/her own learning needs, style and interests.

Course content focuses on hemochromatosis as one of several diagnostic considerations in many clinical settings. Although clinical features, diagnostic testing, and patient treatment and management are addressed at length, the course avoids prescribing a specific course of physician action. Instead, the course integrates concepts related to hemochromatosis, iron overload and genetic diseases into everyday practice, and focuses on:

- learning to recognize the early, non-specific symptoms of hemochromatosis (e.g. fatigue, joint pain, weakness, weight loss, abdominal pain),
- learning about the recommended methods for diagnosing hemochromatosis,
- phlebotomy (bloodletting) treatment to reduce iron overload, and
- counseling hemochromatosis patients about the importance of family-based detection.

The course includes colorful, downloadable patient educational materials, as well as physician letter templates that can be customized to provide information for patients to pass on to family members. Links to additional resources are available, including links to referenced articles from the professional literature. Information on genetic testing, genetic counseling, and family-based detection are also included in the course, together with an easy-to-follow chart suggesting when genetic testing may be appropriate for hemochromatosis diagnosis.

Hemochromatosis: What Every Clinician and Other Health Care Professional Needs to Know
http://www.cdc.gov/hemochromatosis/training/index.htm

Core Curriculum
- Epidemiology,
- Pathophysiology,
- Clinical Features,
- Diagnostic Testing,
- Treatment and Management,
- Family-based Detection, and
- Case Studies.

Who Can Take This Course?
Physicians, health education specialists, nurses and others will benefit from this course.

Course Format
The Web-based format allows convenient, self-paced instruction over the Internet using a personal computer. Learners can focus on course components to suit their personal information needs. In addition, learners can "book mark" their place in the course and return to the Web site to complete the course in segments if desired.

Continuing Education Credits
The course provides free continuing education credits (CME, CNE, CHES and CEU) through CDC's online Public Health Training Network. Learners may immediately print a Continuing Education Credit Certificate upon completing the course.

Conclusion

CDC's Web-based training course *Hemochromatosis: What Every Clinician and Other Health Care Professional Needs to Know* provides a response to the need for easily accessible, reliable information on this genetic disease. The Web-based format of the course also meets the need for rapid, individualized learning and immediate access to additional resources; this makes it possible to update the course easily as new knowledge becomes available.

In addition, the course also serves as a model of Web-based instruction specifically designed for physicians. As new genetic variants are identified, physicians face the ongoing challenge of learning, interpreting, and applying new knowledge in their practice settings. CDC's course on hemochromatosis represents a positive step towards helping health care providers become prepared to meet these challenges.

References

1. Hanson EH, Imperatore G, Burke W. HFE gene and hereditary hemochromatosis: a HuGE review. *Am J Epidemiol* 2001;154:193-206.

2. McDonnell SM, Preston BL, Jewell SA, Barton JC, Edwards CQ, Adams PC, et al. A survey of 2,851 patients with hemochromatosis: symptoms and response to treatment. *Am J Med* 1999;106:619–24.

3. Morrison AS. Screening in chronic disease. *Monograph in Epidemiol Biostat,* New York: Oxford University Press, 1992;19.

4. Feder JN, Tsuchihashi Z, Irrinki A, Lee VK, Mapa FA, Morikang E, et al. The hemochromatosis founder mutation in HLA-H disrupts beta2-microglobulin interaction and cell surface expression. *J Biol Chem* 1997; 272:14025–8.

5. EASL International Consensus Conference on Haemochromatosis. *J Hepatol* 2000; 33: 485–504.

6. Burke W, Thomson E, Khoury MJ, McDonnell SM, Press N, Adams PC, et al. Hereditary hemochromatosis: gene discovery and its implications for population-based screening. *JAMA* 1998; 280:172–8.

7. Bradley LA, Haddow JE, Palomaki GE. Population screening for haemochromatosis: expectations based on a study of relatives of symptomatic probands. *J Med Screen* 1998;3:171-7.

8. McLaren CE, Barton JC, Adams PC, Harris EL, Acton RT, Press N, et al. Hemochromatosis and Iron Overload Screening (HEIRS) study design for an evaluation of 100,000 primary care-based adults. *Am J Med* 2003;325: 53-62.

9. Higashi MK, Veenstra DL. Managed care in the genomics era: assessing the cost effectiveness of genetic tests. *Am J Manag Care* 2003;9:493-500.

10. Bradley LA, Haddow JE, Palomaki GE. Population screening for haemochromatosis: a unifying analysis of published intervention trials. *J Med Screen* 1996;3:178-84.

11. Asberg A, Hveem K, Thorstensen K, Ellekjter E, Kannelonning K, Fjosne U, et al. Screening for hemochromatosis: high prevalence and low morbidity in an unselected population of 65,238 persons. *Scand J Gastroenterol* 2001;36:1108-15.

12. Beutler E, Felitti V, Koziol J, Ho N, Gelbart T. Penetrance of the 845G - A(C282Y) HFE hereditary haemochromatosis mutation in the USA. *Lancet* 2002;359:211-8.

13. Bulaj ZJ, Ajioka RS, Phillips JD, LaSalle BA, Jorde LB, Griffen LM, et al. Disease-related conditions in relatives of patients with hemochromatosis. *N Engl J Med* 2000;343:1529-35.

14. Olynyk JK, Cullen DJ, Aquilia S, Rossi E, Summerville L, Powell LW. A population-based study of the clinical expression of the hemochromatosis gene. *N Engl J Med* 1999;341:718-24.

Chapter 12

Genomics Training for Public Health Practice: The Michigan Experience

Janice Bach and Sarah Raup

Why Does the Public Health Workforce Need Genomics Training?

Recent scientific discoveries are illuminating the role of genes as risk factors for common diseases affecting the public's health. New applications of genomics to medicine are expected to become important tools for health promotion and disease prevention. The full benefits of genomics in public health will not be realized, however, without a workforce capable of interpreting and applying relevant genomic information to the practice setting.

What Has Been Done to Develop Genomics Training?

To address the need for a genomically literate workforce, CDC and others have initiated efforts to train public health practitioners. Beginning in 2000, the Office of Genomics and Disease Prevention (OGDP) and Public Health Practice Program Office (PHPPO) convened working groups to outline a set of "Genomic Competencies for the Public Health Workforce". These are available online at http://www.cdc.gov/genomics/training/competencies/, and include a set of general competencies for all members of the public health workforce and specific competencies for each of six professional groups: administrators, clinicians, epidemiologists, health educators, laboratorians, and environmental health workers.

In 2001, CDC established three Centers for Genomics and Public Health at Schools of Public Health (http://www.cdc.gov/genomics/activities/fund2001.htm), which were charged with developing strategies for providing genomics training and technical assistance to the public health workforce.

Simple Training Strategies and Available Courses

Practical strategies for training the public health workforce in genomics are listed in Table 1, along with specific examples used in Michigan. Ideally, local expertise should be enlisted as much as possible. While many training materials are available from various sources, including books, CD-ROMs and the Internet, nothing beats a scheduled, easy-to-attend, in-person session. Genetic counselors, medical geneticists, genetic epidemiologists, and other professionals with genetics or public health experience should be engaged in training the public health

workforce. Existing materials should be shared and utilized as much as possible to avoid "reinventing the wheel."

Table 1. Overview of Michigan's Training Strategies

Strategy	Example
1. Building a Foundation—Know Your Audience	The Genomics Workgroup at the Michigan Department of Community Health (MDCH)
2. Raising Awareness and Stimulating Interest	*An Introduction to Genomics for Public Health Professionals* developed by CDC and Centers for Genomics and Public Health at the Universities of Michigan, North Carolina, and Washington.
3. Increasing Knowledge	*Six Weeks to Genomic Awareness* developed by the Michigan Center for Genomics and Public Health and delivered to MDCH staff
4. Strengthening Skills	*Graduate Summer Session in Epidemiology* at the University of Michigan School of Public Health with scholarships sponsored by the Michigan Center for Genomics and Public Health
5. Using Evaluation to Improve Training	Evaluation by organizers, trainers and participants

Strategy 1: Building a Foundation—Know Your Audience

Getting to know your target audience—who they are and what they do—is an essential first step in designing training. This might be accomplished through both formal and informal channels, such as attending conferences or workshops about public health genomics, requesting permission to sit in on staff meetings, or holding individual "orientation" meetings with program staff. A working relationship with the intended audience serves a two-fold purpose: it provides information about specific training needs and acts as a catalyst for raising awareness and stimulating interest in genomics among the intended audience.

Recognize that public health encompasses many disciplines, and that the workforce represents professionals from diverse backgrounds. Training should be either broad enough to include examples relevant to a range of public health professionals, or targeted specifically to a particular group.

Example: The Genomics Workgroup

At the Michigan Department of Community Health, staff members, representing a wide range of public health programs, participate in the Genomics Workgroup. The group was originally convened in Spring 2000 as a joint effort by the state genetics coordinator and chronic disease director. Its mission is to identify and facilitate relevant opportunities for the integration of genetics into public health science and practice with a special emphasis on chronic disease prevention and control. Quarterly meetings serve several purposes, including:

- allowing program staff members who ordinarily would not work together to meet and get to know each other,
- providing an opportunity to share updates on state and national genomics initiatives,
- serving as a forum for training and education to increase the genomic competencies of the MDCH workforce,
- monitoring developments related to family history, screening and prevention of adult disorders,
- helping to identify potential funding sources for further genomics integration into various programs, and
- allowing for planning and discussion of multi-disciplinary approaches to genomics integration.

The Genomics Workgroup is also used as a "real life" learning laboratory to provide the Michigan Center for Genomics and Public Health with feedback that can be used to plan training activities. For more information about the role this workgroup has played at MDCH, contact genetics@michigan.gov.

Strategy 2: Raising Awareness and Stimulating Interest

Since genomics is not yet a common word in the public health vocabulary, it is important to raise awareness and stimulate interest about the potential relevance of genomics to various programs among public health practitioners.

Basic information that will motivate public health practitioners to become genomically competent increases the odds that specific training efforts will be effective later on. Such introductory efforts may not necessarily give specific knowledge or skills to practitioners, but will begin to lay the groundwork for later training efforts.

"However it is not only the future of genomics that warrants the attention of public health education. Because few in the current public health workforce have the level of understanding of genomics that is required today, major continuing education efforts must be undertaken to ready practicing public health professionals to use genomics effectively. 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 the basic public health sciences." (Who Will Keep the Public Healthy? Educating Public Health Professionals in the 21st Century, IOM, 2003)

Example: An Introduction to Genomics for Public Health Professionals

A workgroup consisting of representatives from the CDC and Centers for Genomics and Public Health at the University of Michigan, University of North Carolina, and University of Washington developed a Web-based presentation entitled *An Introduction to Genomics for Public Health Professionals*. This presentation defines basic genetic terms, provides an overview of the current and potential role for genomics in public health practice, lists recommended action steps, and reviews an example of how genomic information is currently used in public health. The presentation is meant to generate interest in and excitement about genomics and to motivate public health professionals to participate in training opportunities that would further enhance their knowledge and skills.

An Introduction to Genomics for Public Health Professionals was presented to staff at the Michigan Department of Community Health as part of a DNA Day Open House in April 2003, that was organized to commemorate the discovery of the double helix and promote awareness of genetics in public health. This presentation is expected to be available online in Summer 2004 at www.cdc.gov/genomics (http://www.cdc.gov/genomics/GPHP/menu.html), and can be used by anyone desiring to raise awareness about and to stimulate interest in genomics among public health practitioners.

Strategy 3: Increasing Knowledge

Although knowledge about genomics is increasing every day, most public health professionals lack an understanding of even the most basic concepts. Practitioners also find it difficult to keep up with the growing body of knowledge and to identify the most relevant information for their particular work area. Reviewing basic genetic terminology, concepts, and associated issues—as well as arming public health professionals with tools to keep up with the advances in genomics—is therefore an important step in the training process. A workforce familiar with the genomics vocabulary and the potential of genomics for public health is more likely to engage in projects and activities aimed at integrating genomics into public health.

Example: Six Weeks to Genomic Awareness

The Michigan Center for Genomics and Public Health has developed a new course, *Six Weeks to Genomic Awareness*, to familiarize participants with important terms, concepts, and issues. The six sessions include:

- The Human Genome & Heredity
- Genes in Populations
- Genetic Testing
- Gene-Environment Interactions
- Ethical, Legal, and Social Issues Associated with Genomic Applications
- Genomic Resources at the State and National Levels.

The series was piloted at the Michigan Department of Community Health in May-June 2003. Expert speakers were chosen to present each topic. Seventy program staff attended at least one session and 32 attended three or more sessions. Participants included staff members from all areas of the health department, including epidemiology, laboratory, vital statistics, and chronic disease. The Centers for Genomics and Public Health are evaluating Six Weeks to Genomic Awareness with the goal of making the entire series available online in Summer 2004.

Strategy 4: Strengthening Skills

The final step in ensuring a genomically competent public health workforce is to develop practical training opportunities that allow public health practitioners to incorporate genomics into the skill sets necessary for their particular job functions. Training efforts are needed to address integration of genomics into the skill sets of administrators, clinicians, epidemiologists, health educators, environmental health specialists, and laboratorians (see http://www.cdc.gov/genomics/training/competencies/). Plenty of "hands on" activities, encouraging practitioners to apply what they have learned, should be included in these efforts.

Example: Graduate Summer Session in Epidemiology

The Michigan Center for Genomics and Public Health provided scholarships for several state public health personnel to attend Genetic Epidemiology courses offered through the University of Michigan *Graduate Summer Session in Epidemiology* in 2002 and 2003. Although these courses were not tailored specifically to practicing public health professionals, they did provide in-depth exposure to genetics in the context of epidemiology and allowed practitioners to apply what they had learned in problem sets and other exercises. Public health attendees, who did not necessarily have a pre-existing background in genetics, gave these courses a very favorable review and were grateful for the opportunity to participate.

Strategy 5: Using Evaluation to Improve Training

It is very important to measure the effectiveness of existing training courses so that they can be improved and new courses can be developed. Building an evaluation component into the development of training tools is critical to evaluating and modifying training courses and tools effectively.

Example: Evaluation Data from Six Weeks to Genomic Awareness

Participants Who Rated Relevance to Their Work Very Good or Excellent, Currently and in the Future, as Percent of Those Who Completed Evaluations		
Material	**Currently**	**Future**
The Human Genome & Heredity	48%	77%
Genes in Populations	54%	70%
Genetic Testing	44%	69%
Gene-Environment Interactions	60%	88%
ELSI (Ethical, Legal and Social Issues)	55%	65%
Genomic Resources	40%	80%

Lessons Learned

It is critical to involve representatives from the target audience in planning training content and format. Training opportunities should be made as convenient as possible for participants. We organized *Six Weeks to Genomics Awareness*, for example, as a brown-bag lunch series at the Michigan Department of Community Health. In addition to the foundation that had been laid to increase interest in genomics through the DNA Day event and articles in an employee newsletter, the convenient location, minimal interference with work schedules, and no cost to participants likely contributed to the large attendance at the sessions.

While strides have been made in addressing the training needs of the public health workforce over the past few years, there is still a long way to go in developing a genomically competent public health workforce.

- Current training efforts need to be extended to a broader audience. Technology should be used to make this happen. For example, Web-based distance learning courses are being planned by the Centers for Genomics and Public Health. Training resources, including slide presentations and other tools, should be shared among those interested in training the public health workforce.

- Future training efforts should be tailored to the knowledge and skills sets specific to various disciplines of public health, and should also include

practical opportunities for public health professionals to apply what they have learned.

- The effectiveness of training efforts should be assessed. The acquisition of new knowledge and skills by public health practitioners and the incorporation of this knowledge into public health programs should be measured. Coordination and collaboration among a number of public and private entities will be the key to achieving the goal of a genomically competent workforce.

Chapter 13

Genomics Tools for Public Health

Timothy Baker and Kristin L. Peterson-Oehlke

What are Genomic Tools?

As we continue to learn more about the role that genes play in health and disease, public health practitioners will need genomic tools—approaches and products based on genomic information that can be used to address public health issues. These tools may be used at the same time as other, more familiar approaches, or integrated so seamlessly that they are not recognized as "genomic".

A good example is family history, which is an amalgam of genetic, environmental, behavioral, social, and cultural data that has significant impact on health. *Chapter 6, The Family History Public Health Initiative*, emphasizes that genomic tools are meant to be immediately relevant, practical, responsive to needs, and somewhat proven prior to their promotion and use. New developments in genomics create the need for tools in order to transfer that development into practice effectively. These tools will need to be updated consistently and replaced as knowledge and practice evolves.

Genomic Tools in Practice and The Genomics Toolkit

Currently, genomic tools (that have been developed and used by several states and community-based programs, and exist in one form or another) may address all three of the public health core functions:

- assessment,
- policy development, and
- assurance.

Innovative states that produced the initial tools received an overwhelming volume of requests, resulting in the initiation of a "toolkit" project designed to collect these tools and reduce the burden on the states. The Association of State and Territorial Health Officials (ASTHO) coordinated this effort to begin identifying and collecting tools that have been shown to be effective in public health settings. This project was supported with funding from the CDC and developed by a workgroup of representatives from ASTHO affiliates. The idea was to provide a rolling inventory of the best tools to use in program technical assistance.

Table 1 lists the groups that were represented on the Genomics Toolkit Project Workgroup:

Table 1. Groups Represented on the Genomics Toolkit Project Workgroup

ASTHO	Association of State and Territorial Health Officials http://www.astho.org/
AMCHP	Association of Maternal and Child Health Programs http://www.amchp.org/
APHL	Association of Public Health Laboratories http://www.aphl.org/
ASTDHPPHE	Association of State and Territorial Directors of Health Promotion and Public Health Education http://www.astdhpphe.org/
CDC OGDP	Centers for Disease Control and Prevention http://www.cdc.gov Office of Genomics and Disease Prevention http://www.cdc.gov/genomics
CDD	Chronic Disease Directors http://www.chronicdisease.org/
CSGC	Coalition of State Genetics Coordinators http://www.stategeneticscoordinators.org/
CSTE	Coalition of State and Territorial Epidemiologists http://www.cste.org/
NACCHO	National Association of County and Community Health Officials http://www.naccho.org/
NCSL	National Council of State Legislatures http://www.ncsl.org/

As part of the Genomics Toolkit, a broad guidance document was developed with the purpose of providing assistance for initial program development efforts; this document is available online at http://www.genomicstoolkit.org/index.shtml.

- It provides an overview of the role of genomics in health and disease, and why genomics is important to public health activities.

- It provides guidance and materials for identifying stakeholders, stimulating interest, recruiting an advisory committee, identifying needs and goals, developing a work plan and evaluating the process of integrating genomics into public health.

- The resource guide section of the toolkit includes information on associations and organizations, education and training, funding, planning and policy, publications and communications, tools, and presentations.

In developing this toolkit document, ASTHO collected input from several states. Many of the states also provided specific tools used for various applications; these tools can be found on their Web sites. The State Snapshots in Table 2 describe how those health agencies have applied genomics into public health practice and disease prevention programs.

Table 2. State Snapshots

Indiana	http://www.genomicstoolkit.org/moxie/gettingstarted/forums/indiana.shtml
Michigan	http://www.genomicstoolkit.org/moxie/gettingstarted/forums/michigan.shtml
New York	http://www.genomicstoolkit.org/moxie/gettingstarted/forums/newyork.shtml
North Carolina	http://www.genomicstoolkit.org/moxie/gettingstarted/forums/ncarolina.shtml
Utah	http://www.genomicstoolkit.org/moxie/gettingstarted/forums/utah.shtml
Washington	http://www.genomicstoolkit.org/moxie/gettingstarted/forums/washington.shtml

Table 3 provides a list of specific activities and strategies taken by some states to integrate genomics into public health practice and disease prevention programs.

Table 3. Specific Activities and Strategies for Integrating Genomics into Public Health

Genomics Integration Strategies:	Some of the States Using These Tools:
Models of genomics workgroups made up of members from across the state health agency	Michigan, North Carolina
Assessing needs related to public health goals and genomics across the state	Michigan, North Carolina
Centralized grants writing functions that consider genomics approaches in the development of funding requests	Indiana
Establishing policies for using dried blood spots as source of population-based DNA samples	Michigan, New York
Statewide Genomics Advisory Committees that advise on genomics across all areas of public health policy and practice	North Carolina, Michigan, Utah
Genetics Taskforce for developing public policy related to uses of genetic information and technology	Washington, New York, Michigan
Using family health history as a tool for chronic disease prevention	Utah
Planning, developing and delivering genomics education to multiple audiences, including public health	Michigan, New York, Washington, North Carolina
Regulation of genetic testing practices	New York

Genomics Tools We Need, But Don't Currently Have

Extensive research in human genomics has created a large and growing body of data that must be translated into practical knowledge, so that public health practitioners can apply this knowledge to real-life situations. New and existing genomic tools must be grounded in scientific data, and must be able to accommodate new knowledge as it becomes available.

Public health agencies need guiding principles, processes and strategies to help understand and define the role of genomics in public health. Public health workers also need education to equip them with the knowledge and skills to help interpret genomic information for the general public. See *Chapter 12, Genomics Training for Public Health Practice: The Michigan Experience*, for more information.

Genomics has entered the lexicon of popular culture, and increasing public understanding of this area is important to build confidence and to avoid risks from inappropriate use, as well as to let more people know about the relevant benefits. As genomics increasingly enters health practice, health professionals must be informed, and must also be able to inform the public accurately, using tools that are reliable. Each community will require tools, matched to local population needs, which will allow policy makers to support genomics in practice.

How Will New Tools Be Developed?

New tools will be developed (and old tools refined through use in other settings) in the context of practice in state and local public health agencies and in collaboration with academic partners, such as the Centers for Genomics in Public Health (http://www.cdc.gov/genomics/activities/fund2001.htm). These centers are housed within the following schools of public health at their parent universities:

- North Carolina (http://www.sph.unc.edu/nccgph/),
- Michigan (http://www.sph.umich.edu/genomics/index.html), and
- Washington (http://depts.washington.edu/cgph/).

These centers have a primary responsibility for responding to program development needs at the state and community levels, and thus finding, refining, applying, and using tools that directly support those needs. Each center has the capacity and resources to assess needs and develop tools with their practicing partners.

In 2002, the Chronic Disease Directors association convened a Chronic Disease Summit at CDC to focus on the emerging role of genomics in chronic disease prevention (http://www.chronicdisease.org/genomics___chronic_disease_con.html). This meeting focused on disease-specific issues, with emphasis

on specific tools/priorities for states. In response to recommendations from the summit, the National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP, www.cdc.gov/nccdphp) began development of state-based capacity through funding to four states (Michigan, Minnesota, Oregon, and Utah) for integrating genomics into chronic disease prevention programs. The purpose of this program is to develop genomics leadership and coordination within state agencies to allow planning, development, integration and evaluation of genomics as a tool for chronic disease prevention and health promotion. Documenting the activities, experiences and achievements of these states will produce model processes and applications that should be useful to other states. See *Chapter 14, State Capacity Grants for Integrating Genomics into Chronic Disease Prevention Programs*, for more information.

Thinking Genomically—the Vision for the Future

Thinking genomically means including genomics as another factor that is routinely considered when addressing any public health problem, and applying genomic information when it makes sense to achieve public health goals. In the future, genomics will be integrated into the fabric of public health activities as seamlessly and universally as epidemiology is today.

The time will soon be upon us when it is impossible to consider any health or medical condition without considering its genomic basis. In the not-too-distant future, a complete approach to any public health problem will include an assessment of the role of human genes in the life processes underlying health and disease. The tools, approaches, and capacity that we develop today will form the basis of the increasing integration of genomics knowledge into future public health practice.

Chapter 14

State Capacity Grants for Integrating Genomics into Chronic Disease Prevention Programs

Jennifer Singh and Catherine A. Hutsell

Introduction

In order to integrate genomics into a wider of range of disease control and prevention programs, state and community health agencies are recognizing the need to expand existing genetics expertise in maternal and child health and newborn screening to agency-wide capacity. In July 2003, the National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP), CDC, addressed this need by establishing cooperative agreements with state health departments in Michigan, Minnesota, Oregon and Utah to strengthen programs for genomics and chronic disease prevention. The purpose of this project is to assist states in developing or expanding capacity for genomics leadership and to promote coordination.

Michigan, Minnesota, Oregon and Utah Genomics and Chronic Disease Prevention Programs

The overall goals of this five-year project are to:

- integrate genomics and family history into ongoing and new population-based strategies for identifying and reducing the burden of specific chronic, infectious and other diseases,
- enhance planning and coordination for integrating genomics into core state public health specialties (such as epidemiology, laboratory activities, and environmental health), and
- facilitate use of family history and new knowledge about gene-environment interactions to enhance chronic disease prevention.

State Work Plans

The four states selected to participate in the Genomics and Chronic Disease Prevention Program identified the following common objectives in their work plans:

- *Capacity and Infrastructure:*
  Develop state and local leadership capacity and infrastructure for integrating genomics into public health.

- *Training and Technical Assistance:*
  Educate the pubic health workforce, policy makers and the general public about the role of genomics in public health.

- *Data Collection:*
  Develop and implement population-based assessments using existing surveillance and data systems.

- *Assessment and Use of Genomics Tools:*
  Coordinate the use and evaluation of targeted genomic risk assessment strategies and family history tools.

Progress to Date
In January 2004, the first Genomics Program Directors Meeting was held in Atlanta to bring together representatives from the four funded states, CDC program staff and directors of the three CDC-funded Centers for Genomics and Public Health to discuss progress, plans and potential collaboration. At that time, the states also described specific activities initiated in the first four months of the project that would build on each state's unique experiences and capacity. Specific year-one state activities reported at the meeting are highlighted below.

Michigan

The Michigan Department of Community Health (MDCH) has created a detailed work plan for integrating genomics capacity across the spectrum of public health practice. The MDCH has initiated an array of training activities, such as:

- partnering with the University of Michigan Center for Genomics and Public Health to plan and conduct an informational session for Michigan legislators, and to begin development of a "Cancer Genetics" training module,

- initiating collaboration with Michigan State University to develop sessions on genomics and chronic disease for "Frontiers in Science" teacher education series,

- developing and pre-testing family history questions for a behavioral risk factor survey, and studying the feasibility of adding family history information to the Cancer Registry, and

- participating in the MDCH Cardiovascular Health Task Force, Diabetes Primary Prevention Project, and Primary Care Systems/Barriers to Prevention Working Group.

Minnesota

The Minnesota Department of Health (MDH) is addressing the rapidly expanding need for genomics leadership in Minnesota's public health programs, especially in the areas of policy, planning and intervention. Minnesota's initial activities have focused on building relationships, communication and capacity, including:

- establishing relationships by participating in existing groups to provide genomics perspectives, such as:
  Diabetes Program Steering Committee,
  Cardiovascular Health Planning Committee, and
  Comprehensive Cancer Control Planning;

- creating a Genomics Team by recruiting members from across the agency and establishing roles, procedures and a work plan; and

- developing a training agenda for the agency after evaluating the CDC and the National Coalition for Health Professional Education in Genetics (NCHPEG) genomic competencies.

Oregon

The Oregon Department of Human Services (ODHS) has proposed a program that will strengthen Oregon's public health capacity to address current and emerging genomics issues, ultimately improving the health and well being of individuals and families impacted by heritable conditions, including common chronic diseases. Project activities conducted by the ODHS Office of Family Health, in collaboration with the ODHS Office of Disease Prevention and Epidemiology, include:

- acquiring new agency expertise by hiring a genetic epidemiologist and genetic program coordinator,

- partnering with the University of Washington Center for Genomics and Public Health to develop a model assessment process for integrating genomics,

- completing a comprehensive literature review of diabetes and genetics,

- collecting existing program assessment materials and tools and initiating the development of a conceptual model of the Diabetes Program, and

- identifying the structure of and potential members for the Agency Genomic Coordinating Team, which will enhance cross-program communication and coordination between the Genetics program and Health Promotion and Disease Prevention Programs.

Utah

The Utah Department of Health (UDOH) is developing public health leadership capacity and infrastructure to better integrate genomics into public health practice, particularly in chronic diseases. Since becoming fully staffed, the UDOH has been engaged in several activities, such as:

- establishing an Internal Working Group of approximately 35 public health professionals that has met and established subcommittees for policy, data and surveillance, and education and training,
- convening the External Chronic Disease Standing Subcommittee of the State Genetics Advisory Committee,
- revising the portion of the state genetics plan relevant to chronic disease,
- meeting with chronic disease program managers to identify appropriate objectives for their state chronic disease funding applications, and
- documenting and reviewing experience of the Utah Health Family Tree Program, to gain a historical perspective and recommend a new family history-based approach.

Next Steps

Genomics Program Directors Meeting Report

The four states are collaborating with CDC in the development and publication of a report that will summarize the results of the first Genomics Program Directors Meeting, held in January 2004. This report will describe the logic model developed by the states to guide genomics program efforts in both funded and non-funded participating states; it will also identify short-, medium- and long-term goals, as well as a description of the shared vision for integrating genomics in chronic disease and other public health programs.

Forthcoming Year-One Activities

Indicators for milestones that demonstrate progress over the next three to five years for diseases with promising genomic public health applications (e.g., cardiovascular disease, breast cancer and diabetes) will be identified this year through a series of conference calls between the states and CDC. Each state will also continue to build capacity by developing, hiring and/or training full-time genomics positions and developing internal and external genomics work groups. As part of the training agenda, the states plan to conduct a training needs assessment and an evaluation of existing training programs within the next year.

Genomics sessions have also been scheduled at the 2004 statewide chronic disease conferences, as well as at other state and local public health meetings. Year-one data collection efforts will include feasibility studies of statewide registries, such as a statewide hereditary cancer registry, and pilot studies to test the usability of archived NBS dried blood spot cards.

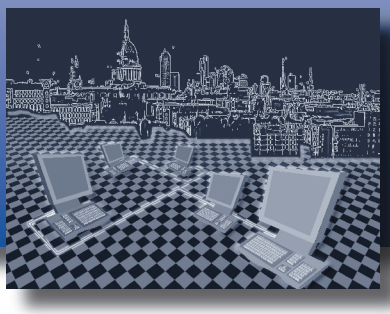
Individual State Genomics Plans
The following table provides Web links to individual state genomics plans:

Table 1. State Genomics Plans

Michigan	http://www.migeneticsconnection.org/staticSP.html
Minnesota	In development
Oregon	http://www.dhs.state.or.us/publichealth/genetics/plan.cfm
Utah	http://genes-r-us.uthscsa.edu/resources/genetics/utah_geneticsplan.pdf

Chapter 15

Internet Resources for Genomics and Disease Prevention



Jennifer Singh and Kate Reed

The Internet offers many resources that may be useful to national, state and local public health professionals interested in learning more about genomics and public health. This chapter provides a selected list of sites that offer starting points; a longer list is available in the online version of this report, available at http://www.cdc.gov/genomics/activities/ogdp/2003.htm. Many other online resources are available; this list is only a snapshot of some that may be useful for integrating genomics into health promotion and disease prevention programs. Please refer to the disclaimer at the end of this chapter.

CDC Office Of Genomics And Disease Prevention (OGDP)

http://www.cdc.gov/genomics/

This site provides information about ways that human genomic discoveries can be used to improve health and prevent disease. It provides links to activities in public health genomics across the lifespan, including links to programs throughout CDC.

- **Weekly Update:**
  http://www.cdc.gov/genomics/update/current.htm
  A weekly update on the impact of human genetic research on disease prevention and public health. To receive notification of this update by e-mail, please send the following message:
  To: listserv@listserv.cdc.gov
  Subject: (leave blank)
  Message: subscribe genetics

- **Public Health Perspectives Series:**
  http://www.cdc.gov/genomics/info/perspectives/series.htm
  On the Highlights page on the OGDP Web site, each *Public Health Perspective* focuses on a single topic and provides information relevant to public health practice. Past topics include family history, *BRCA1/2* testing, obesity, and others.

- **Genomics and Disease Prevention Information System (GDPInfo):**
  http://www2a.cdc.gov/genomics/GDPQueryTool/default.asp

The GDPInfo query tool allows you to define your search of the OGDP Web site with a combination of genes, diseases/conditions, topics and other factors. The search provides a list of all related documents and links to other sites.

Human Genome Project

Human Genome Project Information from the US Department of Energy: http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml
The U.S. Department of Energy and the National Institutes of Health formally initiated the Human Genome Project in 1990. The project originally was planned to last 15 years, but rapid technological advances allowed it to be completed in 2003. This site provides an overview of the Human Genome Project and links to other sites.

National Human Genome Research Institute (NHGRI): http://www.nhgri.nih.gov/
The NHGRI supports genetic and genomic research, investigation into the ethical, legal and social implications surrounding genetics research, and educational outreach activities in genetics and genomics.

The Human Genome—A Guide to Online Information Resources from the National Library of Medicine: http://www.ncbi.nlm.nih.gov/genome/guide/human/
A comprehensive site that provides information and links to information about specific genes and genetic diseases.

Selected articles:

- **Celebrating the 50th Anniversary of the Double Helix: http://www.annals.org/content/vol138/issue7/**
  Articles from Annals of Internal Medicine 1 April 2003 Volume 138 Issue 7

- **Primer on Medical Genomics: History of Genetics and Sequencing of the Human Genome: http://www.mayo.edu/proceedings/2002/aug/7708mgl.pdf**

- **A Vision for the Future of Genomics Research: http://www.nature.com/cgi-taf/DynaPage.taf?file=/nature/journal/v422/n6934/full/nature01626_fs.html**

- **New England Journal Of Medicine: Genomic Medicine Series (2002-2003): http://content.nejm.org/misc/genmed.shtml**
  The full text of all thirteen articles in this series is available free to all users.

Genomic Research

Human Genetics and Medical Research: http://history.nih.gov/exhibits/genetics/
An online exhibit for the public providing information about the use of genetics in medicine sponsored by the National Institute of Health (NIH), http://www.nih.gov/

Genes and Populations: http://www.nigms.nih.gov/news/science_ed/genepop/
A series of questions and answers for patients considering participation in research studies from the National Institute of General Medical Sciences, http://www.nigms.nih.gov/

August 2003 Issue Brief "Applied Public Health Research in Genomics": http://www.astho.org/pubs/AppliedPHResearchinGeneticsIssueBrief.pdf
An issue brief released by ASTHO that outlines the importance of applied public health research in genomics and the types of research needed, the ethical, legal, and social issues that accompany this type of research, current public health genomics research activities, and future research directions.

Genetic Testing

GeneTests/GeneClinics: http://www.genetests.org/
A publicly-funded medical genetics information resource developed for physicians, other healthcare providers, researchers, and others needing information about existing genetic tests. This site includes expert-authored reviews, directories of laboratories and clinics offering genetic tests, and educational materials.

National Academy of Sciences: Human Gene Testing: http://www.beyonddiscovery.org/content/view.article.asp?a=239
A summary of human genetic testing that ranges from the unraveling of the nature of the gene to the social dilemmas posed by genetic testing.

Understanding Gene Testing: http://press2.nci.nih.gov/sciencebehind/genetesting/genetesting00.htm
Illustrates what genes are, explains how mutations occur and how they are identified within genes, and discusses the benefits and limitations of gene testing for cancer and other disorders. Provided by the National Cancer Institute.

Family History

Genetics & Your Practice:
http://www.marchofdimes.com/gyponline/index.bm2
A resource that provides practical information and resources to assist the busy professional in integrating genetics into their patient care.

- Family Health and Social History: (Link same as above)
  A timesaving method of family history taking and sample family history questionnaires.

The Genetic Family History in Practice newsletter for health care professionals from NCHPEG's Family History Working Group:
http://www.nchpeg.org/newsletter/newsletter.asp

Your Family History:
http://genetics.faseb.org/genetics/ashg/educ/007.shtml
A family history tool developed through the collaboration with the American Society of Human Genetics, the National Society of Genetic Counselors and Genetic Alliance.

Genes and Diseases

Disease InfoSearch™:
http://www.geneticalliance.org/DIS/index.html
A tool to assist in finding specific and quality information about genetic conditions, provided by the Genetic Alliance, http://www.geneticalliance.org

GeneReviews:
http://www.geneclinics.org/servlet/access?id=8888891&key=EU5gttBEabgRZ&fcn=y&fw=wlJK&filename=/home/grcover.html
An online publication of expert authored disease reviews from GeneTests, http://www.geneclinics.org/

Genetics Home Reference:
http://ghr.nlm.nih.gov/ghr/template/Home.vm
Provides consumer information about genetic conditions and associated genes. From the National Library of Medicine, http://www.nlm.nih.gov/nlmhome.html

Office of Rare Diseases (ORD):
http://rarediseases.info.nih.gov/
This Web site provides information about ORD-sponsored scientific activities, an ORD cosponsored genetic and rare diseases information center, and a portal to databases that provide information on major topics of interest in rare diseases research.

Genes and Diseases:
http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=gnd
A collection of articles that discuss genes and the diseases that they cause from the National Center for Biotechnology Information (NCBI), http://www.ncbi.nlm.nih.gov/

Online Mendelian Inheritance of Man (OMIM):
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM&cmd=Limits
A database providing a catalog of human genes and genetic disorders authored by the Johns Hopkins University Medical School and developed by the National Center for Biotechnology Information (NCBI), http://www.ncbi.nlm.nih.gov/ at the National Library of Medicine, http://www.nlm.nih.gov/

Genes and Diseases: Cancer

National Cancer Institute:
http://www.cancer.gov/

- Cancer Genetics:
  http://www.cancer.gov/cancerinfo/prevention-genetics-causes/genetics
  A comprehensive list of cancer genetics information ranging from general to specific cancer information, policy, and cancer genetics research and information.

Genes and Diseases: Birth Defects

March of Dimes Birth Defects Foundation:
http://www.marchofdimes.com/home.asp
A not-for-profit organization with the mission to improve health of babies by preventing birth defects and infant mortality.

- Birth Defects and Genetic Conditions:
  http://www.marchofdimes.com/pnhec/4439.asp

National Birth Defects Prevention Network:
http://www.nbdpn.org/
A group with the mission to establish and maintain a national network of state and population-based programs for birth defects surveillance and research to assess the impact of birth defects upon children, families, and health care; to identify factors that can be used to develop primary prevention strategies; and to assist families and their providers in secondary disabilities prevention.

Genes and Diseases: Newborn Screening

National Newborn Screening and Genetics Resource Center (NNSGRC):
http://genes-r-us.uthscsa.edu/index.htm
Provides information and resources in the area of newborn screening and genetics

to benefit health professionals, the public health community, consumers, and government officials:

- a report on the characteristics of state NBS programs,
- state newborn screening program resources, and
- resources for state genetics planning.

Association of Public Health Laboratories (APHL) Newborn Screening and Genetics Program:
http://www.aphl.org/Newborn_Screening_Genetics/index.cfm

March of Dimes Newborn Screening Recommendations:
http://www.marchofdimes.com/professionals/580_4043.asp

Public Health Ethical, Legal and Social Issues (PHELSI)

The U.S. Department of Energy Human Genome Project:
http://www.ornl.gov/sci/techresources/Human_Genome/elsi/elsi.shtml
An educational and informational site about the human genome project. This is a publication of the U.S. Department of Energy Human Genome Program.

Genetics Education and Counseling Program:
http://www.pitt.edu/~edugene/resource
A public health initiative for community and professional education and awareness on genetics. This Web site is sponsored by the University of Pittsburgh.

Public Health Genetics from University of Sheffield-School of Health and Related Research (Scharr):
http://www.shef.ac.uk/~scharr/publich/research/genetics/index.html
A catalogued series of articles on various topics including technical issues, genetic testing in the workplace, and experiences of individuals affected by genetic diseases from the U.K.

Michigan Centers for Genomics and Public Health:
http://www.sph.umich.edu/genomics/index.html
The Michigan Center for Genomics & Public Health seeks to integrate genomic discoveries into public health practice, with consideration of the ethical, legal, and social issues associated with the application of these discoveries, as well as the involvement of the community at large.

Genetics and Ethics Page:
http://genethics.ca/index.html
A clearinghouse for information on the social, ethical and policy issues associated with genetic and genomic knowledge and technology.

Policy

National Conference of State Legislatures (NCSL) Genetic Technologies Project Web Site:
http://www.ncsl.org/programs/health/genetics.htm
A group commissioned to provide state legislators and other policymakers with objective, comprehensive, and scholarly information from a non-partisan source to facilitate the drafting of sound genetics-related legislation.

Secretary's Advisory Committee on Genetics, Health and Society:
http://www4.od.nih.gov/oba/sacghs.htm
"A forum for expert discussion and deliberation and the formulation of advice and recommendations on the range of complex and sensitive medical, ethical, legal and social issues raised by new technological developments in human genetics."

Genetics and Public Policy Center:
http://www.dnapolicy.org/index.jhtml
Information on genetic technologies and genetic policies for the public, media and policymakers. The Genetics and Public Policy Center is funded through a grant from The Pew Charitable Trusts.

Public Health Resources

Genomics: A Guide for Public Health:
http://www.genomicstoolkit.org/index.shtml
A guide to help state public health agencies integrate genetics into their programs. This guide provides integration strategies, tools for needs assessment, priority setting guides, snapshots of current integrated programs, many resources, and much more.

Coalition of State Genetic Coordinators:
http://www.stategeneticscoordinators.org/index.html
An organization of state and territorial genetics coordinators and others who support the mission to promote core public health functions as they apply to genetics.

Genomics and Chronic Disease Summit Report, 2002:
http://www.chronicdisease.org/Genomics_Summit_Report.pdf
A report from the Association of State and Territorial Chronic Disease Directors.

Harnessing Genetics to Prevent Disease & Improve Health:
http://www.prevent.org/publications/GeneticsReport.pdf
A guide to help states shape genetics policies for the purpose of advancing individual and collective health. The report highlights recommendations for

policymakers to address the social, legal and ethical implications of genetics in their states.

Centers for Genomics and Public Health:
http://www.cdc.gov/genomics/activities/fund2001.htm

- University of Washington Center for Genomics and Public Health: http://depts.washington.edu/cgph/
- University of Michigan Center for Genomics and Public Health: http://www.sph.umich.edu/genomics/
- University of North Carolina Center for Genomics and Public Health, the Genomics Revolution and Public Health: http://www.sph.unc.edu/nciph/phgenetics/index.htm

The WHO Genetics Programme:
http://www.who.int/genomics/en/
Information about activities undertaken by the WHO Human Genetics Program to help control the "most common hereditary diseases and those having a genetic predisposition."

Educational Resources

National Coalition for Health Professional Education in Genetics (NCHPEG):
http://www.nchpeg.org/
A national effort to promote health professional education and access to information about advances in human genetics:

- Genetic Resources on the Web (GROW),
- Genetic Family History Resources, and
- Educational Resources.

Genetic Educational Materials Database (GEMS):
http://www.gemdatabase.org/GEMDatabase/index.asp
Searchable listing of public health genetics policy documents and clinical genetics educational materials from the National Newborn Screening and Genetics Resource Center (NNSGRC).

OGDP List of Training Tools:
http://www.cdc.gov/genomics/training/tools.htm
A list of available training tools, courses, and multi-media educational materials designed to assist public health professionals and educators integrate genomics into public health practice.

Disclaimer: The CDC Office of Genomics and Disease Prevention makes this information available as a public service only. Providing these links does not constitute an endorsement of these organizations or their programs by CDC or the federal government, and none should be inferred. Exclusion of information does not mean there are no other useful resources available. The CDC is not responsible for the content of the individual organization Web pages found at these links. Note that some links may become invalid over time.

List of Authors

Barbara Adam, MS
Supervisor, Research Chemist
National Center for Environmental Control, CDC
Atlanta, GA 30341

Janice Bach, MS, CGC
Hereditary Disorders Program
Michigan Dept. of Community Health
Lansing, MI 48909

Timothy Baker, MPH
Deputy Director
Office of Genomics and Disease Prevention, CDC
Atlanta, GA 30333

Heidi Michels Blanck, PhD
Epidemiologist
National Center for Chronic Disease Prevention and Health Promotion, CDC
Atlanta, GA 30341

Linda A. Bradley, PhD
Public Health Service Team Leader
Office of Genomics and Disease Prevention, CDC
Atlanta, GA 30333

Wylie Burke, MD, PhD
Professor and Chair
Department of Medical History and Ethics
University of Washington
Seattle, Washington 98195

Bin Chen, PhD, FACMG
Health Scientist/Geneticist
Laboratory Practice Evaluation and Genomics Branch
Division of Laboratory Systems,
Public Health Practice Program Office, CDC
Atlanta, GA 30341

Toby Citrin, JD
Director, Community-Based Public Health
University of Michigan
Ann Arbor, MI 48109-2029

Ralph J. Coates, PhD
Associate Director for Science
National Center for Chronic Disease Prevention and Health Promotion, CDC
Atlanta, GA 30341

Mary Dott, MD
Medical Officer, II
National Center for Chronic Disease Prevention and Health Promotion, CDC
Atlanta, GA 30341

Diane Dunet, PhD, MPA
Health Scientist
National Center for Chronic Disease Prevention and Health Promotion, CDC
Atlanta, GA 30341

Karen Edwards, PhD
Public Health Genetics Program
University of Washington
Seattle, Washington 98195

Scott Grosse, PhD
Health Economist
National Center on Birth Defects and Developmental Disabilities, CDC
Atlanta, GA 30341

Daurice Grossniklaus, MS, MED, RN
Health Education
National Center for Chronic Disease Prevention and Health Promotion, CDC
Atlanta, GA 30341

Marta Gwinn, MD, MPH
Associate Director for Science
Office of Genomics and Disease Prevention, CDC
Atlanta, GA 30333

Tabitha Harrison, MPH
Research Coordinator
Center for Genomics and Public Health
University of Washington
Seattle, WA 98105-6099

Catherine A. Hutsell, MPH
Health Education Specialist
National Center for Chronic Disease Prevention and Health Promotion, CDC
Atlanta, GA 30341

Muin J. Khoury, MD, PhD
Director, Office of Genomics and Disease Prevention, CDC
Atlanta, GA 30333

Mary Lou Lindegren, MD
Medical Epidemiologist
Office of Genomics and Disease Prevention, CDC
Atlanta, GA 30333

Jairam Lingappa, MD, PhD
Partners in Prevention
University of Washington
Seattle, WA 98104

Ira Lubin, PhD, FACMG
Geneticist, Laboratory Practice Evaluation and Genomics Branch
Division of Laboratory Systems
Public Health Practice Program Office, CDC
Atlanta, GA 30341

Elizabeth Mahanna, BA
North Carolina Center for Genomics and Public Health
Chapel Hill, NC 27599-8165

Ann Malarcher, PhD
Senior Scientific Advisor
Office of Smoking and Health
National Center for Chronic Disease Prevention and Health Promotion, CDC
Atlanta, GA 30341

Monica R. McClain, PhD
Assistant Director of Biometry/Epidemiology
Foundation for Blood Research
Scarborough, Me 04070-0190

Stephen M. Modell, MD, MS
School of Public Health
University of Michigan
Ann Arbor, MI 48109-2029

Glenn E. Palomaki, BS, BA
Director of Biometry/Epidemiology
Foundation for Blood Research
Scarborough, ME 04070-0190

Kristin L. Peterson-Oehlke, MS, CGC
Geneticist, Minnesota Department of Health
Minneapolis, MN 55414

Sarah Raup, MPH
Research Manager
Center for Genomics and Public Health
University of Washington
Seattle, WA 98105-6099

Kate Reed, MPH
National Human Genome Research Institute, NIH
Bethesda, MD 20892-2032

Michele (Shelley) Reyes, PhD
Epidemiologist, Team Leader
National Center for Chronic Disease Prevention and Health Promotion, CDC
Atlanta, GA 30341

Maren Scheuner, MD, MPH
Visiting Associate Professor
UCLA School of Public Health
Los Angeles, CA 90095-1772

Jennifer Singh, MPH
ASPH Fellow
Office of Genomics and Disease Prevention, CDC
Atlanta, GA 30333

Roberta C. M. Wines, MPH
ASPH Fellow
National Center on Birth Defects and Developmental Disabilities, CDC
Atlanta, GA 30333

Paula Yoon, ScD, MPH
Epidemiologist and Public Health Science Team Leader
Office of Genomics and Disease Prevention, CDC
Atlanta, GA 30333

For additional information, please e-mail the CDC Office of Genomics and Disease prevention at genetics@cdc.gov or call (404) 498-1420.

We welcome your comments and suggestions about CDC's first report on Genomics and Population Health: United States 2003.

_____

_____

_____

_____

_____

_____

_____

_____

_____

Thank you for your candid response!

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention (CDC)
Atlanta, Georgia 30333

Return After Five Days

OFFICIAL BUSINESS
Penalty for Private Use $300

Return Service Requested

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES

BUSINESS REPLY MAIL
FIRST CLASS PERMIT NO. 99110 ATLANTA, GA 30333

Postage Will Be Paid by Department of Health & Human Services

Centers for Disease Control and Prevention
Office of Genomics and Disease Prevention
Attn: Health Communications Specialist
1600 Clifton Road, N.E., MS E-82
Atlanta, Georgia 30329-9946

DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention (CDC), MS E-82
Atlanta, GA 30333

Official Business
Penalty for Private Use $300

Return Service Requested

Media Mail
Postage & Fees Paid
PHS/CDC
Permit No. G 284