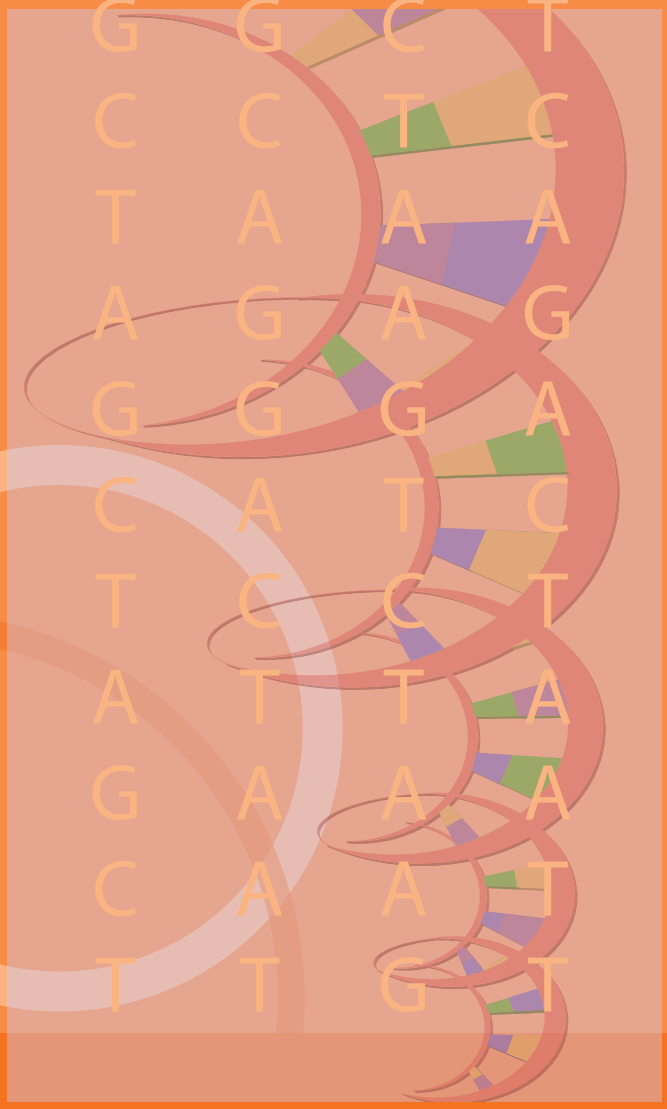
Genomics



National Office of Public Health Genomics
(NOPHG)

2006 Program Review Book

DEPARTMENT OF HEALTH & HUMAN SERVICES USA

CDC
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Contents

PRIORITIES

Public health genomics is a multidisciplinary field that uses the effective and responsible translation of genome-based knowledge and technologies to improve population health. Public health genomics uses population-based data on genetic variation and gene-environment interactions to develop evidence-based tools for improving health and preventing disease. Since 1998, the Office of Genomics and Disease Prevention has been at the leading edge of this development in the United States and internationally. In 2006, CDC changed the name of the office to the "National Office of Public Health Genomics (NOPHG)" to better reflect the focus on public health. NOPHG provides national public health leadership while building partnerships with other federal agencies, public health organizations, professional groups, and the private sector.

Genomics has the potential to provide insights into why some people get sick from certain infectious agents, environmental exposures, and behaviors, while others do not. Better understanding of the gene-environment interactions that contribute to health and disease will help to identify more effective ways to prevent and treat diseases.

Most human diseases—especially common diseases, like cancer and diabetes—result from interactions of genetic factors with modifiable environmental and behavioral factors. Very few diseases can be attributed to single genes. Calling a disease *genetic* implies that no environmental or behavioral interventions exist, and that biology is destiny. Conversely, calling a disease *environmental* ignores the influence of genetic variation on disease susceptibility, progression, and response to treatment.

Both nature and nurture are important. The way genes interact with each other and with environmental factors to cause disease, however, is largely unknown. Clinical and epidemiologic studies are needed to identify and better characterize genetic and environmental factors and their interactions. This new knowledge will lead to more effective ways to prevent disease and improve health.

Although public health has used genomics in newborn screening programs since the 1960's, future genomic applications will require broader program models. While the accelerating rate of genomic discoveries is exciting, immense gaps currently exist in the knowledge needed for successful translation of these discoveries into population health benefits. This *translation gap* calls for public health leadership in shaping the agenda for applied research, policy development, and practice.

Anticipating the potential of genomic research for improving population health, CDC developed a strategic plan and formed the Office of Genetics and Disease Prevention in 1997. The office was renamed the Office of Genomics and Disease Prevention (OGDP) in 2003, and this year, as mentioned, the name was changed to the National Office of Public Health Genomics (NOPHG).

NOPHG Vision

- To use genomic knowledge to improve the lives and health of all people.

NOPHG Mission

- To integrate genomics into public health research, policy, and programs.

NOPHG Goals

1. Integrate genomics into public health research.
2. Assess the role of family history in risk assessment and disease prevention.
3. Evaluate the use of genetic tests for population health.

1. Integrate Genomics into Public Health Research

CDC is recognized around the world for conducting public health investigations of health problems and emergencies and, by doing so, improving people's daily lives. Collecting and analyzing human genomic data in public health investigations has the potential to enhance the ability to understand variation in disease outcomes, characterize environmental exposures more accurately, and refine public health interventions such as vaccination, chemoprophylaxis, exposure reduction, and health promotion.

2. Assess the Role of Family History in Risk Assessment and Disease Prevention

Family history is known to be a risk factor for many chronic diseases including coronary heart disease, stroke, cancer, and diabetes. These common diseases result from the interactions of multiple genes with multiple environmental factors in complex patterns that, despite progress in sequencing the human genome, are not yet well understood. In the meantime, a person's family health history can be used as a low-cost, low-tech "genomic tool" to capture the interactions of genetic, environmental, and behavioral factors in determining that person's disease risk. A family history assessment is also the first step toward identifying families with increased risk who may benefit from genetic testing as well as appropriate health education and behavior modification strategies.

3. Evaluate the Use of Genetic Tests for Population Health

More than 1,000 genetic tests are currently available for clinical testing. Most are used for diagnosis of rare single-gene disorders and a few for newborn screening. A growing number of genetic tests may have population-based applications, such as determining the risk of developing a disease or condition in the future (e.g., predictive testing for breast cancer) and identifying genetic variations that can influence response to medicines (pharmacogenomics). These genetic tests have the potential for broad public health impact, and concerns have been raised about the need for pre- and post-market test assessment and surveillance.

Current Priorities Related to Goals

- Using the National Health and Nutrition Examination Survey (NHANES) III, analyze and publish data on the prevalence of the top 100 genetic variants of public health significance, and correlate genetic variation with multiple indices of health status in the U.S.
- Test a CDC family history tool that will be used for prevention of 6 common chronic diseases.
- Evaluate a model process for systematic assessment of genomic applications in translation from research to practice (Evaluation of Genomic Applications in Practice and Prevention—EGAPP initiative).

Major Accomplishments Related to Goals and Priorities

1. Integrate Genomics into Public Health Research

National Health and Nutrition Examination Survey (NHANES) III

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative survey of the U.S. population conducted by CDC's National Center for Health Statistics. The NHANES database includes thousands of data points on survey participants, including demographic, health history and health behavior characteristics; physical and physiological measurements; and detailed nutritional and biochemical analyses. During the second phase of NHANES III (1991–1994), white blood cells were used to create a DNA bank.

A CDC-NCI working group of epidemiologists, geneticists, and laboratory scientists is conducting a collaborative study for determining the prevalence of selected genotypes of public health importance for variants in six major pathways using DNA from NHANES III:

- Nutrient metabolism;
- Immune and inflammatory responses;
- Activation and detoxification pathways;
- DNA repair pathways;
- Hemostasis and renin/angiotension pathways; and
- Developmental pathways.

The National Cancer Institute has completed the genotyping work. Data from this study will provide the first-ever national genotype prevalence estimates for the United States. Such data are important for interpreting the results of studies of gene–disease associations and gene–environment interactions. Establishing the prevalence of gene variants known to interact with specific environmental factors provides an important foundation for developing and assessing the potential impact of environmental interventions.

Major Accomplishments Related to NHANES

1. Completed genotyping of more than 80 genetic variants in approximately 7,300 NHANES III specimens in July 2006 through partnership with NCI.
2. CDC-NCI Working Group developed a collaborative research plan to investigate genotype-phenotype correlations in multiple health outcomes such as asthma, diabetes, obesity, and selected infectious diseases.
3. CDC-NCI Working Group Analytic Committee developed new statistical methods to analyze genetic data from studies using complex survey design such as NHANES III.
4. CDC-NCI Working Group submitted a successful proposal in March 2006 to extend the collaborative project to genotype variants in an additional 100 genes of public health importance and assess genotype-phenotype correlations for a number of common complex disorders.

Develop a Knowledge Base on Genomics and Population Health: Human Genome Epidemiology (HuGE)

Human genome epidemiology (HuGE) is the basic science of translation from gene discovery to clinical and public health practice. The HuGE Network (HuGENet) is a global collaboration of individuals and organizations that bridges the fields of genetics, medicine and public health to promote harmonization, systematic review and synthesis of population-based data on genetic factors in health and disease.

Major Accomplishments Related to HuGENet

1. Established an international network to promote translation of knowledge and technologies into public policies, programs and services for the benefit of public health. The Genome-based Research and Population Health International Network (GRaPH-Int, http://www.graphint.org/) was launched at the 4th International DNA Sampling Conference in Montreal in June 2006.
2. Curates the HuGE Published Literature database (HuGE Pub Lit), a continually updated and accessible knowledge base on the World Wide Web that tracks the growing published literature of human genome epidemiologic studies. The system contains more than 23,000 abstracts and is currently undergoing an extensive remodeling and upgrade to improve searching and add new capabilities.
3. Established additional hubs in Cambridge (UK), Ottawa (Canada), and Ioannina (Greece).
4. Published a "roadmap" in Nature Genetics for the development of a "network of investigator networks" to capture and curate unpublished data, conduct meta-analysis, provide data for policy development and identify research gaps.

Seed Funding for Public Health Genomics Research

In March 2006, NOPHG announced the availability of seed funding for innovative CDC projects that integrate genomics into pubic health research and programs. Thirty-two proposals were received and eleven were selected, with priority given to those with potential to demonstrate health impact within two years. The following descriptions provide information about 2006 seed funding recipients.

Genetic Predictors of Developing Hemolytic-Uremic Syndrome among persons infected with Shiga toxin-producing *Escherichia coli* (STEC)

Principal Investigators: Frederick J. Angulo and Linda J. Demma (NCID)

Escherichia coli O157:H7 and other Shiga toxin-producing enterohemorrhagic *E. coli* (STEC)are estimated to cause over 110,000 illnesses, 3000 hospitalizations, and 90 m deaths each year in the U.S. Approximately 8% of persons infected with *E. coli* O157 develop hemolytic-uremic syndrome (HUS). HUS is associated with substantial morbidity and mortality, with case fatality rates as high as 5%; HUS is the leading cause of renal failure in children. This project will apply genomic methods to determine host factors associated with HUS within a large, population-based cohort study persons infected with STEC.

Microarray Analyses of MHC Genetic Variations in Diisocyanate-induced Occupational Asthma
Principal Investigators: Michael I. Luster(NIOSH), Berran Yucesoy (NIOSH), Victor J. Johnson(NIOSH), and Eugene Demchuk (ATSDR)

Diisocyanates are the most common cause of occupational asthma from low-molecular weight chemicals, still causing disease in 5-15 % of chronically exposed workers despite improved industrial hygiene efforts. With the recent development of genotype microarrays we are now capable of rapidly examining a large number of variants in the highly relevant MHC region in a case-control study of exposed workers. The results could be used to assess the genetic contribution in the risk of OA, identify the most susceptible (genetic) populations and apply relevant information to the risk assessment process by determining safe exposure levels for the most susceptible groups of workers.

Maternal Smoking, Polymorphisms of Genes Involved with Metabolism of Tobacco Smoke, and Risk for Gastroschisis and Anorectal Atresia/ Stenosis in the National Birth Defects Prevention Study
Principal Investigators: Margaret A. Honein (NCBDDD), Mary Jenkins (NCBDDD), Margaret (Peg) Gallagher (NCEH), Sonja A. Rasmussen (NCBDDD), Patricia Richter (NCCDPHP), Robert Merritt (NCCDPHP)

Gastroschisis and anorectal atresia/stenosis are two common, major birth defects. Gastroschisis, a herniation of the intestines through a defect in the abdominal wall, affects approximately 3.7 infants per 10,000 US births; anorectal atresia/stenosis, the congenital absence or narrowing of the anal or rectal canal, affects approximately 4.8 infants per 10,000 US births. Both of these birth defects are believed to have a multifactorial etiology, including both environmental and genetic risk factors. Because some studies have reported maternal smoking as a risk factor for both defects, this case-control study will focus on potential interaction of maternal smoking with genes involved in metabolizing tobacco smoke (*CYP2A6*, *CYP2B6*, *CYP2D6*, *CYP1A1, CYP1A2, CYP2E1, GSTT1, NAT1,* and *NAT2*).

Identifying Genetic Determinants of Susceptibility to *M. tuberculosis*
Principal Investigator: Mary Reichler (NCHHSTP)

Tuberculosis continues to be a major global health problem. Each year 54 million people worldwide are infected with Mycobacterium tuberculosis, 8.8 million develop clinical disease, and 1.75 million die of tuberculosis. In 1999, CDC's Division of Tuberculosis Elimination launched a prospective multi-site study of epidemiologic, immunologic, and immunogenetic correlates of susceptibility to TB among contacts of infectious TB patients in a U.S. and Canadian-born study population. A total of 1,947 contacts have been enrolled in the study to date, with a total planned enrollment of 2,500. Specimens are being tested for three cytokine surrogate markers, HLA, and a dozen candidate gene single nucleotide polymorphisms (SNPs). This proposal seeks to 1) strengthen laboratory capacity, expanding testing from 18 candidate gene SNPs to all 33 SNPs with demonstrated associations with tuberculosis or strong biologic plausibility, and 2) to build specialized capacity to perform complex analyses, including haplotype analysis, while carefully evaluating multiple potential gene-gene and gene-environment interactions.

Investigation of Immunoglobulin (Ig) GM and KM Gene Polymorphisms in Susceptibility to and Pathogenesis of Malaria and HIV in Children and Pregnant Women in Kenya
Principal Investigator: Ya Ping Shi (NCID)

Malaria is a major global public health problem, currently estimated to cause 300-500 million clinical cases and 1.1-2.7 million deaths annually throughout the world. Sub-Saharan Africa (SSA) accounts for 90% of all these cases and the disease exerts an adverse impact on the health of young children, pregnant women and their unborn infants. Previous studies conducted in Kenya, a malaria holoendemic and HIV epidemic area, have shown that gene polymorphism of the Fc receptor IIa for Ig (FcgRIIa), which determines differential affinity for human IgG subclasses, is associated with 1) high density malaria infection in children, 2) malaria infection in HIV positive women, and 3) perinatal HIV infection. The specific objectives of the proposed study are 1) to determine the association between Ig GM/ KM gene polymorphisms and malaria morbidity, including severe anemia, and mortality in children, 2) to determine the association of gene polymorphisms of Ig GM/ KM with outcomes of malaria infection in pregnant women, including maternal anemia, birth defects, and vertical transmission of HIV, 3) to determine the effects of Ig GM/ KM gene polymorphisms on the interaction between malaria and HIV-1 infection during pregnancy, and 4) to determine the differential interaction between Ig GM gene haplotype profiles and FcgRIIa genotypes and acquired antibody responses in relation to the above epidemiological and clinical parameters.

Effectiveness and Cost-effectiveness of Using Family History of Diabetes for Population–level Health Promotion
Principal Investigator: Scott Grosse (NCBDDD)

Type 2 diabetes is a growing national health problem because of its rapidly increasing incidence and associated health impacts, including premature mortality, disabling sequelae, and risk of birth defects in offspring. Family history has been shown to be a strong predictor of diabetes risk, which could reflect both genetic risk and shared behaviors or environment. This project will develop a decision analytic and cost-effectiveness model to assess the likely outcomes of health promotion efforts that focus on the use of family history information on type 2 diabetes. The two specific aims are: 1) to develop a decision analytic and cost-effectiveness model to assess the effects on health outcomes and costs of health promotion efforts that focus on the use of family history of diabetes; and 2) to use this decision model to assess the effects of targeting health promotion efforts based on family history of diabetes on the outcomes and costs of: i) individuals with a family history of diabetes, ii) individuals without a family history of diabetes, and iii) the overall population of individuals.

Should Genetic Testing Be Used to Guide Warfarin Therapy? An Evidence-based Cost-Utility Analysis
Principal Investigator: Scott Grosse (NCBDDD)

Warfarin is a common, chronically administered oral anticoagulant; 16 million prescriptions were dispensed in 2004. Warfarin reduces the risk of thromboembolic events by 50-79% in atrial fibrillation (AF) patients, yet is prescribed for only about half of the 2 million patients diagnosed with AF in the US each year, due in part to concerns about the risk of major bleeding and the challenges of closely monitoring and adjusting warfarin therapy. Recently, variants in the *CYP2C9* and *VKORC1* genes have been

shown to significantly influence warfarin dose requirements, and in the case of *CYP2C9*, the risk of major bleeds. The use of *CYP2C9* and *VKORC1* genetic testing has thus been proposed to help guide warfarin therapy. Although the analytic and clinical validity of these associations has been established, their clinical utility is just beginning to be evaluated. This project will develop a disease-based simulation model and perform a cost-utility analysis from multiple stakeholder perspectives to help inform treatment decisions and guidelines and reimbursement policies.

Effect of Folic Acid Intake on Blood Folate and Homocysteine Levels in Persons Classified by Genotype of Folate-related Genes
Principal Investigators: Quanhe Yang (NCBDDD), Margaret Gallagher (NCEH), David Erickson (NCBDDD), and Karen Steinberg (CoCHP)

Abnormalities in the metabolism of folate and homocysteine are associated with cardiovascular disease and other conditions that contribute significantly to morbidity and mortality in the United States. Recently, researchers have identified several common polymorphisms of genes related to folate and homocysteine metabolism, including the *C677T* and the *A1298C* alleles of 5, 10 methylenetetrahydrofolate reductase (*MTHFR*), the *844ins68* allele of cystathionine-beta-synthase (*CBS*), and the *A66G* allele of methionine synthase reductase (*MTRR*). These genetic variants may influence folate metabolism and disease risk, and that some of their effects may be mediated by gene-gene and gene-environment interactions. This study will assess whether the effect of folic acid intake on the blood levels of folate and homocysteine varies by genotype of folate-related genes, using data and DNA samples from NHANES III.

A Proposal to Evaluate Use of the CDC Web-based Family Healthware™ Assessment Tool Among Specific Public Health Program and Project Healthcare Providers
Principal Investigator: Susan True (NCCDPHP)

CDC supports a collaborative study set in primary care clinics to determine whether family history risk assessment and classification using the Family Healthware™ (FHW) tool--an interactive Web-based tool that collects information on personal health behaviors, screening, and family health history and offers personalized prevention messages--can influence health behaviors and the use of preventive medical services. This project will assess provider and consumer receptivity to the use of the Family Healthware™ (FHW) tool among providers in the National Breast and Cervical Cancer Early Detection Program (NBCCEDP), the Division of Cancer's Colorectal Cancer (CRC) demonstration project, and the CDC-funded WISEWOMAN programs. Outcomes from this proposal will be used to inform research on expanding use of FHW into community health settings.

An Early Childhood Mortality Study Using a Newborn Blood Spot Screening Test for Severe Combined Immunodeficiency Disorder (SCID)
Principal Investigators: Barbara Adam and Robert Vogt (NCEH), Richard Olney (NCBDDD), Franco Scinicariello (ATSDR), Chin-Yih Ou (NCHSTP)

Severe Combined Immunodeficiency Disorder (SCID) is a group of genetic conditions characterized by profound defects in both cellular and humoral immunity. Caused by the nearly complete failure to develop functional T-cells, SCID leads to severe bacterial and viral infections; without treatment, affected infants usually die within a year of birth. NIH

and CDC have developed assays to detect profound T-cell lymphocytopenia by testing dried blood spots. Both assays use realtime PCR to measure T-cell recombination excision circles (TREC), the episomal circular DNA that is excised from T-cells when their V-genes recombine with the constant region genes of the T-cell receptor. The goals of this proposal are: 1) to establish authoritative methods for the standardization of the TREC assay to foster its systematic translation to public health newborn screening; 2) to determine the extent to which SCID contributes to early childhood mortality; and 3) to establish an ongoing partnership with the Newborn Screening Program in the California Department of Health Services to facilitate the investigation of other occult contributors to early childhood mortality.

Osteoporosis: A Multi-determinate Approach to Prevention: Implications for the CDC Health Protection Goal of Living Better and Longer
Principal Investigator: Anne Looker (NCHS)

Osteoporosis is a major cause of morbidity in the elderly. Inherited factors are important determinants of peak bone mass, although the influence of genetic factors on bone turnover and changes in bone mass with aging is less clear. Over the past 20 years, several candidate genes have been associated with bone mineral density (BMD); however, most studies have been conducted on relatively small convenience samples and few have examined the role of candidate genes on bone loss or fracture occurrence. This study will help fill these gaps by examining the relationship between these endpoints and two candidate genes (low-density lipoprotein -receptor related protein 5 (*LRP5*) gene (6), and the 116 T/G (Ser37Ala) polymorphism of the bone morphogenetic protein 2 (*BMP2*) gene (7) in a very large, community-based sample. The study takes advantage of an existing relationship with Kaiser Permanente of San Diego.

2. Assess the Role of Family History in Risk Assessment and Disease Prevention

Beta Version of Family Healthware™

Family history is known to be a risk factor for many chronic diseases—including coronary heart disease, cancer, and diabetes—but it is underutilized in preventive medicine. To facilitate the systematic collection, interpretation, and use of family health history, the CDC has developed a new, interactive, Web-based family history screening tool. Family Healthware™ was developed by a multi-disciplinary team with support from a commercial communications firm and a software development company. Part of the development effort included assessing family history tools currently used or being developed and identifying key design principles for a new tool, as well as developing criteria for selecting diseases to include in the tool. Qualitative and quantitative formative research on lay understanding of family history and genetics helped shape the tool's content, labels, and messages. Lab-based usability testing helped refine messages and tool navigation.

Family Healthware™ assesses familial risk for 6 diseases (coronary heart disease, stroke, diabetes, and colorectal, breast, and ovarian cancer) and provides a personalized "prevention plan" for lifestyle changes and screening. The tool collects data on health behaviors, screening tests, and disease history of a person's first- and second-degree relatives. Algorithms in the software analyze the family history data and assess

familial risk. A second set of algorithms uses the data on familial risk level, health behaviors, and screening to generate personalized prevention messages. The tool is being evaluated by three academic centers, which are using a network of primary care practices in turn; to determine if prevention messages tailored to familial risk will motivate people to change lifestyle or screening behaviors.

Family History Controlled Clinical Trial

The University of Michigan School of Medicine, Evanston Northwestern Healthcare Research Institute, and Case Western Reserve University School of Medicine have been funded by CDC to collaborate on a study, set in primary care practices, to assess the clinical utility of Family Healthware™. The purpose of this study is to determine whether family history risk assessment, stratification, and personalized prevention messages influence health behaviors and use of medical services. The study will consist of approximately 6,000 patients aged 35-65 years who attend primary care practices that are part of research networks affiliated with the three research centers. The practices are randomized into two groups. Patients in Group 1 complete a pre-test and Family Healthware™ and receive the report with the familial risk assessment and personalized prevention recommendations. After six months, Group 1 patients complete a post-test. Patients in Group 2 complete the pre-test and receive standard prevention messages for the same diseases. After 6 months, Group 2 patients complete the post-test and Family Healthware™. The pre- and post-test includes assessment of risk factors, use of medical services (especially preventive services), interest in modifying health behaviors, risk perceptions, etc. The analysis will compare changes in health behaviors between patients in Groups 1 and 2 and will also examine differences by familial risk strata. The study began enrolling patients in December 2005 and is expected to be completed by October 2007. Results from the study and others will be used to modify the tool for use as PC-based software for the general public and as a component to new or existing electronic medical records and decision support systems for preventive medicine.

Material Transfer Agreements (MTAs)

In addition to the study described above, CDC is making the beta version of Family Healthware™ available for research and further pilot testing. Interested researchers can view the software on a password-protected Web site for a limited time after signing a confidentiality disclosure agreement. Those who are interested in obtaining a copy of Family Healthware™ for research purposes can establish a Materials Transfer Agreement (MTA) with CDC and receive a copy of the software. To date we have established 2 MTAs, one with an academic partner and another with a federal agency.

Surgeon General's Family History Initiative Resource Packets

As part of the Surgeon General's Family History Initiative, CDC developed a resource packet for state health departments. The packets contained case studies, fact sheets, PowerPoint presentations, a poster, a list of on-line resources, brochures, and suggestions for promoting family history in communities. The packets were distributed in November 2005 to coincide with the Surgeon General's focus on Thanksgiving as National Family History Day, and the materials have continued to be useful educational tools in 2006.

Major Accomplishments Related to Family History

1. Completed quantitative and qualitative formative research on lay understanding of family history and genetics to shape content, labels, and messages in Family Healthware™ tool.
2. Completed lab based usability testing to refine messages and tool navigation.
3. Developed Family Healthware™ tool that assesses familial risk for 6 diseases (coronary heart disease, stroke, diabetes, and colorectal, breast, and ovarian cancer).
4. Study of Family Healthware™ tool underway at three academic centers to evaluate the effectiveness of the tool for motivating health behaviors and use of medical services based on familial risk factors (completion of study scheduled for October 2007).
5. Filed for patent for Family Healthware™.
6. Engaged all state health departments in the Surgeon General's Family History Initiative by providing them with information and resources that will allow them to participate in future activities.

3. Evaluate the Use of Genetic Tests for Population Health

As genetic tests with potential for public health impact increase in number and complexity, timely and reliable information that helps healthcare providers and consumers use genetic tests appropriately is urgently needed. A coordinated process is needed to synthesize currently available data on specific genomic applications and clearly identify gaps in knowledge as well as the studies needed to resolve them.

To address this need, the National Office of Public Health Genomics launched the Evaluation of Genomic Applications in Practice and Preventions (EGAPP) model project in 2004. The EGAPP initiative aims to develop and evaluate a coordinated, systematic process for assessing genomic applications (i.e., genetic tests and other applications of genomic technology) in transition from research to clinical and public health practice.

EGAPP Working Group

A CDC-wide and HHS interagency Steering Committee provided early guidance on development of project objectives and also selected members of the independent, non-federal, multi-disciplinary EGAPP Working Group in April, 2005, after a national recruitment. The roles of this 13-member Working Group (http://www.cdc.gov/genomics/gtesting/EGAPP/group.htm) are to establish methods and process for evidence reviews, identify, prioritize and select topics; monitor the review process, and develop conclusions and recommendations based on the evidence. An important objective is to provide clear linkage between the scientific evidence developed and the recommendations and information subsequently disseminated. Supported by project staff and consultants, the EGAPP Working Group meets three times per year, and the work of the Methods, Products, and Topics Subcommittees continues between meetings by teleconference.

Evidence Reports

Through an Interagency Agreement between CDC and the Agency for Healthcare Research and Quality (AHRQ), three evidence reviews will be completed by AHRQ

Evidence-based Practice Centers (EPCs) in 2006; two more EPC-based evidence reviews are being initiated, to be completed in 2007. Other models for evidence review are also being utilized to investigate the feasibility and quality of more targeted reviews completed on a shorter timeline.

EGAPP Products

Primary products of the EGAPP initiative will include evidence reports on specific tests; published summaries of the evidence reports; and published recommendations of the EGAPP Working Group based on the evidence reports. Secondary products will consist of shorter and less technical multi-media informational messages developed for specific target audiences from the evidence reports and Working Group recommendations. Methods for dissemination of the information developed will include Web postings and distribution through professional organizations, health plans/payers, and public health programs.

Evaluation Plan

Evaluation of the success of the EGAPP initiative in raising awareness about the process and addressing the need of key stakeholder groups for information about new genetic tests is critical to understand how to move forward with a sustainable EGAPP-like process, and to determine its potential impact on the integration of genomics into public health and health care. In collaboration with a contracted evaluation consultant, a plan has been developed to survey key stakeholder groups about their awareness of EGAPP and their perception of the utility of EGAPP products (e.g., evidence reviews, published summaries, Working Group recommendations, informational messages), and to identify changes in clinical practice or coverage/reimbursement that might result.

Collaboration between EGAPP and the Centers for Genomics and Public Health

To maximize the impact of these products, the CDC-sponsored University of Michigan and University of Washington Centers for Genomics and Public Health (CGPH) are collaborating with this project to engage stakeholders and to develop strategies for translating and disseminating informational messages based on evidence reports and EGAPP Working Group recommendations. The University of Washington CGPH has developed Web pages that provide background information on genetic testing and the process of evidence review. The Michigan CGPH developed the *Stakeholder Advisory Group for EGAPP* (SAGE), with feedback going directly to the EGAPP Working Group through the Products Subcommittee.

Moving Toward a Sustainable Process

By the end of 2006, the EGAPP Steering Committee and the EGAPP Working Group will begin to consider the products and knowledge gained by the project, in order to provide recommendations regarding the design and support of a sustainable EGAPP-like assessment process.

Major Accomplishments Related to EGAPP

1. EGAPP Working Group meetings and subcommittee teleconferences well attended and productive with many activities underway or completed.

2. Completed evidence reports on three applications of genomic technology:
    - *Testing for Cytochrome P450 Polymorphisms in Adults with Depression Treated with Selective Serotonin Reuptake Inhibitors (SSRIs)*
    - *Testing for Hereditary Nonpolyposis Colorectal Cancer in Newly Diagnosed Colorectal Cancer Patients and Their Families*
    - *UGT1A1 Testing for Patients with Colorectal Cancer Treated with Irinotecan*
3. Completed fourth evidence report on *Genomic Tests for Ovarian Cancer Detection and Management* through collaboration between CDC's Division of Cancer Prevention and Control and the EGAPP Project.
4. Completed development of recommendations based on two of the four completed evidence reports, with finalization of recommendations based on the two pending reports.
5. Comprehensive plan to obtain feedback from stakeholders completed, received IRB exemption, has been posted for comment in the Federal Register and is pending OMB review and approval.
6. Approval pending from HHS for a waiver request for an independent web site for the EGAPP Working Group products - **egappreviews.org**.
7. Three additional topics selected for review:
    - *Impact of Gene Expression Profiling Tests on Breast Cancer Outcomes*
    - *Use of Genomic Profiling to Assess Risk for Cardiovascular Disease and Identify Individualized Prevention Strategies*
    - *Screening for CYP450 Polymorphisms to Predict Response to Pain Management with Codeine*
8. University of Michigan Center for Genomics and Public Health initiated *Stakeholder Advisory Group for EGAPP* (SAGE).

State Examples Related To Goals and Priorities

In collaboration with the Association of Schools of Public Health, CDC established the first Centers for Genomics and Public Health at the Universities of Michigan, North Carolina and Washington in 2001. These Centers became hubs of expertise that built on and complemented existing university programs and created links with state and local health departments. In collaboration with CDC, these centers completed two web-based training programs for public health professionals:

- *Genomics for Public Health Practitioners*, describes the application of genomics to public health, dispels myths about genomics and identifies challenges in public health genomics.
- *Six Weeks to Genomic Awareness* was a series of six presentations aimed at helping public health professionals understand how genomic advances are relevant to their work.

In 2005, the Universities of Michigan and Washington were awarded funding to continue their work in public health genomics. Current objectives are to facilitate the integration of genomics by:

- Providing technical assistance and competency-based training.
- Collaborating with CDC projects such as the *Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Project* and the *Family History Public Health Initiative.*
- Disseminating credible and impartial information.
- Collaborating with public health agencies and other external partners.

In July 2003, CDC established cooperative agreements with the state health departments in Michigan, Minnesota, Oregon, and Utah to assist in developing and expanding their capacity to integrate genomic tools (e.g., family history assessments) and knowledge into state public health programs for improved health outcomes. These states are demonstrating that genomics can be successfully integrated into programs by:

- Establishing infrastructure and collaborations within their state health departments.
- Developing partnerships with CDC, Centers for Genomic and Public Health, and other states and partners.
- Educating the public health workforce.
- Assessing the integration of genomics into population-based surveillance, for example by adding genetic questions to Behavior Risk Factor Surveillance System (BRFSS) surveys.
- Promoting family history as a screening tool to identify high risk populations and target prevention messages and collaborating with CDC's Well Integrated Screening and Evaluation for Women Across the Nation (WISEWOMAN) project.

Assess the Role of Family History in Risk Assessment and Disease Prevention

Public Health Problem

Family health history reflects both shared genetic susceptibility and exposure to common environmental, behavioral, and cultural factors that may contribute to diseases, such as diabetes and heart disease. This information can be used to identify individuals who are

at increased risk for these diseases. Such individuals can then be targeted for preventive measures, such as health screening and behavior change strategies.

Family health history is often underutilized in preventive medicine, or it is used ineffectively. Certain types of family history information (e.g., relationship of affected family member, type of disease, age of diagnosis, and number of affected family members and their lineage) should be collected to accurately assess risk. This information should be collected, recorded, and updated in patient charts in a way that is accessible to physicians. However, this information is often not documented at all, or only partial information is documented in the patient charts.

Program Example (Michigan and Utah)

In 2005, NOPHG-funded genomics programs in Michigan and Utah departments of health conducted medical chart reviews within clinics in their respective states. The purpose of these reviews was to identify whether family health history was being recorded and updated in patients' charts, and to examine the types of information recorded, by whom, and through what means.

- The Michigan genomics program collaborated with the Michigan Cancer Registry to conduct medical chart reviews in 23 clinics randomly selected throughout Michigan. In all, 853 charts from December 2003 to October 2004 were systematically reviewed for the presence or absence of documented information on family history of cancer. The reviews revealed that about 83% of charts included family history information. Of these charts, 89% included the gender of the affected family member, and 82% included the tumor-site of the family members' cancer diagnosis. However, 94% did not have information on the family members' ages at diagnosis.

- The Utah genomics program contracted with the University of Utah School of Medicine to conduct medical chart reviews in 12 family practice clinics randomly selected from four counties in Utah. In all, about 400 charts from July to September 2005 were systematically reviewed. Documentation of family history of chronic health conditions was found in 60% of charts reviewed. This information was documented most often using a questionnaire format (39%), or in physicians' notes (34%). Of those charts with family history, 64% included the family relationship for each chronic condition reported, 17% included family relationship for some conditions, and 18% did not include this information. Of the charts with family relationship, 8% included the age of onset for all conditions reported, and 18% included this information for some of the conditions reported.

Results and Impacts to Date

The chart reviews conducted by the Michigan and Utah genomics programs showed that, although many charts documented family history, important types of information were lacking, such as family relationship and age of onset for reported chronic health conditions. This information is critical for assessing hereditary risk. Also, the charts did not have a standardized approach for recording and updating the family history information, nor was there a standard list of diseases for which this information should be documented.

Key impacts of these chart reviews include:

- The Michigan genomics program is working with the Michigan Cancer Registry to improve the documentation and use of family history information by physicians, and to increase awareness among patients. Key activities are inclusion of a mandatory family health history question in the Michigan Cancer Registry in 2007, educating physicians on recommended practices, and encouraging patients to routinely collect and record their family history information and share this information with their physicians.

  The success of this project prompted the Michigan genomics program to work with an insurance plan, HealthPlus of Michigan, to conduct a second chart review in 2005, this time on chronic health conditions. In all, 250 charts from 50 physicians were reviewed, and showed similar findings on the presence or absence of family history information. Another chart review is planned for 2006, using a revised data collection tool which has been expanded to include questions about physician referrals for genetic services, use of folic acid, and birth defects.

- The Utah genomics program, in collaboration with the University of Utah School of Medicine, has developed a set of recommendations for family physicians to collect and document family history. These recommendations aim to standardize this process by providing a list of chronic health conditions for which family history information should be documented, and by describing specific information to be collected using suggested approaches or tools.

  The Utah genomics program is working with the American Academy of Family Physicians, Utah chapter, to raise awareness of the chart review results and recommendations (mentioned above) among the academy's membership. In 2005, the Utah Genomics Program published articles in the membership newsletter, and collaborated on genomics activities (e.g., workshop).

Future Directions

Integrating Genomics into Public Health Investigations: CDC Influenza Public Health Genomics Initiative

The CDC Influenza Public Health Genomics Initiative is a model project to demonstrate integration of human genomics into public health investigations.

With the ongoing threat of seasonal influenza and the potential emergence of new, more virulent strains of influenza, CDC and its partners are developing an initiative to investigate the role of population genetic variation in the epidemiology of influenza morbidity and mortality and the effectiveness of public health interventions (e.g., vaccination).

Project Goal
Improve influenza preparedness by advancing studies of human genetic variation in relation to influenza infection.

Anticipated Products and Public Health Impact
1. Protocols for acquiring DNA and other biologic samples in the epidemic setting, including appropriate methods for obtaining informed consent and for sample transport, preparation and storage. An "off-the-shelf" protocol will be available for immediate use in epidemic settings.
2. NOPHG has contracted with America's Health Insurance Plans (AHIP) to develop a multi-site DNA bank from patients within group health plans that can be used to study the role of genetic factors in influenza disease severity and vaccine effectiveness and side effects response to therapy.
3. NOPHG will host a workshop January 11-12, 2007 to develop priorities for public health genomics research in influenza, focusing on the epidemic and managed care settings.

Beyond Gene Discovery (BGD) Initiative: Developing a National Genomic Profile for the U.S. Population

In collaboration with public, private and academic partners, CDC will assess population genetic variation in the U.S. in relation to health and disease and develop strategies for using genetic information to impact health and eliminate disparities among population groups. The NHANES provides the unique national resource for investigating the effects of genetic variation on health and will serve as the initial focus of BGD. Genetic samples are available for nationally representative probability samples of approximately 15,000 persons enrolled in two NHANES. The survey oversamples the two largest race/ethnic minority groups, non-Hispanic blacks and Mexican Americans, along with other subgroups of the population. Information on multiple aspects of health obtained through interview, laboratory tests and direct examinations is also available for the NHANES participants. BGD marks the first large-scale effort in the U.S. to coordinate the comprehensive identification of the associations among variations in genotype, phenotype, and risk factors in a representative sample of the population, laying the groundwork for understanding the relation between human genome variation and health status.

BGD will offer an opportunity for an unprecedented look at interactions among numerous genetic variants, environmental exposures and behavioral factors contained in the clinical, biochemical, and metabolic profiles of a large number of people of all ages. This research will enhance the value of many ongoing gene discovery studies, helping to translate findings into new targets for prevention, diagnosis, and treatment of common diseases. By measuring the population prevalence of key genetic variants, BGD will provide the basis for estimating the numbers of people who may benefit from particular genotype-based screening or diagnostic tests, drugs, or other preventive or therapeutic interventions. BGD represents the whole U.S. population, including minority racial/ethnic groups. By taking an inclusive, evidence-based approach to personalized medicine, BGD can help address disparities with data instead of oversimplification.

Applying Genomic Applications to Population Health

A new team is being formed in NOPGH to develop and evaluate genomic applications that use clinical and genomic information such as familial risk assessment, signs and symptoms recognition, and genetic testing to promote the prevention and early detection of both traditional genetic disorders and common chronic diseases. For many years, integration of genomic applications into clinical practice has been focused on genetic testing for individually rare single gene disorders. More recently, we are seeing the introduction of genomic applications for common chronic diseases such as using genetic markers in early identification of cancer or targeting therapies based on genotype that optimize response and avoid adverse drug reactions. With the completion of the human genome sequence, we can expect in the coming years the increasingly rapid development of new genetic tests – including concurrent testing of multiple genetic markers using microarray technologies (i.e., multiplex testing) – that will be used to help refine diagnoses, improve risk prediction, and target therapies for both traditional genetic disorders as well as common chronic diseases. In the meantime, there are already genomic applications being used to some extent in clinical medicine which could be applied at the population level to assess disease risk, influence early disease detection, and provide guidance for disease prevention or management. These applications, including familial risk assessment, signs and symptoms recognition, and genetic testing, when used as public health strategies, could lead to overall population health benefits.

Family history is an important tool for identifying individuals and families with genetic susceptibility to common chronic diseases such as coronary heart disease, stroke, diabetes and most cancers, as well as the rare single gene disorders like cystic fibrosis, sickle cell anemia, hereditary forms of breast and colorectal cancer, and hemochromatosis. As an integral part of primary care and preventive medicine, familial risk assessment has the potential to identify individuals at risk of disease, those with subclinical disease, and those who may already be affected but are undiagnosed.

There are many single gene disorders across the life span that could benefit from early disease detection and interventions through a closer partnership between medicine and public health. Many affected persons with genetic diseases such as hereditary hemochromatosis (HH), familial hypercholesterolemia (FH), and primary immune deficiency disorders, for example, are either missed by the healthcare system or not diagnosed early enough for effective and appropriate interventions to work. Thus valuable opportunities for disease and disability prevention are lost. A public health approach employing public and provider education about symptom recognition, surveillance strategies, screening, and referral to appropriate services, could be used to enhance existing health care practice leading to earlier diagnosis of these disorders.

While efforts are underway to examine the validity and utility of genetic tests that are being transitioned from research to clinical and public health practice, there is little being done to examine the uptake of specific tests and the outcomes of genetic testing services. There is a need for genetic testing surveillance and applied research in primary care to monitor the integration and penetration of genetic testing into the healthcare delivery system. Genetic tests for more than 1,200 diseases have been developed, with more than 1,000 currently available for clinical testing. Most are used for diagnosis of rare genetic diseases, but a growing number have population-based applications, including carrier identification, predictive testing for inherited risk for common diseases, and pharmacogenetic testing for variation in drug response. These tests and other anticipated applications of genomic technologies for screening and prevention have the potential for broad public health impact.

The NOPHG team will work with CDC collaborators and external partners to identify the genomic applications and diseases that are ready and most appropriate for a public health approach. Activities for the team might include:

- Developing an internal CDC working group to define the scope and the plan for the team's activities.
- Seeking appropriate partnerships and input from outside CDC.
- Assembling background information on diseases that could potentially benefit from genomic applications, including familial risk assessment, signs and symptoms recognition, and genetic testing.
- Identifying gaps in knowledge and research needs for implementing these genomic applications in clinical practice and public health.
- Developing a research and evaluation agenda and sponsoring demonstration projects that can show the population health benefits of genomic applications.
- Establishing a network of research centers that might include academia, states, professional organizations, and other agencies.

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