10 years of

Public Health Genomics at CDC 1997-2007

National Office of Public Health Genomics

Centers for Disease Control and Prevention

December 2007

Produced by the National Office of Public Health Genomics in the Coordinating Center for Health Promotion at the Centers for Disease Control and Prevention (CDC).

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Abbreviations and Acronyms

ATSDR	Agency for Toxic Substances and Disease Registry
BRFSS	Behavioral Risk Factor Surveillance System
BGD	Beyond Gene Discovery
CIO	Center, Institute, or Office
CDC	Centers for Disease Control and Prevention
CGPH	Center for Genomics and Public Health
CoCHP	Coordinating Center for Health Promotion
DHHS	Department of Health and Human Services
ELSI	Ethical, Legal, and Social Issues
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
HuGE	Human Genome Epidemiology
HuGENet™	Human Genome Epidemiology Network
MMWR	Morbidity and Mortality Weekly Report
NCI	National Cancer Institute
NCBDDD	National Center for Birth Defects and Development Disabilities
NCCDPHP	National Center for Chronic Disease Prevention and Health Promotion
NCEH	National Center for Environmental Health
NCHS	National Center for Health Statistics
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCHPEG	National Coalition for Health Professional Education in Genetics
NHIS	National Health Interview Survey
NHANES	National Health and Nutrition Examination Survey
NHGRI	National Human Genome Research Institute
NIOSH	National Institute of Occupational Safety and Health
NIH	National Institutes of Health
NOPHG	National Office of Public Health Genomics
PHI	Public Health Investigations
RFA	Request For Applications
SAGE	Stakeholders' Advisory Group on EGAPP
WISEWOMAN	Well–Integrated Screening and Evaluation for Women Across the Nation

1.0 Public Health Genomics at CDC: 1997-2007

Public Health Genomics

The news media report on advances in genomics research with increasing frequency, contributing to raised expectations that human genomics and related fields will lead to enhanced personalized health care and disease prevention. In contrast, the translation of these advances into interventions to improve health and prevent disease has been slow, resulting in relatively few genomics discoveries that have led to evidence-based applications for health practice. Public health research, including population studies in epidemiology, policy and communication sciences, and health services research, is needed to translate promising genomic discoveries into individual and public health interventions.

Public health genomics is a multidisciplinary field concerned with 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.

Through the National Office of Public Health Genomics (NOPHG), CDC provides national and international leadership in public health genomics, while building partnerships with other federal agencies, public health organizations, professional groups, and the private sector.

History of Public Health Genomics at CDC

In 1997, CDC established the Office of Genetics and Disease Prevention following the recommendations of an agency-wide, ad hoc Task Force on Genetics and Disease Prevention. The Task Force was appointed by then-CDC director Dr. David Satcher, to propose a strategic plan through which the agency might coordinate and strengthen its activities in genetics and public health. Since its formation, the Office of Genetics and Disease Prevention has been renamed twice—first in 2003, the year marking

National Office of Public Health Genomics
Major Initiatives, Projects, and Events At A Glance

1997:
- CDC published a Strategic Plan on Genetics and Public Health
- CDC established the Office of Genetics and Disease Prevention

1998:
- 1st National Conference on Genetics and Public Health was held in Atlanta
- HuGENet™ was established

1999:
- 1st extramural grants: prevention research

2001:
- 1st Centers for Genomics and Public Health were established
- ACCE Project was initiated
- Genomic Competencies for the Public Health Workforce developed

2002:
- NHANES III Collaborative Genomics Project was started
- Family History Public Health Initiative launched

2003:
- ACCE framework was published
- Four state health departments were funded to build genomics capacity

2004:
- EGAPP project was initiated
- NOPHG and CSTE organized a workshop on the role of genomics in public health investigations

2005:
- International Biobank and Cohort Studies meeting

2006:
- OGDP renamed National Office of Public Health Genomics
- CDC Public Health Genomics Collaboration (PHGC) was established
- NOPHG provided intramural seed funding for eleven CDC projects
- NOPHG and NCIRD established the CDC Influenza Public Health Genomics Initiative

2007:
- NOPHG hosted 2nd CDC PHGC meeting
- NOPHG provided intramural seed funding for nine CDC projects

2008:
- NOPHG will celebrate its 10th year anniversary

the completion of the Human Genome Project, as the Office of Genomics and Disease Prevention, and then again in 2006, as the National Office of Public Health Genomics (NOPHG), in recognition of its national scope and public health focus. The office has had several locations within CDC's organizational structure, moving from the National Center for Environmental Health (NCEH) to the CDC Office of the Director (OD) before arriving at its current home, the National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) in the Coordinating Center for Health Promotion (CoCHP).

NOPHG Vision, Mission, and Goals

The vision, mission, and goals of NOPHG have evolved over time in response to ongoing input from internal and external CDC partners, lessons learned from NOPHG projects, priorities of CDC agency-wide initiatives including the Goals process and the Futures Initiative, and the changing identity and location of the office within the CDC organizational structure. The central tenet upon which the vision, mission, and goals are based is the role of public health in translating human genome discoveries into population health benefits.

Although fundamental to many CDC programs, legislation has not been the primary influence in directing specific NOPHG activities. Instead, priorities are continually shaped by NOPHG leadership, input from internal and external CDC partners, the roles of other government agencies and the private sector, availability of funding, and the state of the science. NOPHG's research and program portfolios are dedicated to closing the gap between genome discoveries and public health impact.

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: to improve public health interventions through population-based genomic research, assessment of the role of family history in determining risk and for disease prevention, and the evaluation of genetic tests.

NOPHG Major Projects 1997-2007

The major NOPHG projects are briefly summarized below, with their location along the continuum from gene discovery to public health impact illustrated in the figure on the following page. More detail on each initiative is provided in Section 2.0.

NHANES III Collaborative Genomics Collaborative Project:
Measuring population variation in selected genes of public health significance

In February 2002, NOPHG formed a multidisciplinary working group with members from across CDC to develop a proposal to measure the prevalence of selected genetic variants of public health significance in a representative sample of the U.S. population. NOPHG is coordinating a CDC/NCI collaboration to determine the prevalence of 90 genetic variants in the Third National Health and Nutrition Examination Survey (NHANES III) sample, and to conduct additional analyses to examine the associations between the selected genetic variants and disease outcomes available in NHANES III data.

Public Health Investigations:
Integrating genomics into public health investigations and surveys

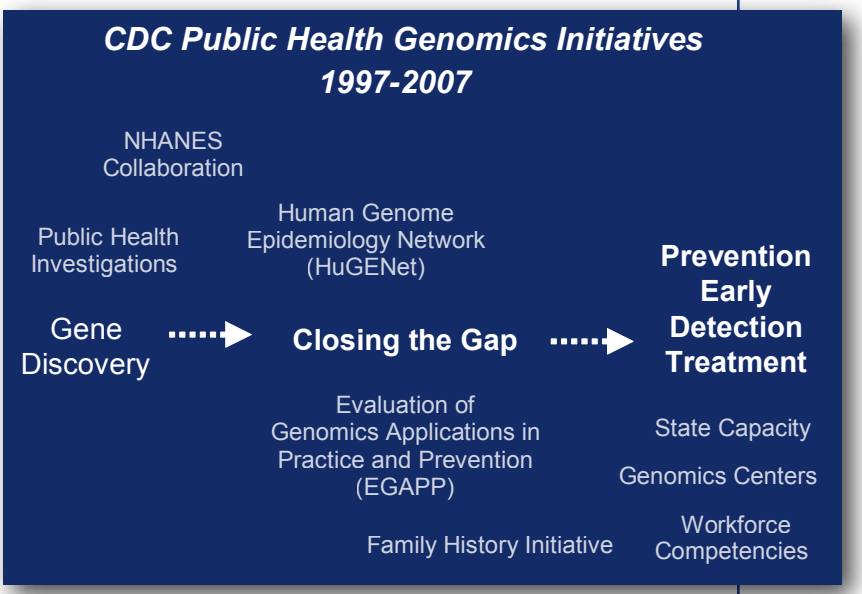
In 2004, NOPHG and the Council of State and Territorial Epidemiologists (CSTE) held a workshop to discuss incorporating human genetics into public health investigations.

In 2006, NOPHG provided seed funding for 11 innovative CDC projects that integrate genomics into public heath research and programs, including projects focused on infectious disease, chronic disease, birth defects, pharmacogenomics, and environmental exposures. Nine of these projects were funded in 2007 for a second year, with completion anticipated in April 2008.

In 2006, NOPHG and the National Center for Influenza and Respiratory Diseases (NCIRD) developed a pilot CDC Influenza Public Health Genomics Initiative to investigate the role of population genetic variation in the epidemiology of influenza morbidity and mortality and the effectiveness of public health interventions.

Human Genome Epidemiology Network (HuGENet™):
Developing a knowledge base on genomics and population health

In 1998, NOPHG established the Human Genome Epidemiology Network (HuGENet™), a global collaboration for assessing the role of human genome variation in population health. HuGENet™ promotes the publication of systematic reviews of population-based data on gene-disease associations and gene-environment interactions. A multi-authored book, Human Genome Epidemiology, was published in 2004 and a second edition is currently under development. In 2006, HuGENet™ published the first edition of an online handbook for systematic reviews, which are peer reviewed and published in partnership with ten scientific journals.



Evaluation of Genomic Applications in Practice and Prevention (EGAPP):
Developing methods for evaluating genetic tests in transition from research to practice

In 2004, CDC launched the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) project, a national collaborative initiative to develop a coordinated process to synthesize available data on the validity and utility of specific genetic tests and identify gaps in knowledge as well as the studies needed to resolve them. Three evidence reports commissioned by the NOPHG-supported, independent, non-federal, multidisciplinary EGAPP Working Group, have been released by AHRQ Evidence-based Practice Centers in the past nine months, and more evidence reports are in progress. The EGAPP Working Group released its first recommendation statement in December 2007.

Family History Public Health Initiative:
Developing and evaluating family history tools for disease prevention and health promotion

CDC is collaborating with federal agencies, academia, and state health departments on the Family History Public Health Initiative to evaluate how family history information can be used effectively to assess risk for common diseases and influence early detection and prevention strategies. In 2005, CDC completed the development of a web-based tool, Family Healthware™, which collects information about health behaviors, screening tests, and personal family histories for six diseases. CDC funded three research centers to conduct a clinical trial to evaluate the clinical utility of this tool.

Centers for Genomics and Public Health:
Establishing regional hubs of expertise in genomics and public health in the United States

NOPHG funds Centers for Genomics and Public Health at schools of public health at the University of Michigan and the University of Washington. These centers provide expertise in genomics and public health with a focus on translating genomic information into useable public health knowledge, providing technical assistance to state and community public health agencies, and integrating genomics into programs and practice.

State Genomics Programs
Integrating genomics into chronic disease prevention programs in state health departments

NOPHG funds genomics programs in four state health departments, Michigan, Minnesota, Oregon, and Utah, to integrate genomics knowledge, tools (e.g., family history assessments), and surveillance findings into the strategies and activities of chronic disease prevention programs.

Partnerships

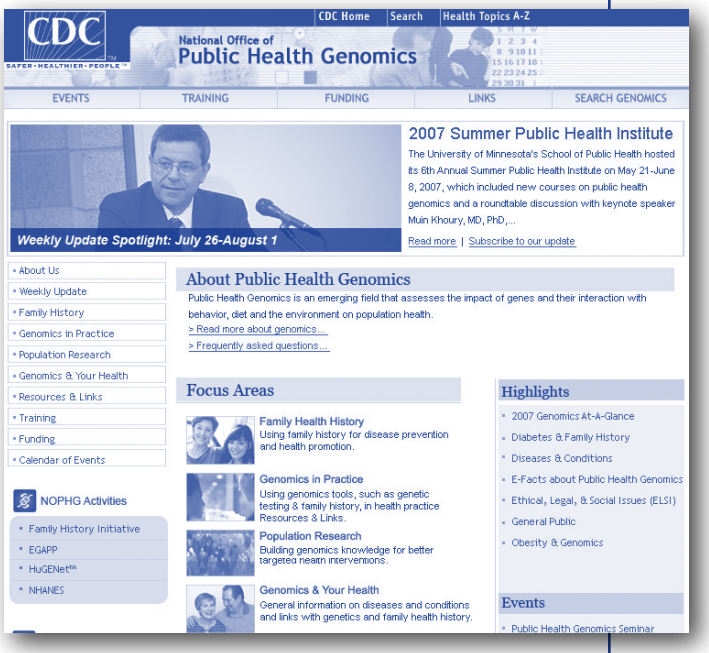
Through its various initiatives, NOPHG has developed a large array of partnerships with other federal agencies, particularly NHGRI, NCI, and institutes of NIH, state public health organizations, academia, health care organizations, patient advocacy groups, and the private sector. In addition, NOPHG has spearheaded global collaborations in human genome epidemiology, genetic testing, and public health genomics by engaging with researchers and policy makers worldwide. (See HuGENet™ and EGAPP in section 2.0) NOPHG has helped lead the development of an international public health genomics network called Genome-based Research Population Health International Network (GRAPHInt).

In 2006, NOPHG facilitated the establishment of the CDC Public Health Genomics Collaboration (PHGC) in response to the high level of interest in genomics at CDC. The PHGC is a network of CDC professionals working in or interested in public health genomics. The goals are to provide a forum for the ongoing exchange of ideas, research, and information; to determine points of synergy for improving health by using genomics; and

to integrate public health genomics into research, policy, and programs across CDC. The PHGC coordinates stimulating and informative meetings throughout the year, highlighting relevant topics in public health genomics and facilitating discussions of cutting edge research, methodology, and technology. To date, hundreds of CDC employees across every Center, Institute or Office (CIO) have participated in PHGC activities.

Communications

NOPHG's communication strategy targets a broad range CDC audiences and external audiences, including health care providers, public health practitioners, genetic and genomic researchers and practitioners, health care payers/purchasers, policy makers, and the general public. The communication strategy aims to encourage the integration of genomics into research, policy, and practice by developing and disseminating credible resources in public health genomics. Principal activities and products include: the NOPHG website which has more than 2,000 main pages of genomics information and resources and approximately 4,000 pages of presentations and interactive materials; a weekly online publication called *Genomics & Health Weekly Update*, which reaches more than 4,000 subscribers worldwide; NOPHG conferences, meetings, workshops, and seminars; media interviews; presentations and exhibit booths at public health events; publications; campaigns; and a public inquiry mailbox.



NOPHG's website is at the top of search results in Google, Altavista, AOL, DHHS, and other search engines for the terms public health genomics or genomics and disease prevention. The website receives more than 100,000 visits per year.

Increased interest in genetics and genomics by the news media has led to NOPHG interviews with numerous newspapers, magazines, and other publications that are widely disseminated to various audiences nationally and internationally. Since January 2007, NOPHG has interviewed with the *Wall Street Journal, Atlanta Journal Constitution, Sun Sentinel, AAPA News, Men's Health*, and other publications on topics such as genetic testing, family history, and personalized medicine.

NOPHG has organized approximately 100 conferences, workshops, meetings, and seminars, involving partners from across CDC and collaborators for NOPHG initiatives. NOPHG participates and exhibits at annual health promotion events, such as the American Public Health Association conference and the DHHS/CDC Disease Prevention and Health Promotion conferences. In January 2008, NOPHG will host a meeting to celebrate its 10th anniversary of public health genomics at CDC, inviting experts to present on genomics and population research, human genome epidemiology, genetic testing, family history, and public health practice.

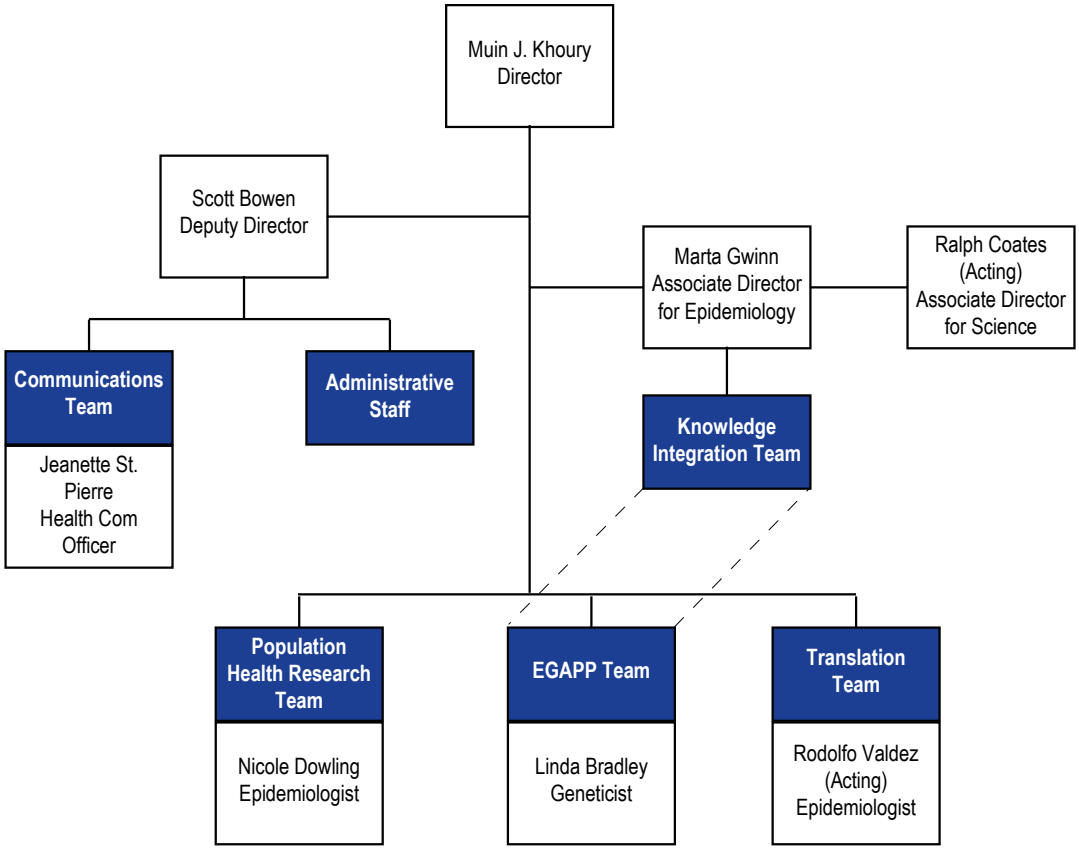
NOPHG Organizational Structure and Personnel

The director and deputy director provide strategic leadership for NOPHG with support and input from the associate director for epidemiology, and the associate director for science, and the other senior staff. Day-to-day operations are supported by management and operations staff.

NOPHG has dedicated teams to support the major initiatives and the communications functions. These teams include: the Knowledge Integration Team; the Population Health Research Team; the EGAPP Team; the Prevention and Translation Research Team; and the Communications Team. Each team has a designated lead staff member and support staff. The organizational structure is depicted in the figure and includes personnel who possess a wide array of professional disciplines and skills.

Currently, NOPHG supports a total of 45 staff, which includes 18 federal full-time employees. Since 1997, NOPHG staff has grown considerably but the office remains a relatively small cross-cutting entity in terms of absolute personnel resources.

National Office of Public Health Genomics



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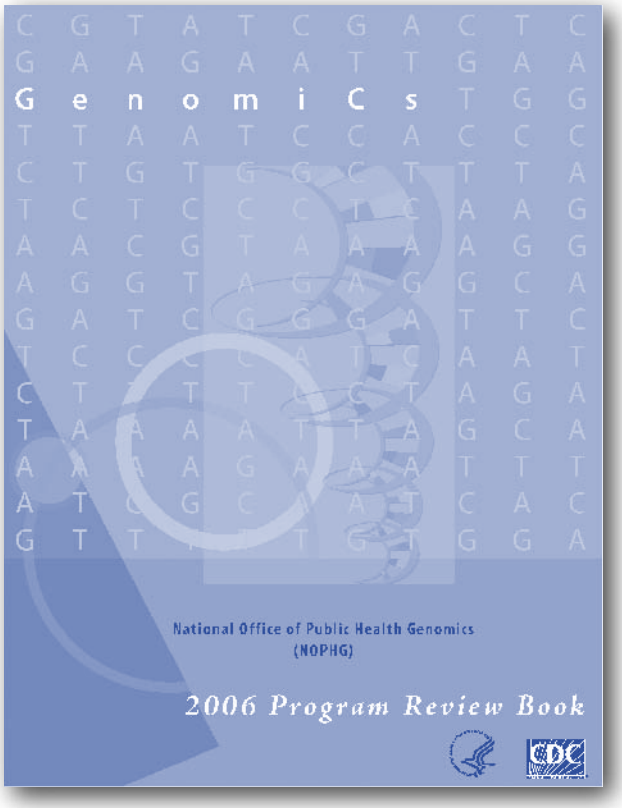
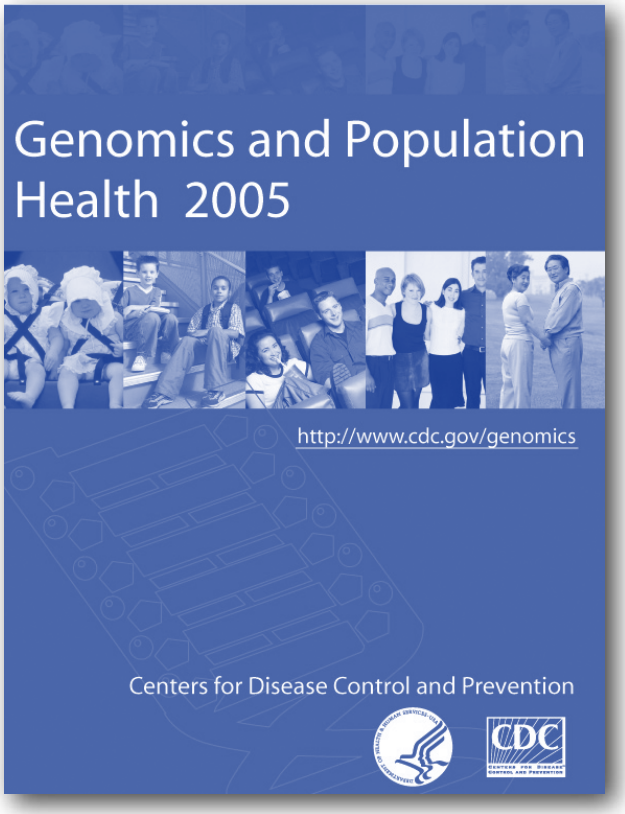
2.0 Projects of the National Office of Public Health Genomics

The following section highlights six major NOPHG projects that support the goals of the office. These initiatives are:

- NHANES III Collaborative Genomics Project
- Public health genomics investigations
- Human Genome Epidemiology Network (HuGENet™)
- Evaluation of Genomic Application in Practice and Prevention (EGAPP)
- Family History Initiative
- Public health genomics capacity building

Summaries are provided for each of these projects, which include the rationale, overview, structure, resources, key accomplishments, current activities, next steps, and a list of selected publications of the project. Supporting materials and copies of some of the selected publications are included as annexes.





NHANES III Collaborative Genomics Project

Most human disease results from the interactions between inherited genetic variations and environmental risk factors such as lifestyle, social conditions, chemical exposures, and infections. Collecting and analyzing human genomic data in public health research has the potential to enhance our ability to understand individual variation in disease susceptibility and outcomes, to determine the contribution of genetic and environmental factors to human health, and to refine public health interventions such as vaccination, exposure reduction, and health promotion.

Although there has been a rapid increase in the number of published investigations of gene-disease associations, there are a number of methodological shortcomings that make it difficult to integrate the evidence and thereby assess its value for public health. Recent reviews of the existing body of work have underscored that many significant associations have not been replicated. In view of the universal appreciation of the importance of identifying the genetic contribution to complex disease and gene-environment interactions, researchers have called for studies in larger, well-designed, population-based settings.

Determination of the prevalence of genetic polymorphisms of public health importance in the U.S. population, and in subgroups of the population, is a critical first step in evaluating the genetic epidemiology of complex diseases. Such data would be an invaluable resource for: 1) investigations into U.S. population structure; 2) calculations of population attributable fraction(s) of the U.S. burden of disease associated with genetic variation and gene-environment interaction; and 3) assessment of the potential for screening population subgroups for genes that confer susceptibility to disease. In addition, population-based allele and genotype prevalence data would also serve as a reference for researchers to use in designing future association studies.

However, many studies were based on convenience samples; and often, little information was provided about the selection of study subjects. In addition, many studies included small sample sizes. Consequently, the precision of previous estimates of allele frequency or genotype prevalence has been limited. More specifically, few studies of U.S. populations have determined allele and genotype frequencies for all major racial and ethnic groups or have evaluated frequencies by age group and by sex.

The Third National Health and Nutrition Examination Survey (NHANES III) provides a unique resource for examining the prevalence of genetic variants in the U.S. population and the interactions and correlates of these variants. NHANES is a survey conducted by CDC's National Center for Health Statistics (NCHS) that is designed to provide national estimates of the health and nutritional status of the civilian, non-institutionalized population in the U.S. aged two months and older. It includes thousands of data points on survey participants, including demographic, health history and health behavior characteristics; physical and radiological measurements; and detailed nutritional and biochemical analyses. During the second phase of NHANES III (1991-1994), white blood cells were frozen and cell lines immortalized with Epstein-Barr Virus (EBV), creating a DNA bank. The bank contains specimens from more than 7,000 survey participants aged 12 years and older. It is jointly maintained by both NCHS and the National Center for Environmental Health (NCEH) at CDC.

Further work using NHANES III genetic data includes: a) investigating population substructure in the U.S.; b) investigating the relation between selected genetic variants and phenotypic data collected in NHANES III to generate data on the functional significance of these variants; c) assessing the prevalence of combinations of genetic variants at different loci that may increase the risk for specific diseases, and the relations of these combinations with the phenotypic markers; and d) using the exposure data collected in NHANES III to test the assumption of independence of distribution of genotype and exposure that is the basis of the validity of case-only studies of gene-environment interactions.

NHANES III DNA Bank Analyses

In February 2002, NOPHG formed a multidisciplinary working group with members from across CDC to develop a prototype for a national report on genomics and public health. One of the main goals of the working group was to develop a proposal to measure the prevalence of selected genetic variants of public health significance and publish the findings. In November 2002, the working group submitted a research proposal to NCHS entitled "Prevalence of Genotypes of Public Health Importance in the United States" to use data derived from the NHANES III DNA Bank. The purpose of the study was to determine the prevalence of 87 genetic variants in 57 genes known to be important in at least six major pathways: 1) nutrient metabolism, 2) immune and inflammatory responses, 3) xenobiotic metabolism, 4) DNA repair, 5) hemostasis and renin/angiotensin pathways, and 6) developmental pathways. Future analyses would examine the associations between the selected genetic variants and disease outcomes available in NHANES III data.

The genetic variants of public health significance were defined according to one or more of the following criteria: a) known or hypothesized association with diseases and/or exposures of public health significance (defined by morbidity, mortality, prevalence, and availability of effective interventions), b) role in pathway(s) affecting multiple diseases of public health significance, c) with identified functional variants, d) availability of some evidence that allele frequency or genotype prevalence is not rare (i.e., > 2.0%), e) with reported strength of association(s) with diseases of public health significance, f) relevant to common diseases with evidence of gene-environment or gene-gene interactions; and, g) with phenotypic data available in NHANES III for future analysis to characterize the impact of these variants.

In 2003, the CDC Working Group researched genotyping labs and selected the National Cancer Institute's (NCI) Core Genotyping Facility based on their overall technical capacity and ability to work with the NHANES III samples, which are of low DNA concentration. Work was also completed to further define study methodology.

In 2004, NCI's Core Genotyping Facility began genotyping the NHANES III samples and developing genotyping assays as needed. The NCI lab also agreed to genotype additional variants they had available in genes for which we had received IRB approval. Genotyping at NCI (all single nucleotide polymorphisms, SNPs) continued through 2005 and 2006. In 2006 and 2007, genotyping of an additional panel of variants, including repeats and insertion/deletions, was conducted by the Division of Laboratory Services of the National Center for Environmental Health (NCEH). As of July 2007, the total number of polymorphisms successfully genotyped and that have passed quality control measures is 90 variants in 50 genes.

NHANES III Collaborative Genomics Project At A Glance

2002:
- CDC formed a Working Group to develop a prototype for a national report on genomics and public health, and a proposal to measure the prevalence of selected genetic variants of public health significance
- NCHS announced a call for research proposals using data from the NHANES III DNA Bank
- CDC Working Group submitted a research proposal to NCHS to determine the prevalence of 87 genetic variants in 57 genes with a known or proposed role in diseases of public health importance

2003:
- CDC evaluated options for genotyping labs and selected NCI's Core Genotyping Facility
- CDC further developed study methodology

2004:
- CDC/NCI proposal was approved by the NCHS Institutional Review Board
- NCI lab began genotyping and developing necessary genotyping assays

2005:
- CDC/NCI Working Group investigators submitted individual research proposals to NOPHG to use NHANES III genetic data in genotype-phenotype association analyses

2006:
- NOPHG developed six large, collaborative genotype-phenotype research proposals based on disease outcomes to submit to NCHS, and began working with investigators to develop their analytic models
- Analysts developed statistical methods for genetic data analyses in a complex survey design and began analyses of preliminary data

2007:
- NCI and CDC laboratories completed final genotyping - 90 variants in 50 genes passed quality control
- Analysts continue work on genotype-phenotype analyses

While the genotyping was underway, investigators from the CDC/NCI Working Group developed and submitted to NOPHG individual research proposals to examine associations between their genetic variants of interest and numerous phenotypic data available in the NHANES III public-use datasets. NOPHG received approximately 35 mini-proposals outlining numerous analyses to investigate genotype-phenotype correlations with multiple health outcomes such as asthma, diabetes, obesity, cardiovascular disease, reproductive health, osteoporosis, cancer, lead toxicity, and selected infectious diseases. NOPHG staff performed literature reviews and condensed the mini-proposals into six large collaborative research proposals, which were submitted to NCHS between March 2006 and February 2007 for Technical Panel and/or Institutional Review Board (IRB) approval.

In addition, the complex survey design of NHANES III presents difficulties for data analysis. To date, there have been no published statistical methods for analyzing genetic data for a study of this design. NOPHG statisticians and analysts have developed a method for weighted Hardy-Weinberg Equilibrium testing which will be used in analyses by the Working Group.

Working Group Structure

The CDC/NCI NHANES III Genomics Working Group is made up of a multidisciplinary team of epidemiologists, geneticists, laboratory scientists, statisticians, and analysts from across CDC. The role of the NOPHG in the NHANES III Collaborative Genomics Project is to:

- provide overall coordination of the NHANES III genomics study, including oversight of the laboratory aspects of the study,
- develop collaborative research proposals for the prevalence analysis and for genotype-phenotype analyses,
- maintain a central repository of CDC/NCI NHANES III Genomics Working Group documents and processes (see figure on the next page),
- provide statistical and analytic support to help collaborators work with the NHANES III datasets and develop their analytic frameworks, and
- support a full-time data analyst in the NCHS Research Development Center (RDC) to work exclusively on the project.

A Quality Control/Quality Assurance (QC/QA) Committee was formed from members of the Working Group to monitor and test genotyping data. An Analytic Committee has been formed as well, the purpose of which is to decide which statistical analyses to perform, to help investigators develop their analytic plans for the genotype-phenotype association analyses, and to perform all data analyses.

CDC/NCI NHANESIII Genomics Working Group

CDC
- Office of the Director
- National Office of Public Health Genomics
- National Center for Infectious Diseases
- National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
- National Center for Immunization and Respiratory Diseases
- National Center for Environmental Health
- National Institute for Occupational Safety and Health
- National Center for Chronic Disease Prevention and Health Promotion
- National Center for Birth Defects and Developmental Disabilities
- National Center for Health Marketing
- National Center for Health Statistics
- Agency for Toxic Substances and Disease Registry

NCI
- NCI's Core Genotyping Facility
- Division of Cancer Epidemiology and Genetics Group

Key Accomplishments

- In 2005, NOPHG developed a communication plan for the Working Group and an NHANES III web board for posting and storage of pertinent documents and data output (see figure on the next page).
- In 2005 and 2006, NOPHG, in collaboration with the Working Group, developed six large, integrated research proposals based on disease outcomes for submission to NCHS. The proposals received IRB approval in late 2006 and early 2007.
- In 2006 and 2007, NOPHG statisticians and epidemiologists developed statistical methods for analysis

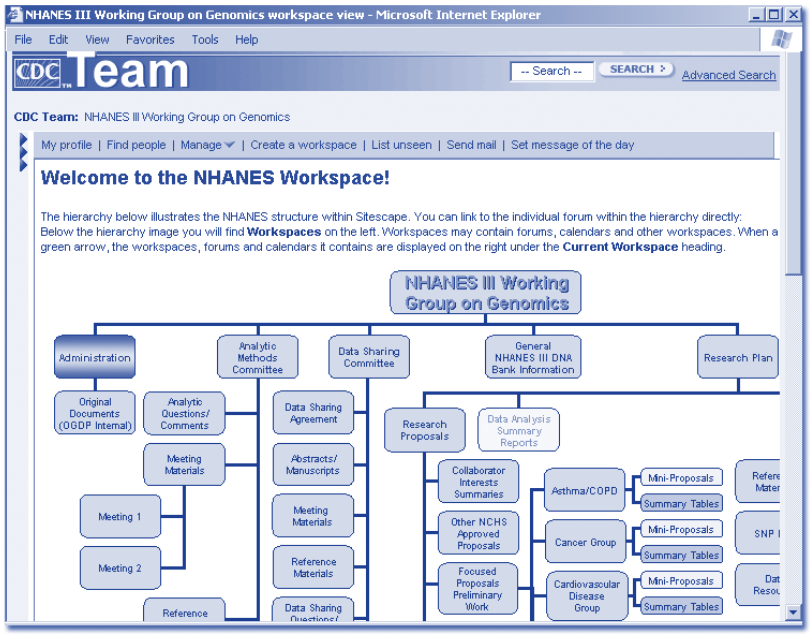
of complex survey data, and began analyses of preliminary data.

- By July 2007, successful genotyping results for 90 variants in 50 genes have been deposited at NCHS.

Current Activities

- The CDC/NCI Working Group has written the first manuscript entitled "Prevalence in the United States of Variants in Genes of Public Health Importance: Third National Health and Nutrition Examination Survey (NHANES III), 1991-1994" and plans to submit it to a research journal in winter 2007.
- NOPHG statisticians and analysts are preparing a second manuscript describing the statistical methods that have been developed for use with genetic data in complex surveys.
- Statistical analysis for each of the approximately 35 genotype-phenotype correlation studies is in progress at NCHS. CDC/NCI Working Group members, including several NOPHG personnel, are reviewing their preliminary data analyses and finalizing their analytic plans for their genotype-phenotype association analyses.

Communication in the NHANES IIII Collaborative Genomics Project



Next Steps

In the immediate future, the CDC/NCI NHANES III Genomics Working Group will focus their efforts on completion of genotype-phenotype association analyses, manuscript preparation, and dissemination of findings. Additional statistical evaluation of population substructure is also underway. This analysis will utilize both race/ethnicity and geographic information to conduct a focused examination of the genetic substructure of the U.S. population and its subpopulations. This issue is generating increased interest, as latent population substructure has been discovered recently in populations previously thought to be relatively homogeneous. Such analyses are especially important for the highly heterogenous U.S. population, and considering the high levels of admixture among African-Americans and Mexican-Americans.

Over the next few years, NOPHG plans to begin a project termed Beyond Gene Discovery (BGD), which will use a whole-genome approach (approximately one million SNPs and copy number variants) to assess the prevalence of genetic polymorphisms in the NHANES III DNA Bank. Completion of the project will enhance the value of many ongoing gene discovery studies, helping to translate their findings into new targets for prevention, diagnosis, and treatment of common diseases, and 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.

Selected Publications and Poster Presentations

1. Moonesinghe, R, Khoury, MJ, Janssens, CJW. Most Published Research Findings Are False—But a Little Replication Goes a Long Way. PloS Medicine. 2007 Feb; 4(2) e28:0218-20.
2. Lindegren, ML, CDC Working Group. NHANES III DNA Bank: Prevalence of Gene Variants of Public Health Significance. Presented at Genomics and the Future of Public Health Symposium, Atlanta, Georgia. May 2003.

Integrating Genomics into Public Health Investigations

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

NOPHG's efforts to integrate genomics into public health investigations have been concentrated in three areas: 1) a seed funding program for CDC public health researchers, 2) the Public Health Influenza Genomics Initiative, and 3) a review of CDC research protocols that include human genetics, with a goal of identifying best practices and developing guidance.

Building Public Health Genomics Research Capacity at CDC

In March 2006, NOPHG announced the availability of seed funding (maximum $100,000 per proposal) for innovative CDC projects that integrate genomics into public health research and programs. Projects with the most potential to demonstrate health impact within the two-year funding period received priority. Funds were available to support 11 of the 32 proposals submitted.

Projects receiving seed funding in 2006 are listed in the table. The CDC centers and offices represented are: NCID, NCBDDD, NCEH, National Center for HIV/AIDS Viral Hepatitis, STD, and TB Prevention (NCHHSTP), National Institute of Occupational Safety and Health (NIOSH), NCCDPHP, and the Agency for Toxic Substances and Disease Registry (ATSDR).

Brief descriptions of the projects can be found in Annex 1 of this section.

Projects receiving seed funding, 2006

	Project title	Investigators
1.	Genetic Predictors of Developing Hemolytic-Uremic Syndrome among persons infected with Shiga toxin-producing Escherichia coli (STEC).	Frederick J. Angulo, Linda J. Demma, (NCID)
2.	Microarray Analyses of MHC Genetic Variations in Diisocyanate-induced Occupational Asthma.	Michael I. Luster (NIOSH), Berran Yucesoy (NIOSH), Victor J. Johnson (NIOSH), and Eugene Demchuk (ATSDR)
3.	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.	Margaret A. Honein (NCBDDD), Mary Jenkins (NCBDDD), Margaret (Peg) Gallagher (NCEH), Sonja A. Rasmussen (NCBDDD), Patricia Richter (NCCDPHP), Robert Merritt (NCCDPHP)
4.	Identifying Genetic Determinants of Susceptibility to M. tuberculosis.	Mary Reichler (NCHHSTP)
5.	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.	Ya Ping Shi (NCID)

	Project title	Investigators
6.	Effectiveness and Cost-effectiveness of Using Family History of Diabetes for Population–level Health Promotion.	Scott Grosse (NCBDDD) , David Meltzer, Anirban Basu, Elbert Huang, Xuejie Zhang (University of Chicago)
7.	Should Genetic Testing Be Used to Guide Warfarin Therapy? An Evidence-based Cost-Utility Analysis.	Scott Grosse (NCBDDD), Craig Hooper (NCBDDD) , David Veenstra (University of Washington, Seattle)
8.	Effect of Folic Acid Intake on Blood Folate and Homocysteine Levels in Persons Classified by Genotype of Folate-related Genes.	Quanhe Yang (NCBDDD), Margaret Gallagher (NCEH), David Erickson (NCBDDD), and Karen Steinberg (CoCHP)
9.	The Interaction of Community-level Social and Environmental Stress and Inflammatory Pathway Genes with the Risk for Very Preterm Birth.	Althea Grant (NCCDPHP), Christopher Bean (NCCDPHP), Glen Satten (NCCDPHP), Rebecca Buus (NCCDPHP), Karon Abe (NCCDPHP), Craig Hooper (NCBDDD)
10.	An Early Childhood Mortality Study using a Newborn Blood Spot Screening Test for Severe Combined Immunodeficiency Disorder (SCID).	Barbara Adam and Robert Vogt (NCEH), Richard Olney (NCBDDD), Franco Scinicariello (ATSDR), Chin-Yih Ou (NCHSTP)
11.	Osteoporosis: A Multi-determinate Approach to Prevention: Implications for the CDC Health Protection Goal of Living Better and Longer.	Anne Looker (NCHS)

The second year of funding of these projects started in April 2007, and will continue through March 2008. NOPHG documents the progress of these projects by obtaining periodic reports from the principal investigators. These updates are also used to evaluate the success of the CDC seed funding initiative.

Key Accomplishments

The projects are currently underway. Three seed funding project investigators presented preliminary results of their work at the March 2007 meeting of the PHGC, an internal CDC human genomics interest group. They noted the value of these grants for enhancing research capacity and stimulating new collaborations.

Current Activities

The 11 seed funding projects are currently completing genotyping and data analysis, and anticipate writing and submitting manuscripts in 2008. NOPHG funded nine of these projects in 2007 for a second year, with anticipated completion date of April 2008.

Next Steps

In the immediate future, NOPHG plans to assess the effectiveness of seed funding programs in developing innovative research, building capacity, and stimulating new collaborations. NOPHG will continue to provide opportunities for other seed funding investigators to present the results of their projects at PHGC meetings, the 10th Anniversary Meeting of Public Health Genomics at CDC, and in other appropriate forums. A call for new seed funding proposals was sent in fall 2007, and funds will be awarded in spring 2008.

CDC Influenza Public Health Genomics Initiative

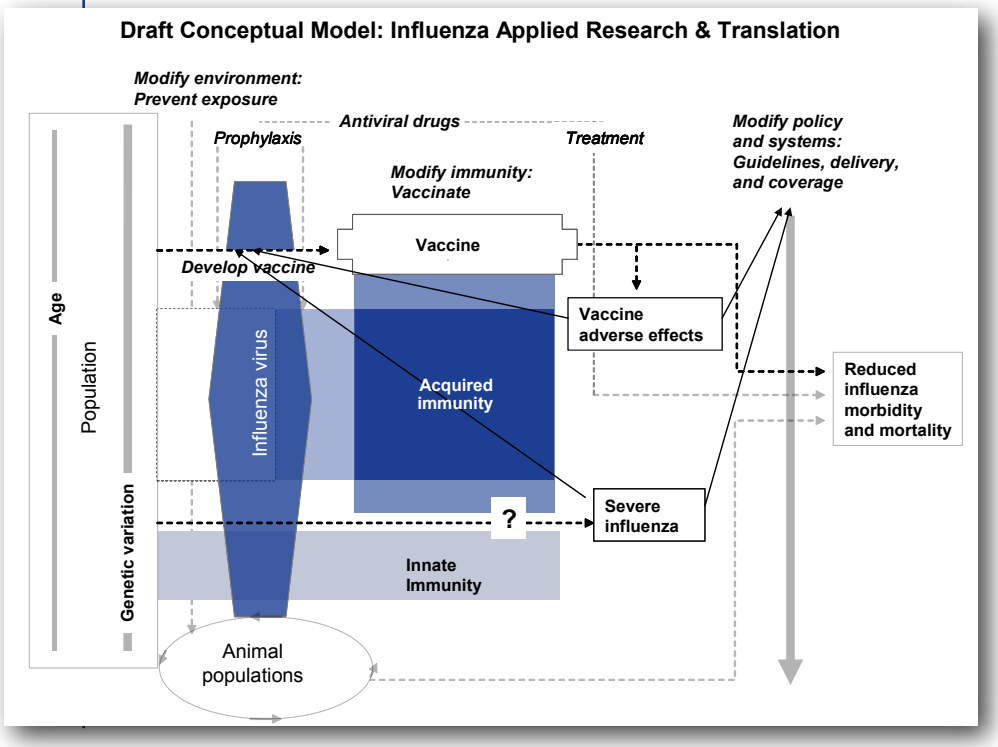
In response to the ongoing threat of seasonal influenza and the potential emergence of new, more virulent strains, NOPHG and the National Center for Influenza and Respiratory Diseases (NCIRD) developed a pilot CDC Influenza Public Health Genomics Initiative to investigate the role of population genetic variation in the epidemiology of influenza morbidity and mortality and the effectiveness of public health interventions.

The initiative proposed four activities:

1. Complete a study of human genetic variants in approximately 45 children who died with influenza infection during the severe 2003-04 season.
2. Invite experts to a workshop to discuss public health research on human genetics and influenza.
3. Develop an "off-the-shelf" protocol for use in field investigations of severe influenza.
4. Develop a biobank to store DNA samples from persons with severe influenza for future study.

Key Accomplishments

- A NOPHG molecular geneticist demonstrated the feasibility of amplifying and genotyping DNA from paraffin-embedded lung tissue obtained at autopsy. This was necessary to proceed with protocol for study of fatal influenza in children.
- In January 2007, NOPHG and NCIRD held a workshop to discuss opportunities for public health research on the role of human genomics in influenza disease and vaccine response. More than 100 participants from diverse fields—including immunology, virology, epidemiology, medicine and public health—working in government, academia, and private-sector research organizations attended the workshop. The workshop concluded by proposing priorities for genomics research on determinants of influenza disease severity and vaccine response and side effects (as illustrated in the figure on the left).
- Preliminary work on an "off-the-shelf" protocol has been folded into the protocol for study of fatal influenza in children.
- NOPHG has contracted with America's Health Insurance Plans (AHIP) to develop a pilot study examining the feasibility of a multi-site DNA bank from patients within group health plans that could be used to study the role of genetic factors in influenza disease severity and vaccine effectiveness and side effects response to therapy.



Current Activities

- The protocol for study of fatal influenza in children is currently undergoing CDC IRB review.
- The draft workshop report is being edited; a manuscript reviewing candidate genes for severe influenza infection is in draft form.
- NOPHG continues to review CDC protocols and human subjects requirements to inform development of guidance for public health research involving human genetics (see next section).
- Discussions are ongoing with AHIP to develop a useful pilot study, given absence of continued funding.

Next Steps

Next steps for the CDC Influenza Public Health Genomics Initiative include:

- conducting genetic analysis of fatal pediatric influenza case samples (NCIRD) and control samples from NHANES III (NOPHG),
- publishing the 2007 workshop report on the NOPHG website,
- discussing influenza as an example in protocol guidance that NOPHG is developing (see next section), and
- developing a pilot study with AHIP, with specific roles for NCIRD and NOPHG.

Guidance for CDC Research Protocols Including Human Genetics

Analysis of microbial genetics is a mainstay of public health research and surveillance. Genetic markers are used to identify the source of an epidemic and monitor its spread, detect antimicrobial resistance, and guide public health interventions (e.g., annual influenza vaccine). Until now, public health interest in human genetics has been limited largely to newborn screening programs for inherited diseases. Rapid advances in the science of human genetics and development of new technology have created new opportunities for public health research to collect and analyze human genetic information.

In May 2004, NOPHG and the Council of State and Territorial Epidemiologists (CSTE) held a workshop to discuss incorporating human genetics into public health investigations. Participants came from the National Institutes of Health, state and local health departments, and academic medicine. They concluded that the decision to collect genetic information should be based on potential public health value, feasibility, availability of resources, practicality, and community understanding.

One of NOPHG's aims in supporting pilot projects, including the Seed Funding grants and Influenza Public Health Genomics Initiative described above, has been to gain additional insight into these issues. In addition, NOPHG has systematically gathered and reviewed existing, IRB-approved CDC research protocols that involve human genetics, with the aim of identifying common challenges and best practices.

Resources

NOPHG has one staff position dedicated to ethics in public health genomics, including human subjects research issues.

The molecular geneticist detailed to assist with influenza projects also chairs the Tri-Center Human Genomics Working Group, an interest group composed of researchers from three CDC Centers focused on infectious diseases. This group has provided a forum for discussion of issues in research conduct.

Key Accomplishments

- NOPHG staff collected CDC IRB-approved research protocols including human genetics and reviewed key components, such as explanation of research objectives; informed consent for participation, sample banking, and future research; data and sample sharing with secondary investigators; and returning research results to participants. NOPHG staff also interviewed CDC genomics investigators and research administrators to collect information on human subjects protection challenges and solutions generated by human genetic research protocols. Lessons learned from the protocols and interviews were presented at a meeting of CDC IRB chairs and incorporated into a two-hour training session for human subjects

protection administrators at CDC.

- NOPHG and NCIRD staff collaborated on development of protocol for examining human genetics in severe pediatric influenza. This project provided useful experience for developing "off-the-shelf" protocols that can be reviewed and approved quickly for urgent public health investigations.
- NOPHG staff organized and presented to the CDC Public Health Ethics Advisory Committee a proposal for developing guidance on conduct of public health research involving genetics. Three case studies from diverse research groups illustrated key challenges.

Current Activities

- Continue to develop guidance, with input from CDC researchers and internal and external ethics advisory committees.

Annex 1: 2006 Seed CDC Funding for Public Health Genomics Research

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

Microarray Analyses of MHC Genetic Variations in Diisocyanate-induced Occupational Asthma. *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. *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 U.S. births; anorectal atresia/stenosis, the congenital absence or narrowing of the anal or rectal canal, affects approximately 4.8 infants per 10,000 U.S. 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. *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. *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. *Scott Grosse (NCBDDD), David Meltzer, Anirban Basu, Elbert Huang, Xuejie Zhang (University of Chicago)*

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. *Scott Grosse (NCBDDD), Craig Hooper (NCBDDD) , David Veenstra (University of Washington, Seattle)*

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 U.S. 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. *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.

The Interaction of Community-level Social and Environmental Stress and Inflammatory Pathway Genes with the Risk for Very Preterm Birth. *Althea Grant (NCCDPHP), Christopher Bean (NCCDPHP), Glen Satten (NCCDPHP), Rebecca Buus (NCCDPHP), Karon Abe (NCCDPHP), Craig Hooper (NCBDDD)*

This study builds upon an existing population-based investigation of the role of inflammatory and endocrine response genes and very preterm births being conducted in collaboration with the California Department of Health Services. In this additional study, we hypothesize that exposure to certain environmental and social triggers during pregnancy (low SES, high stress, community deprivation, high crime rates, poor housing, etc.) interacts with genetic predisposition, resulting in increased risk of preterm birth. To characterize this association we are conducting a population-based nested case-control study in a cohort of term and very preterm births in California. Maternal and fetal genotypes and haplotypes for genes of interest are being determined from maternal prenatal screening specimens and newborn blood spots. Individual-level data on mothers and infants are being collected from linked data sources including vital records, prenatal and newborn screening records, and abstracted medical records. Community-level variables, based on residence at time of prenatal screening, are being measured using several sources, including data from the 2000 U.S. Census.

An Early Childhood Mortality Study using a Newborn Blood Spot Screening Test for Severe Combined Immunodeficiency Disorder (SCID). *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. *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 San Diego.

Human Genome Epidemiology Network (HuGENet™)

The Human Genome Project has stimulated a rapid increase in genetic research, leading to many new gene discoveries. To realize the potential of genetic research for disease prevention and health promotion, population-based epidemiologic studies are needed to examine the role of genetic variation in population risk of common diseases and to identify the interactions of genetic variants with modifiable risk factors, such as diet and environmental exposures. The results of these population-based studies will help medical and public health professionals to improve and guide medical, behavioral, and environmental interventions. Epidemiologic studies are also needed to assess the clinical validity of genetic tests, including their predictive value in different populations. Epidemiologic surveillance is also important for monitoring the utilization, safety, and effectiveness of genetic tests in clinical and public health practice.

Human Genome Epidemiology (HuGE)

Human Genome Epidemiology (HuGE) uses population-based epidemiologic methods to examine the relationship of genetic variation with health and disease. HuGE combines approaches from genetic epidemiology, molecular epidemiology, and health services research to estimate key measures and compare them among different populations. These measures include:

- prevalence of gene variants,
- relative and absolute risks of disease associated with gene variants,
- contribution of gene variants to occurrence of disease (attributable risk),
- risk of disease associated with gene-gene and gene-environment interactions,
- clinical validity of genetic tests, especially their positive and negative predictive values,
- utilization of genetic tests, and
- impact of genetic tests and services on morbidity, disability, mortality and health care costs.

Building the Knowledge Base

During the last decade, the scientific literature has swelled with genetic association studies of varying size, design, and quality. Increasingly, population-based epidemiologic studies also include genetic analyses. Synthesis and interpretation of human genome epidemiologic information requires coordinated, global collaboration among epidemiologists, clinical geneticists, and basic scientists. Dissemination of research findings depends on broad cooperation and communication among medical and public health professionals from government, academia, industry and consumer organizations worldwide.

Human Genome Epidemiology Network (HuGENet™)

In 1998, NOPHG established the Human Genome Epidemiology Network (HuGENet™). The goal of HuGENet™ is to help translate genetic research findings into opportunities for preventive medicine and public health by advancing the synthesis, interpretation, and dissemination of population-based data on human genetic variation in health and disease.

Human Genome Epidemiology Network (HuGENet™) At A Glance

1998:
- Human genome epidemiology was defined

1999:
- NOPHG hired first staff epidemiologist

2000:
- NOPHG launched HuGENet™ website and database

2001:
- NOPHG collaborated with NCI and NIEHS to host expert workshop to develop HuGE review guidance, Atlanta U.S.

2002:
- First HuGE Workshop, Cambridge U.K.

2003:
- CDC-wide Genomics and Future of Public Health Symposium/HuGE Workshop in Atlanta U.S.

2004:
- Human Genome Epidemiology book was published

2005:
- Network of Networks Workshop, Cambridge U.K.

2006:
- "Roadmap" published in Nature Genetics
- First edition of HuGENet™ Handbook of Systematic Reviews was completed

2007:
- Data mining used to search published literature

HuGENet™ Collaborators

Network of Networks

International
- The Human Variome Project
- Genetic Susceptibility to Environmental Carcinogens (GSEC)
- International Agency for Research on Cancer, Gene-Environment Epidemiology Group
- Public Population Project in Genomics (P3G) and P3G Observatory

Australia
- Western Australian Genetic Epidemiology Resource (WAGER)

Europe
- U.K. HuGENet™ Coordinating Center, Cambridge, U.K.
- University of Ioannina HuGENet™ Coordinating Center, Greece
- GenomeEUTwin
- KORA-gen
- U.K. Biobank
- University of Bristol, Dept. of Social Medicine and CRP HuGE Consortium

North America
- CDC HuGENet™ Coordinating Center, U.S.
- University of Ottawa HuGENet™ Coordinating Center, Canada
- ALFRED-The Allele FREquency Database
- AlzGene Database
- Cancer Genetics Network & InterLymph
- Cartagene Project
- Genetic Association Database
- Marshfield Clinic Personalized Medicine Research Project (PMRP)
- National Cancer Institute
- National Children's Study–Gene-Environment Interaction Working Group
- National Heart, Lung, and Blood Institute (NHLBI)
- National Institute of Environmental Health Sciences (NIEHS)–Environmental Genome Project (EGP)
- University of Pennsylvania Clinical Pharmacogenomic Epidemiology (CPE) Initiatlve

HuGENet™ has continued to grow as an open collaboration of individuals and organizations from around the world. During the last 5 years, NOPHG has been joined by additional HuGENet™ coordinating centers in Cambridge (United Kingdom), Ottawa (Canada), and Ioannina (Greece). In 2005, HuGENet™ launched the "Network of Networks," an informal collaboration among existing research networks and consortia dedicated to the study of genetic factors in common diseases, such as cancer, heart disease, and osteoporosis.

Key Activities

NOPHG provides the overall leadership and coordination of HuGENet™ key activities which include:

HuGENet™ website: Established in 2000, the HuGENet™ free online resources include a curated, weekly summary of newly published scientific articles on human genome epidemiology, a searchable database (HuGE Pub Lit), case studies for training, and information on HuGE workshops and publications. (www.cdc.gov/genomics/hugenet)

HuGE reviews: These peer-reviewed, systematic reviews of gene-disease associations are published in partnership with ten scientific journals. HuGE reviews typically point to gaps in existing epidemiologic and clinical knowledge, thus stimulating further research in these areas.

HuGE Published Literature database: Systematic collection of relevant articles cited in PubMed began in October 2000. The database, which is updated weekly, is accessible on the Internet. Users can search the database by gene, health outcome, or environmental factor. Key information about each study is presented, along with a direct link to PubMed's abstract of the article.

HuGE meetings and workshops: NOPHG and other HuGENet™ coordinating centers collaborate to sponsor meetings and workshops that focus on methods development, network building, and training.

HuGE informatics: Research and development focuses on building tools for retrieving, indexing, and classifying published literature cited in PubMed, producing research summaries, and promoting research collaboration. Other tools include an aid for identifying candidate genes and a calculator for estimating parameters for genetic tests.

Training in human genome epidemiology: NOPHG has supported student internships, post-graduate fellowships, and career development sabbaticals for training.

Key Accomplishments

HuGE Published Literature database: As of July 1, 2007, this searchable, online database indexes 28,254 research studies, referencing 2,924 genes and 3,507 health outcomes/diseases. It includes 60 HuGE Reviews and 508 meta-analyses. Since its inception in October 2000, the database has had the same full-time curator performing weekly updates.

HuGE Navigator: In July 2007, NOPHG launched the beta version of the HuGE Navigator (www.hugenavigator.net), a suite of online applications that mine PubMed to populate the HuGE Published Literature database, identify candidate genes, search for investigators with a particular research focus, and produce knowledge summaries.

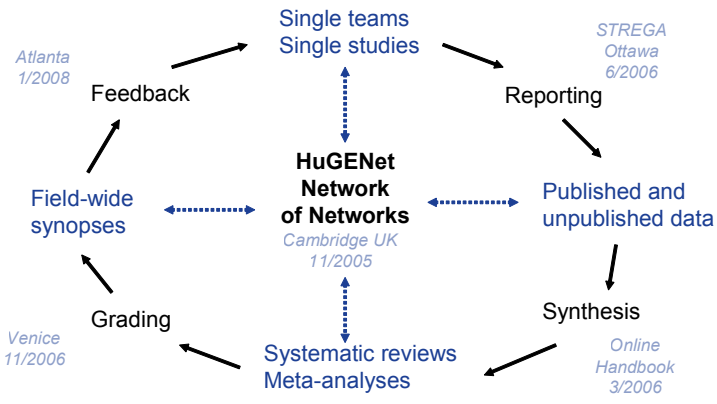
HuGENet™ meetings and workshops: Since 2001, ten international meetings and workshops have focused on methods for evaluating, synthesizing and interpreting population-based data on genetic variation, gene-disease association, and gene-gene and gene-environment interactions. Each of these meetings has produced one or more peer-reviewed publications.

Human Genome Epidemiology: This book, published in 2004 includes chapters by an interdisciplinary, international group of authors. A second edition is underway, with publication planned for 2009.

HuGENet™ Network of Networks: The meeting in 2005 convened members of approximately 30 research networks, ranging from funded consortia to informal collaborating groups. Selected networks are currently piloting approaches to pooled data analysis and knowledge synthesis.

HuGENet™ Meetings and Workshops

- HuGE Meeting: Guidelines for Evaluating Human Genome Epidemiology Studies (January 2001~U.S.) in collaboration with the National Cancer Institute and the National Institute of Environmental Health Sciences
- HuGE Workshop: Scientific Foundation for Using Genetic Information to Improve Health and Prevent Disease (July 2002~U.K.) in collaboration with Public Health Genetics Unit
- HuGE Workshop: Introducing the Concepts of Human Genome Epidemiology (May 2003~U.S.)
- Systematic Review Methodology Workshop (November 2004~U.K.) in collaboration with Cambridge Genetics Knowledge Park
- International Biobank and Cohort Studies Meeting: Developing a Harmonious Approach (February 2005~U.S.) in collaboration with the National Heart, Lung, and Blood Institute (NHLBI) and Public Population Project in Genomics (P3G)
- HuGENet™ Network of Networks Workshop (October 2005~U.K.)
- HuGENet™ Methodological Challenges in the Meta-analysis of Genetic Association Studies Meeting (May 2005~U.K.)
- Strengthening the Reporting of Genetic Associations (STREGA): an international HuGE workshop (June 2006~Canada)
- HuGENet™ Short Course (November 2006~U.K.)
- HuGENet™ Workshop on the Assessment of Cumulative Evidence on Genetic Associations (November 2006~Italy)



A road map for efficient and reliable human genome epidemiology. Commentary, *Nature Genetics* 2006;38:3-5

HuGENet™ Roadmap: Published in Nature Genetics in January 2006, the roadmap outlines an approach to building the knowledge base on human genome epidemiology.

HuGENet™ Handbook of Systematic Reviews: The first edition of this handbook, published in 2006, provides guidelines, systematic review, and meta-analysis of gene disease association studies.

STrengthening the Reporting of Genetic Associations (STREGA): A workshop held in Canada in July 2006 engaged

epidemiologists, geneticists, and journal editors in developing guidance for reporting research results in ways that promote knowledge synthesis (manuscript in preparation.)

Grading the Evidence for Genetic Associations: This workshop, held in Venice in 2006, produced draft guidelines that are being submitted for publication.

Current Activities

HuGE Navigator: NOPHG will release completed components of HuGE Navigator suite, including HuGE Published Literature Finder, Investigator Browser, and Prediction Checker; continue development of other components, including HuGEpedia, which will summarize published evidence for gene-disease associations; publish manuscripts providing open source code for HuGE Navigator and describing applications. (First such article, which described the Investigator Browser, was published in June 2007.)

HuGE informatics: NOPHG is developing customizable data mining tools for use by Network of Networks.

HuGENet™ Meeting, January 24-25, 2008: NOPHG is developing an agenda focused on further development of network approaches. This meeting will follow the NOPHG 10th Anniversary meeting planned for January 23, 2007.

Human Genome Epidemiology, 2nd edition: NOPHG is currently working on the first drafts of chapters, which are due in December 2007.

Next Steps

Pharmacogenomics: preliminary work is underway to characterize the published literature reporting pharmacogenomics research based on epidemiologic study designs; exploratory conversations are scheduled with PharmGKB. HuGENet™ may be able to help enrich the PharmGKB database.

Genetic testing: similar work is needed to characterize the published literature, especially on clinical validity. A pilot project is underway, comparing HuGE Pub Lit with EGAPP review of UGT1A1 testing for colorectal cancer treatment.

HuGENet™ challenges: respond to changing research landscape, especially genome-wide association studies. Find new ways to add value, e.g., via HuGEpedia and other approaches to "field synopses" proposed in 2006 "roadmap" article; reinforce international collaborations and broaden outreach from HuGENet™ to non-English-speaking world; and explore costs, benefits, and consequences of centralized vs. "distributed" (networked) data sharing. Establish collaboration with the National Library of Medicine (PubMed, dbGAP).

Selected Publications

1. Khoury MJ, Dorman JS. The Human Genome Epidemiology Network. *Am J Epidemiol*. 1998 Jul 1;148(1):1-3.
2. Ioannidis JP, Bernstein J, Boffetta P, et al. A network of investigator networks in human genome epidemiology. *Am J Epidemiol.* 2005 Aug 15;162(4):302-4.
3. Ioannidis JP, Gwinn M, Little J, et al. A road map for efficient and reliable human genome epidemiology. *Nat Genet.* 2006 Jan;38(1):3-5.
4. Little J, Higgins J. HuGENet™ HuGE Review Handbook, version 1.0 (Mar 2006). Web site. http://www.genesens.net/_intranet/doc_nouvelles/HuGE%20Review%20Handbook%20v11.pdf
5. Lin BK, Clyne M, Walsh M, Gomez O, Yu W, Gwinn M, Khoury MJ. Tracking the epidemiology of human genes in the literature: the HuGE Published Literature database. *Am J Epidemiol*. 2006 Jul 1;164(1):1-4.
6. Khoury MJ, Little J, Higgins J, Ioannidis JP, Gwinn M. Reporting of systematic reviews: the challenge of genetic association studies. *PLoS Med*. 2007 Jun 26;4(6):e211
7. Yu W, Yesupriya A, Wulf A, Qu J, Gwinn M, Khoury MJ. An automatic method to generate domain-specific investigator networks using PubMed abstracts. *BMC Med Inform Decis Mak*. 2007 Jun 20;7(1):17

Evaluation of Genomic Applications in Practice and Prevention (EGAPP)

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 disorders, but a growing number have population-based applications, including carrier identification, predictive testing for inherited risk of common diseases, and pharmacogenetic testing for variation in drug response. These tests and other anticipated applications of genomic technologies have the potential for broad public health impact.

EGAPP Milestones At A Glance

October, 2004:
- NOPHG established EGAPP Pilot Project
- EGAPP Steering Committee (SC) formed; two SC meetings held

2005:
- Methodology meeting, in-person SC Meeting
- EGAPP Working Group formed
- Three Working Group and four Steering Committee meetings held
- Four evidence reports commissioned (three of which were from AHRQ)

2006:
- Two evidence reports released by the AHRQ Evidence-based Practice Center
- One Steering Committee and three Working Group meetings held

2007:
- In-person SC meeting held
- Two evidence reports finalized (one AHRQ); Draft report in final review
- Three Working Group meetings held
- EGAPPreviews.org website established
- EGAPP Stakeholders Group (ESG) established
- First EGAPP Working Group recommendation statement published

In recent years, a number of issues have been raised about the current status of genetic testing implementation and oversight, including the need to develop evidence to establish efficacy and cost-effectiveness before tests are broadly commercialized. With the growing availability and promotion of genetic tests, clinicians need authoritative advice on their validity and utility. In fact, as new genomic technologies with potential applications in clinical practice continue to become available, there is an increasingly urgent need for timely and reliable information that will allow health care providers and payers, consumers, and policy makers to identify tests that are safe and effective. There has been a natural evolution of evidence-based processes (e.g., U.S. Preventative Services Task Force) that could be modified and applied to address these informational needs.

Validation gaps often exist within the translation continuum leading from gene discovery to clinical use of a genetic test in diagnosis, management or prevention. Often, data from clinical trials are limited or not available, leading to concerns about the safety and efficacy of emerging tests. Approval or clearance of genetic tests by the Food and Drug Administration (FDA) is required only for assay kits marketed to laboratories. However, the vast majority of genetic tests offered are laboratory-developed tests for which the FDA has authority, but currently does not regulate. Concerns continue to be raised about the adequacy of other regulatory (e.g., CMS/CLIA, New York Dept. of Health) and voluntary (e.g., College of American Pathologists) oversight mechanisms.

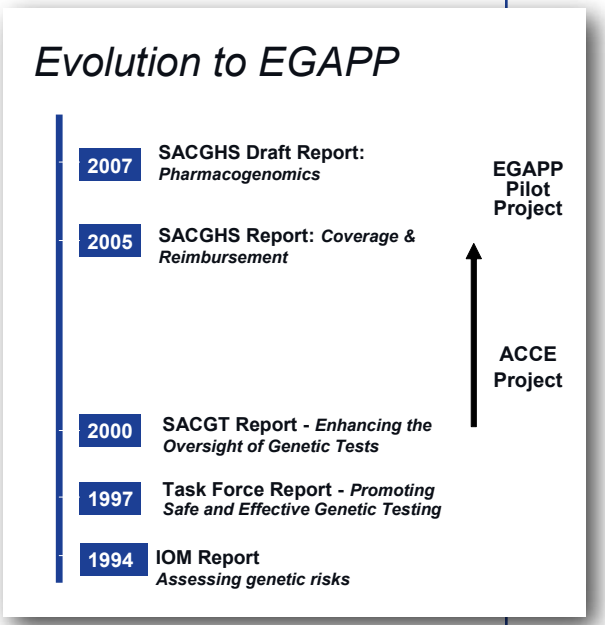
As with any new test or clinical intervention, the availability of practice guidelines can impact clinical practice and patient outcomes. Practice guidelines can be useful in supporting the introduction of new knowledge into clinical practice, translating complex research findings into recommendations, providing balanced information on benefits and limitations of tests and interventions, and improving medical decision making. Evidence-based approaches are critical for the generation of clinical practice guidelines, as they can promote credibility, reproducibility and transparency, while minimizing bias and identifying gaps in knowledge that can underscore where additional research is needed. It has been noted that genetic tests tend to fit less well within the framework of traditional "gold standard" processes of systematic evidence review. In addition to the limited number and quality of studies, many tests are aimed at interventions and outcomes that are not well defined. In addition, there is an overlay of advocacy from industry and patient interest groups surrounding genetic testing, and the ethical, legal, and social implications of genetic test implementation have been less amenable to a traditional evidence-based approach.

Recommendations on the development and implementation of safe and effective genetic tests have been

produced by expert panels, professional organizations, and clinical experts, including the National Institutes of Health - Department of Energy Task Force on Genetic Testing[2], the former Secretary's Advisory Committee on Genetic Testing,[3] and the Secretary's Advisory Committee on Genetics, Health, and Society.[4] The proposed components for evaluation of genetic tests that are generally accepted include analytic validity, clinical validity, clinical utility, as well as the ethical, legal and social implications associated with each evaluation component. However, a coordinated approach for effectively translating genomic applications into clinical practice and health policy is still needed.

Evaluation of Genomic Applications in Practice and Prevention (EGAPP)

In late 2004, NOPHG initiated the pilot project Evaluation of Genomic Applications in Practice and Prevention (EGAPP). The project's main goal is to establish and test a systematic, evidence-based process for evaluating genetic tests and other applications of genomic technology that are in transition from research to clinical and public health practice. The project aims to integrate existing recommendations and guidance on the implementation of genetic tests from professional organizations and advisory committees, as well as knowledge and experience gained from existing processes for evaluation and appraisal (e.g., U.S. Preventive Services Task Force, CDC's Task Force on Community Preventive Services), previous CDC initiatives (e.g., ACCE process; see Annex 1)[1], and the international health technology assessment experience.



Structure

EGAPP is a non-regulatory process focused around an independent, non-federal Working Group established in April, 2005. The Working Group is currently composed of 13 multidisciplinary experts in areas such as evidence-based review, clinical practice, public health, laboratory practice, genomics, epidemiology, economics, ethics, policy, and health technology assessment (Annex 2). Working Group members were selected from a pool of nominated individuals by a Department of Health and Human Services interagency Steering Committee (Annex 3). Nominations were solicited from a wide range of organizations and individuals.

Roles of the Working Group include:

- establishment/adaptation of methods and processes for evidence review,
- identification, prioritization and selection of topics for evidence review,
- participation on technical expert panels for commissioned evidence reviews,
- development of recommendations based on the evidence, and
- publication of methods and experience.

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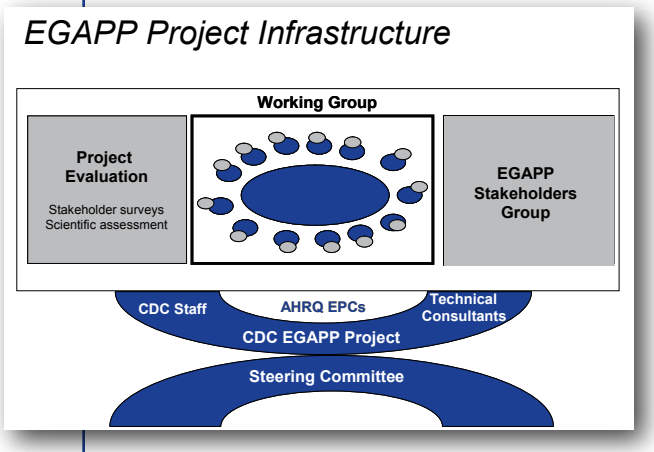
1. Haddow JE, Palomaki GE: ACCE: A Model Process for Evaluating Data on Emerging Genetic Tests. In: Human Genome Epidemiology: A Scientific Foundation for Using Genetic Information to Improve Health and Prevent Disease. Khoury M, Little J, Burke W (eds.), Oxford University Press, pp. 217-233, 2003.
2. Task Force on Genetic Testing. Joint NIH-DOE Ethical, Legal and Social Implications Working Group of the Human Genome Project. April 1995. http://www.genome.gov/10001808; accessed July 11, 2007.
3. Secretary's Advisory Committee on Genetic Testing. http://www4.od.nih.gov/oba/sacgt.htm; accessed July 11, 2007.
4. Secretary's Advisory Committee on Genetics, Health, and Society. http://www4.od.nih.gov/oba/sacghs.htm; accessed July 11. 2007.

Key procedural objectives of the Working Group are a transparent process and the provision of clear linkage between the scientific evidence developed and the conclusions, recommendations and information subsequently disseminated. Primary products of the EGAPP include evidence reports and Working Group recommendation statements.

NOPHG-based EGAPP staff provides support to the Working Group and coordinates EGAPP activities. EGAPP-supported expert consultants provide subject matter expertise in the preparation of methods, evidence reports and recommendation statements.

Process

EGAPP methods have incorporated many aspects of the ACCE process including: formal assessment of analytic validity and relevant ethical, legal and social implications, use of questions to organize collection of information, knowledge synthesis, and identification of gaps in knowledge. EGAPP also integrates knowledge and experience from existing evaluative processes, such as: commissioning comprehensive reviews through Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers (EPCs), development of analytic frameworks with key questions, explicit search strategies, assessment of quality of individual studies and strength of evidence, formulating recommendations with clear linkage to the evidence, and identification of research agendas. The EGAPP approach also adds value to existing processes in several areas. For example, EGAPP maintains a focus on "hard" medical outcomes (morbidity/mortality), but considers a range of specific family or societal outcomes when appropriate. EGAPP is developing systematic approaches for collecting and grading evidence on analytic validity, optimizing existing methods for handling data on clinical validity and utility of genetic tests, assessing the usefulness of modeling, and addressing cost effectiveness and cost-utility. EGAPP is currently investigating methods to generate targeted, practical reviews within a shorter time-frame.



EGAPP Subcommittees

At the first EGAPP Working Group meeting, three subcommittees were established to address Topics, Methods, and Outcomes; in early 2006, a Products Subcommittee was added. Two-day EGAPP Working Group meetings are held three times per year, and the work of the subcommittees continues between meetings through teleconferencing. Based on the agenda and specific tests under consideration or review, members are asked to declare any potential conflicts of interest prior to each meeting.

The Topics Subcommittee develops the processes for review, prioritization, and topic selection, and leads the review and selection of topics for the full Working Group.

The Methods Subcommittee addresses a range of methodological issues, including formulation of key questions and analytic frameworks for specific reviews, development of EGAPP evidence review protocols (e.g., grading quality of studies or strength of evidence), and translation of evidence to recommendations.

The Outcomes Subcommittee completed a lexicon of medical, family and population outcomes from which the outcomes of interest for specific reviews can be selected in early 2006.

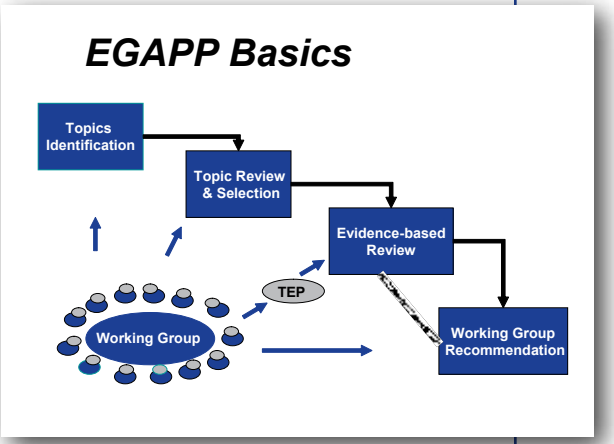
The Products Subcommittee considers content, format and timelines for EGAPP products (e.g., publications, abstracts/presentations, Web postings, recommendations), overseas development, and implementation of

processes for internal and peer review and dissemination of EGAPP written and Web products, and clears products to go to the full Working Group for approval.

EGAPP Working Group members also serve on Technical Expert Panels (TEPs) established to advise the investigators conducting each specific evidence review.

EGAPP Basics: Identification, Review, and Selection of Topics for Evidence Review

Scope of Topics - Because EGAPP is a pilot project with a public health focus, it was decided not to attempt to address the broad range of genetic tests in this first phase, but rather to focus on tests recognized as having wider population application (e.g., higher disorder prevalence, higher frequency of test use), and those with a higher potential to impact clinical and public health practice. Tests could include those used in a specific clinical scenario to guide intervention (e.g., diagnostic workup, treatment, or prevention) or tests used for risk prediction or population screening. However, it is intended that the methods and approaches developed during the pilot phase of EGAPP will have application to other types of testing in the future. In addition to limiting the scope of the pilot project, this early decision also recognized that, in some cases, other translation and evaluation processes are underway. The EGAPP project is not currently focusing on certain large categories of tests, including newborn screening, most testing for rare single gene disorders, or reproductive genetic testing.



Identifying Topics - Potential topics for evidence review in the pilot phase are identified through periodic horizon scanning by EGAPP project staff (e.g., internet and publications searching) and through suggestions from stakeholders, the EGAPP Steering Committee, and EGAPP Working Group members. Individuals, professional organizations, and members of the scientific and general public are encouraged to submit topics for future consideration through the www.egappreviews.org website comments page.

Review, Prioritization, and Formal Selection of Topics - Under the direction of the EGAPP Topics Subcommittee, EGAPP project staff maintains a list of topics suggested for consideration. The EGAPP Working Group considers selection for evidence review based on defining the disorder/effect to be tested for, the specific test to be used, and the clinical scenario(s) in which the test will be used (e.g., diagnosis or screening, population to be tested). All topics submitted are first reviewed to determine if they fall within the current stated project scope. Topics are then considered for review by the EGAPP Working Group based on specific criteria and other considerations related to the research objectives of the pilot project, as shown in Table 1.

Table 1. Selected Criteria and Considerations for Prioritization and Selection of Topics for Evidence Reviews

Criteria Related to Health Burden	Prevalence of disorder Severity/burden of disorder Strength of genotype/phenotype association Availability of effective intervention Relevance to practice
Criteria Related to Practice Issues	Clinical availability of test Likelihood of inappropriate use Potential impact of evidence
Other Considerations	Pilot project objectives/portfolio of tests Availability of evidence Other practical issues (e.g., avoiding duplication of effort) Ensuring diversity of test categories and types in reviews

The focus of topics will be those which are more common (i.e., higher prevalence of disease/disorder or prevalence of test use), and tests used to guide clinical interventions and used for risk prediction or population screening. Tests that do not meet eligibility criteria are listed for future consideration but not developed further. After listing a topic, EGAPP staff develops a short summary, which is a limited review of the published (focused on review articles) and grey literature designed to provide basic descriptive information (disorder, test, proposed clinical scenario) to the Working Group.

The Topics Subcommittee categorizes and ranks topics based on preset criteria, and makes recommendations on topics to be developed further. After discussion with the Working Group, full summaries are requested to selected topics. Full summaries are more in-depth (but not comprehensive) reviews of recent literature, review articles and the grey literature. Completed full summaries go to the Topics Subcommittee and the full EGAPP Working Group for review. After review and discussion of background information, the EGAPP Working Group votes to formally select topics.

Topics currently under review are shown in Table 2. A schematic representation of the process for review, prioritization and selection of topics for evidence review is provided in Annex 4. Topics under consideration are listed in Annex 5.

Table 2. Topics Currently Under Review or Completed

Disorder/Effect	Test to be Assessed*	Clinical Scenario	
		Target Population	Intended Use
Breast Cancer	Gene expression profile	Women diagnosed with breast cancer	Treatment and recurrence risk
Cardiovascular Disease	Multigene panels	General population	Risk prediction or nutritional/lifestyle management
Colorectal Cancer (CRC)	*UGT1A1*	Individuals diagnosed with CRC	Treatment with irinotecan
Depression	*CYP450*	Individuals diagnosed with depression	Treatment with SSRI drugs
Hereditary Nonpolyposis Colorectal Cancer (HNPCC)	Mismatch repair gene mutations	Individuals diagnosed with CRC and their family members	Management of individuals and early detection/prevention for family members
Ovarian Cancer	Genomic Tests	1) General population of women and; 2) women at increased risk for ovarian cancer	1) and 2) Detection and management
Venous Thromboembolism (VTE)	Factor V Leiden and Prothrombin	1) Personal and/or family history of venous thromboembolism, or 2) family history of Factor V Leiden mutation	Diagnosis and management for individuals; prevention for family members

Initiating an Evidence Report

Evidence reports are detailed, systematic, objective assessments of the available evidence on a specific topic. As

such, they represent the first step in the EGAPP evaluation process, and do not include recommendations based on the evidence. Following the identification of scope and outcomes of interest for an evidence report, key questions and an analytic framework are developed by the Working Group and refined where appropriate by the reviewers with guidance from a Technical Expert Panel (TEP). An example of an analytic framework and key questions are provided in Annex 6. Through an interagency agreement, AHRQ Evidence-based Practice Centers (EPCs) conduct some evidence-based reviews for the EGAPP Working Group. Other contracted evidence review centers/groups may also be commissioned to conduct evidence-based reviews.

External Expert Review of Evidence Reports

Draft evidence reports are distributed by the EPC or other contractor for expert peer-review, generally to the TEP (includes EGAPP Working Group members) and selected experts. Objectives for peer review of draft evidence reports are to: 1) ensure accuracy, completeness, clarity, and organization of the document; 2) assess modeling, if present, for parameters/assumptions and clinical relevance; and 3) identify scientific or contextual issues that need to be addressed or clarified in the final evidence report. In general, the selection of reviewers is based on expertise, with consideration given to potential conflicts of interest.

Development and Peer Review of Recommendation Statements

Final evidence reports are reviewed and discussed by the Working Group. Based on their deliberations, selected members develop recommendation statements. These documents are intended to summarize current knowledge on the validity and utility of an intended use of a genetic test (what we know and don't know), consider contextual issues related to implementation, provide guidance on appropriate use, and suggest key gaps and research that is needed.

Proposed external peer reviewers for draft recommendation statements are selected by the Working Group from individuals and organizations that are expected to be impacted by the recommendation, from the TEP and EGAPP Steering Committee members, and from key project target audiences (e.g., health care providers and payers, policy makers, targeted consumer organizations).

The objectives of the peer review process for EGAPP recommendation statements are to:

- ensure the accuracy and completeness of the evidence summarized in the recommendation statement, and transparency of the linkage to the evidence report;
- improve the clarity and organization of EGAPP work products;
- solicit feedback from experts with different perspectives; and
- identify contextual issues that need to be addressed or clarified in the final recommendation statement.

Appropriate written guidance is provided to reviewers regarding background issues and any particular areas they may be asked to focus upon. After review, discussion, and final approval by vote of the Working Group, the final recommendation statement is submitted to *Genetics in Medicine*, along with a list of reviewers that commented on the draft. The external peer review process does not involve public comment, but feedback from the public and other stakeholders is solicited later through evaluation surveys.

Evaluation of EGAPP Processes, Products and Impact

To assess the outcomes of the EGAPP pilot project, an outside evaluation consultant (contracted through McKing Consulting) is overseeing an evaluation plan. The objectives are to: 1) document project processes and timelines (e.g., infrastructure development, Working Group function, development of collaborations/partnerships); 2) collect feedback from stakeholders on the value and impact of EGAPP products developed (e.g., evidence reports, published evidence summaries, published Working Group recommendations, targeted

informational messages); and 3) collect feedback on the effectiveness of dissemination. We plan to obtain feedback by surveying members from each of four key stakeholder groups designated for the EGAPP pilot project, including health care providers (e.g., physicians, genetic counselors, mid-level practitioners, nurses), health care payers/purchasers (e.g., health plans, insurers, companies), policy makers (e.g., professional and other public health organizations), and targeted consumer groups (e.g., members of advocacy organizations and persons with health concerns related to topics). Five web-based surveys have been developed, in order to ensure that the most relevant information is captured from each of the key stakeholder groups. CDC will use the knowledge generated from the surveys and the evaluation activities to inform the further development of the EGAPP project, refine products, and identify priorities for future evaluation of genetic tests.

Key Accomplishments

NOPHG established the EGAPP Steering committee in October 2004. The Steering Committee directed development of the EGAPP Working Group, which was established in April 2005. To date, NOPHG has provided logistical and organizational support for nine EGAPP Steering Committee meetings, two of which have been in-person, as well as nine Working Group meetings.

Since 2004, NOPHG-based EGAPP staff and the Working Group have been successful in establishing and maintaining processes, and commissioning and overseeing seven evidence reviews. To date, four reports have been completed through an interagency agreement with AHRQ:

- *Genomic Tests for Ovarian Cancer Detection and Management* (October 2006) (http://www.ahrq.gov/clinic/tp/genovctp.htm) which was conducted by Duke University AHRQ Evidence-based Practice Center
- *Testing for Cytochrome P450 Polymorphisms (CYP450) in Adults with Non-Psychotic Depression Prior to Treatment with Selective Serotonin Reuptake Inhibitors (SSRIs)* (January 2007) (http://www.ahrq.gov/clinic/tp/cyp450tp.htm) conducted by Duke University AHRQ Evidence-based Practice Center
- *Hereditary Nonpolyposis Colorectal Cancer: Diagnostic Strategies and Their Implications* (May 2007) (http://www.ahrq.gov/downloads/pub/evidence/pdf/hnpcc/hnpcc.pdf) conducted by the Tufts-New England Medical Center AHRQ Evidence-based Practice Center
- *Impact of Gene Expression Profiling Tests on Breast Cancer Outcomes* (pending release)

EGAPP has established an agreement with *Genetics in Medicine* to publish EGAPP Working Group recommendation statements and summary evidence reports. The first recommendation statement was published in December 2007.

- *Recommendations from the EGAPP Working Group: Testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. Gene Med.* 2007:9(12):819-825.

EGAPP has recently launched an independent website – www.egappreviews.org – to provide access to the EGAPP Working Group's processes, methods, and products. This website was developed by Cadence Group contractors, with the support of NOPHG.

Current Activities

The EGAPP Working Group is developing recommendation statements on:

- *UGT1A1 Mutation Analysis in Colorectal Cancer Patients Treated with Irinotecan* (in review)
- *Genomic Tests for Ovarian Cancer Detection and Management* (pending)

EGAPP-commissioned evidence reports currently in progress are:

- *UGT1A1 Mutation Analysis in Colorectal Cancer Patients Treated with Irinotecan* (non-EPC, in review)
- *DNA Testing Strategies Aimed at Reducing Morbidity and Mortality from Lynch Syndrome* (non-EPC, pending)
- *Impact of Factor V Leiden Mutation Testing on Health Outcomes in Individuals with a History of or Increased Risk for Thromboembolic Events* (in development)
- *Use of Genomic Profiling to Assess Risk for Cardiovascular Disease and Identify Individualized Prevention Strategies* (non-EPC, in progress)

NOPHG is supporting the development of an EGAPP Stakeholders Group (ESG). ESG is composed of a broad range of stakeholders with the expertise, experience, and ability to represent the perspectives of their stakeholder categories. Thirty-five ESG members were selected in fall 2007 by a six-person ESG Steering Committee. A stakeholder is considered to be anyone who has an interest in EGAPP products, and suggested categories of stakeholders include: health care providers, public health professionals, health care payers, policy makers, targeted consumer advocacy groups, educators, researchers, clinical professionals, information technologists, and media and science writers. Among other potential roles, the ESG proposes to assist EGAPP in the identification of central or core messages for evidence reports and recommendation statements, and act as facilitators in framing these messages in ways that are appropriate and accessible for specific constituents.

Next Steps

NOPHG will continue to provide technical and organizational support to the EGAPP Working Group as they address objectives for the immediate future, that include publishing recommendation statements and articles on EGAPP methods, topics and outcomes. NOPHG is facilitating the development and dissemination of translational materials for different target audiences based on evidence developed, soliciting feedback through the ESG, and evaluation of the EGAPP project. Long-terms plans for EGAPP include: investigating approaches and methods that may improve the flexibility, cost, speed and efficiency of evaluating evidence on genomic applications; seeking strategic public-private partnerships that will add value to EGAPP processes; engaging ESG talent and expertise to increase the public health impact of EGAPP products; and promoting the transition of EGAPP into a sustainable and transferable entity.

Selected Publications and Products

ACCE

1. Haddow JE, Palomaki GE: ACCE: A Model Process for Evaluating Data on Emerging Genetic Tests. In: Human Genome Epidemiology: A Scientific Foundation for Using Genetic Information to Improve Health and Prevent Disease. Khoury M, Little J, Burke W (eds.), Oxford University Press, pp. 217-233, 2003.
2. Palomaki GE, Bradley LA, Richards CS, Haddow JE. Analytic validity of cystic fibrosis testing: a preliminary estimate. Genet Med. 2003;5(1):15-20.
3. Palomaki GE, Haddow JE, Bradley LA, Richards CS, Stenzel TT, Grody WW. Estimated analytic validity of HFE C282Y mutation testing in population screening: the potential value of confirmatory testing. Genet Med. 2003;5(6):440-3.
4. Haddow JE and Palomaki GE. Population-based prenatal screening for cystic fibrosis via carrier testing: ACCE review. (http://www.cdc.gov/genomics/gtesting/ACCE/fbr.htm)
5. Rowley, PT and Haddow, JE and Palomaki GE. DNA testing strategies aimed at reducing morbidity and mortality from hereditary non-polyposis colorectal cancer (HNPCC): An ACCE Mini-Review. (http://

www.cdc.gov/genomics/gtesting/ACCE/fbr.htm)

6. Screening for Hereditary Hemochromatosis in Adults via HFE Mutation Testing: AACE review. (http://www.cdc.gov/genomics/gtesting/ACCE/fbr.htm)
7. Testing for Factor V Leiden and Prothrombin Mutations as a Risk Factor for Recurrent Venous Thrombosis in Adults: AACE review. (http://www.cdc.gov/genomics/gtesting/ACCE/fbr.htm)
8. Family History and BRCA 1/2 Testing for Identifying Women at Risk for Inherited Breast/Ovarian Cancer: AACE review. (http://www.cdc.gov/genomics/gtesting/ACCE/fbr.htm)

EGAPP Working Group Recommendation Statement

- *Recommendations from the EGAPP Working Group: Testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. Gene Med.* 2007:9(12):819-825.

AHRQ Evidence Reports and Associated Publications

- *Genomic Tests for Ovarian Cancer Detection and Management* (http://www.ahrq.gov/clinic/tp/genovctp.htm)
- *Testing for Cytochrome P450 Polymorphisms (CYP450) in Adults with Non-Psychotic Depression Prior to Treatment with Selective Serotonin Reuptake Inhibitors (SSRIs)* (http://www.ahrq.gov/clinic/tp/cyp450tp.htm#Report)
- *Hereditary Nonpolyposis Colorectal Cancer: Diagnostic Strategies and Their Implications* (http://www.ahrq.gov/clinic/tp/hnpcctp.htm#Report)
- Thakur M, Grossman I, McCrory DC, Orlando LA, Steffens DC, Cline KE, Gray RN, Farmer J, DeJesus G, O'Brien C, Samsa G, Goldstein DB, and Matchar D. *No evidence for the utility of genetic testing for CYP450 polymorphisms as a guide to management of patients with non-psychotic depression with Selective Serotonin Reuptake Inhibitors (SSRIs). Gene Med.* 2007:9(12).

Annex 1: ACCE: A CDC-Sponsored Project Carried Out by the Foundation of Blood Research

Introduction to ACCE

ACCE, which takes its name from the four components of evaluation—analytic validity, clinical validity, clinical utility and associated ethical, legal and social implications—is a model process for evaluating data on emerging genetic tests. The process includes collecting, evaluating, interpreting, and reporting data about DNA (and related) testing for disorders with a genetic component in a format that allows policy makers to have access to up-to-date and reliable information for decision making.

Goals and Attributes of the ACCE Model System:

- Assesses data on DNA-based testing for disorders with a genetic component
  - Broad focus – "first look" at all available data
  - Ad hoc approach to grading quality of evidence to extract maximum information
  - Review, analyze, and integrate data
  - Does not suggest policy or make recommendations
- Provides up-to-date, accurate and complete summaries of available information
- Creates formats useful to policy makers, health care providers and the general public

An important by-product of this process is the identification of gaps in knowledge. The ACCE approach builds on a methodology originally described by Wald and Cuckle[1] and on terminology introduced by the Secretary's Advisory Committee on Genetic Testing [2].

Additional information and ACCE reports are available at http://www.cdc.gov/genomics/gtesting/ACCE/fbr.htm.

Components of ACCE

The ACCE wheel (Figure 1) shows the relation among each of the four components of evaluation and the elements of each component. At the hub are the clinical disorder being evaluated and the setting in which testing is done (e.g., classic cystic fibrosis in the setting of prenatal screening). The evaluation process begins only after the clinical disorder and setting have been clearly established. Specific questions 1 through 7 in Table 1 help to define the disorder, the setting, and the type of testing.

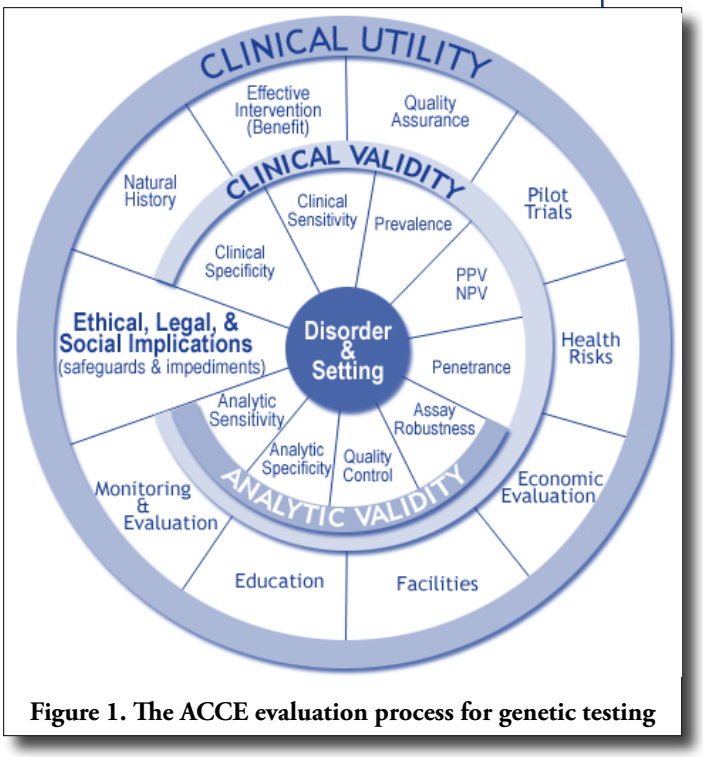


Figure 1. The ACCE evaluation process for genetic testing

The **analytic validity** of a genetic test defines its ability to accurately and reliably measure the genotype of interest. This aspect of evaluation focuses on the laboratory component. The four specific elements of analytic validity include analytic sensitivity (or the analytic detection rate), analytic specificity, laboratory quality control, and assay robustness. Analytic sensitivity defines how effectively the test identifies specific mutations that are present in a sample. Analytic specificity defines how effectively the test correctly classifies samples that do not have specific mutations (although the term "mutation" is used here, the terms "polymorphism" or "variant" may be more

appropriate for certain situations). Quality control assesses the procedures for ensuring that results fall within specified limits. Robustness measures how resistant the assay is to changes in pre-analytic and analytic variables. Specific questions 8 through 17 in Table 1 help organize the information available to document analytic validity.

The **clinical validity** of a genetic test defines its ability to detect or predict the associated disorder (phenotype). The four elements of analytic validity are all relevant to assessing clinical validity, along with six additional elements: clinical sensitivity (or the clinical detection rate), clinical specificity, prevalence of the specific disorder, positive and negative predictive values, penetrance, and modifiers (gene or environmental). Penetrance defines the relation between genotype and phenotype and allows the frequency of the clinical expression of a genotype (expressivity) to be determined. Clinical sensitivity measures the proportion of individuals who have a well-defined clinical disorder (or who will get the disorder in the future) and whose test values are positive. Clinical specificity measures the proportion of individuals who do not have the well-defined clinical disorder and whose test results are negative. Prevalence measures the proportion of individuals in the selected setting who have, or who will develop, the phenotype. The positive and negative predictive values more meaningfully define the genetic test performance by taking into account clinical sensitivity, clinical specificity and prevalence. Specific questions 18 through 25 in Table 1 help organize the information available to document clinical validity.

The **clinical utility** of a genetic test defines the elements that need to be considered when evaluating the risks and benefits associated with its introduction into routine practice. The natural history of the specific disorder needs to be understood so that considerations such as optimal age for testing might be taken into account. Another factor to be considered is the availability and effectiveness of interventions aimed at avoiding adverse clinical consequences (if no interventions are available, for example, testing may not be warranted). Quality assurance assesses procedures in place for controlling pre-analytic, analytic, and post-analytic factors that could influence the risks and benefits of testing. Pilot trials assess the performance of testing under real-world conditions. Health risks define adverse consequences of testing or interventions in individuals with either positive or negative test results. Economic evaluation helps define financial costs and benefits of testing. Facilities assess the capacity of existing resources to manage all aspects of the service. Education assesses the quality and availability of informational materials and expertise for all aspects of a screening service. Monitoring and evaluation assess a program's ability to maintain surveillance over its activities and make adjustments. Specific questions 26 through 41 in Table 1 help organize the information available to document clinical utility.

Ethical, legal, and social issues (ELSI) surrounding a genetic test are represented in Figure 1 by a penetrating pie slice, implying that the safeguards and impediments should be considered in the context of the other components. Specific questions 42 through 44 in Table 1 help organize the information available to document these issues.

Table 1. The ACCE Model's List of Targeted Questions Aimed at a Comprehensive Review of Genetic Testing [3]

Element	Component		Specific Question
Disorder/Setting			
		1.	What is the specific clinical disorder to be studied?
		2.	What are the clinical findings defining this disorder?
		3.	What is the clinical setting in which the test is to be performed?
		4.	What DNA test(s) are associated with this disorder?
		5.	Are preliminary screening questions employed?
		6.	Is it a stand-alone test or is it one of a series of tests?
		7.	If it is part of a series of screening tests, are all tests performed in all instances (parallel) or are only some tests performed on the basis of other results (series)?
Analytic Validity			
	Sensitivity	8.	Is the test qualitative or quantitative?
	Specificity	9.	How often is the test positive when a mutation is present?
		10	How often is the test negative when a mutation is not present?
		11.	Is an internal QC program defined and externally monitored?
		12.	Have repeated measurements been made on specimens?
		13.	What is the within- and between-laboratory precision?
		14.	If appropriate, how is confirmatory testing performed to resolve false positive results in a timely manner?
		15.	What range of patient specimens have been tested?
		16.	How often does the test fail to give a useable result?
		17.	How similar are results obtained in multiple laboratories using the same, or different technology?
Clinical Validity			
	Sensitivity Specificity	18.	How often is the test positive when a mutation is present?
		19.	How often is the test negative when a mutation is not present?
		20.	Are there methods to resolve clinical false positive results in a timely manner?
	Prevalence	21.	What is the prevalence of the disorder in this setting?
		22.	Has the test been adequately validated on all populations to which it may be offered?
		23.	What are the positive and negative predictive values?
		24.	What are the genotype/phenotype relationships?
		25.	What are the genetic, environmental or other modifiers?
Clinical Utility			
	Intervention	26.	What is the natural history of the disorder?
	Intervention	27.	What is the impact of a positive (or negative) test on patient care?
	Intervention	28.	If applicable, are diagnostic tests available?
	Intervention	29.	Is there an effective remedy, acceptable action, or other measurable benefit?
	Intervention	30.	Is there general access to that remedy or action?
		31.	Is the test being offered to a socially vulnerable population?
	Quality Assurance	32.	What quality assurance measures are in place?
	Pilot Trials	33.	What are the results of pilot trials?
	Health Risks	34.	What health risks can be identified for follow-up testing and/or intervention?
		35.	What are the financial costs associated with testing?
	Economic	36.	What are the economic benefits associated with actions resulting from testing?
	Facilities	37.	What facilities/personnel are available or easily put in place?
	Education	38.	What educational materials have been developed and validated and which of these are available?
		39.	Are there informed consent requirements?
	Monitoring	40.	What methods exist for long term monitoring?
		41.	What guidelines have been developed for evaluating program performance?
ELSI			
	Impediments	42.	What is known about stigmatization, discrimination, privacy/confidentiality and personal/family social issues?
		43.	Are there legal issues regarding consent, ownership of data and/or samples, patents, licensing, proprietary testing, obligation to disclose, or reporting requirements?
	Safeguards	44.	What safeguards have been described and are these safeguards in place and effective?

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Annex 2: The EGAPP Working Group

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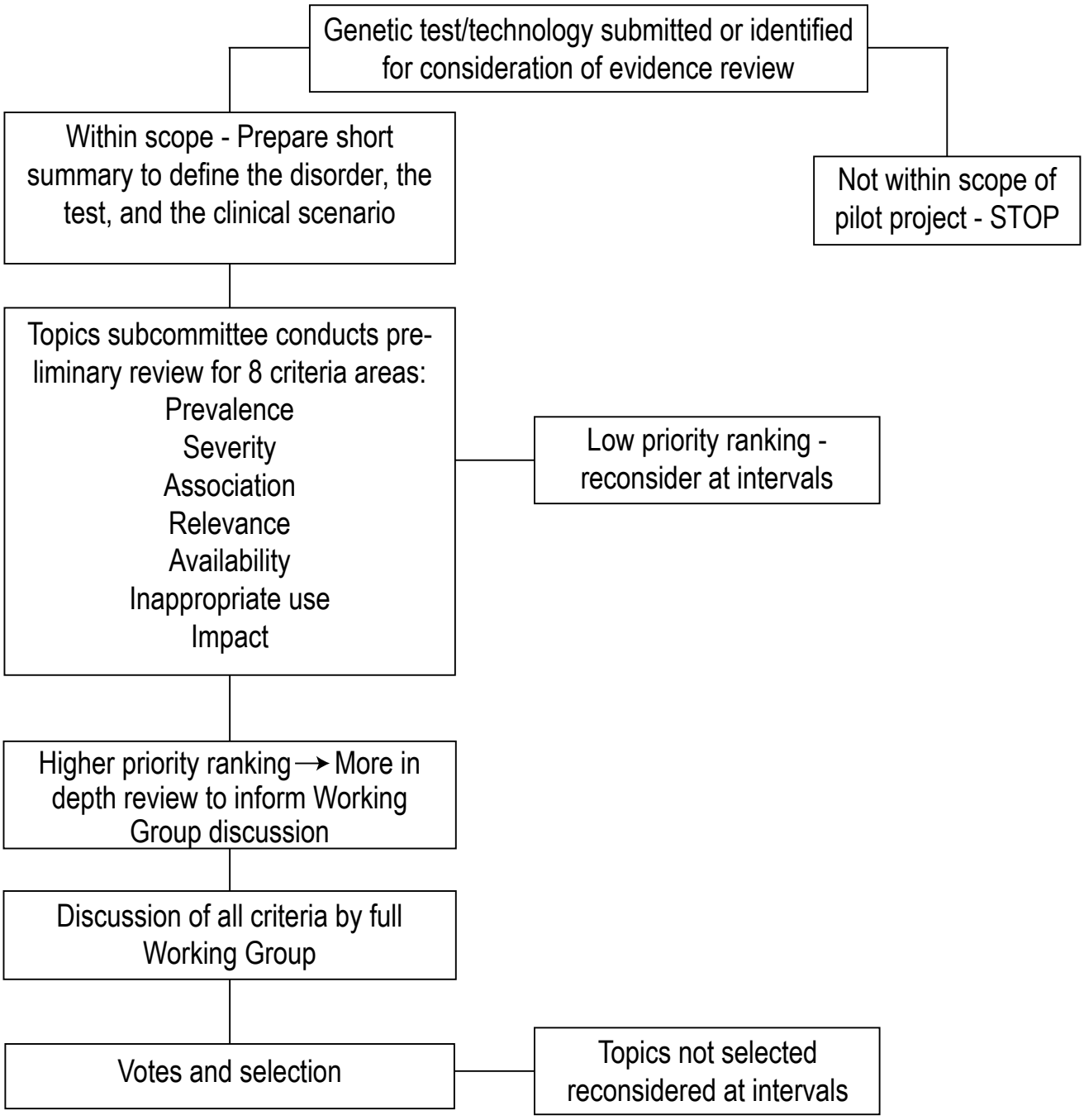
Annex 4: Process for Review, Prioritization and Selection of Topics for Evidence Review



Annex 5: Topics Under Consideration by the EGAPP Working Group

Disorder/Effect	Test to be Used*	Clinical Scenario	
		Target Population	Indication
Acne	*G6PD*	Individuals prior to treatment for acne	Treatment with dapsone
Acute Lymphoblastic Leukemia (ALL)	*TPMT*	Individuals prior to treatment for ALL	Treatment with 6-mercaptopurine
Acute Myeloid Leukemia (AML)	*FLT3*	Individuals prior to treatment for AML	Treatment with standard chemotherapeutic agents or tyrosine kinase inhibitor drugs
Alzheimer's Disease (AD)	*ApoE*	1) Dementia patients; 2) Individuals with a family history of dementia; and 3) General population	1) Diagnosis; 2) and 3) Predictive testing/ risk assessment
Asthma	*ADRB2*	Individuals treated for asthma	Treatment with albuterol
Breast Cancer (BrCa)	Multigene panel	General population of women	Predictive testing/risk assessment
Breast Cancer	*HER-2/neu*	Individuals prior to treatment for BrCa	Treatment with trastuzumab and progression/outcome prediction
Breast Cancer	*BRCA1/2*	Individuals diagnosed with BrCa and their family members	Management of individuals and early detection/prevention for family members
Breast Cancer	*CYP2D6*	Individuals prior to treatment for BrCa	Treatment with tamoxifen
Cardiac Channelopathies	Multigene panel	Clinical suspicion or family history of cardiac channelopathies	Diagnosis and management
Cardiovascular Disease (CVD)	*CYP450*	Individuals treated for CVD	Treatment with beta-blockers and proton pump inhibitor drugs
Cardiovascular Disease	*MTHFR*	Individuals with family history of CVD	Prevention and management
Type III Hyperlipoproteinemia	*ApoE*	Individuals with family history or clinical symptoms of CVD	Diagnosis of Type III hyperlipoproteinemia
Cardiovascular Disease	*ApoE*	General population	Predictive testing - Risk determination

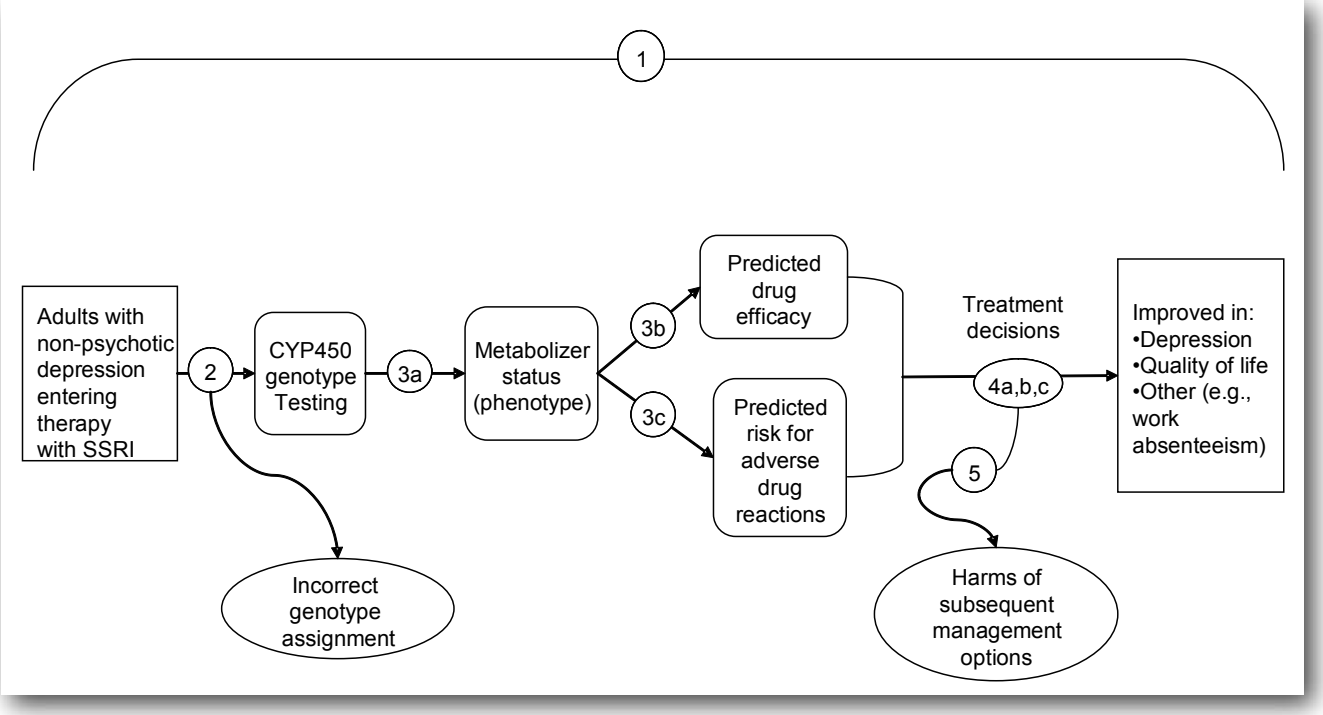
Disorder/Effect	Test to be Used*	Clinical Scenario	
		Target Population	Indication
Chronic Myelogenous Leukemia (CML)	*BCR/ABL*	Individuals with a diagnosis, clinical suspicion or family history of CML	Diagnosis and treatment monitoring
Colorectal Cancer (CRC)	fecal DNA	General population	Population screening
Cystic Fibrosis (CF)	*CFTR*	Individuals with clinical suspicion or family history of CF	Diagnosis and carrier testing
Deafness	*GJB1, GJB2, GJB3, GJB6*	Individuals who failed initial newborn screening hearing tests	Newborn screening follow-up
Diabetes, Type II	*PPARg2*	1) Individuals with clinical suspicion or family history of diabetes; 2) General population	1) Diagnosis; and 2) Predictive testing/risk assessment
Diabetes, Type II	*TCF7L2*	General population	Predictive testing/risk assessment
Mature-Onset Diabetes of the Young (MODY)	Multigene panel	Individuals with suspected or diagnosed MODY	Diagnosis and management
Hereditary Hemochromatosis (HHC)	*HFE*	1) Individuals with clinical suspicion of HHC; 2) General population	1) Diagnosis; 2) Predictive testing/risk assessment
Lung Cancer	*GSTM1*	Individuals with clinical suspicion of lung cancer	Predictive testing/risk assessment
Lung Cancer, Non-Small Cell (NSC)	*EGFR*	Individuals prior to treatment for NSC lung cancer	Treatment with tyrosine kinase inhibitor (TKI) drugs (gefitinib, erlotinib)
Malignant Hyperthermia	*RYR1*	High risk individuals prior to surgery	Management in surgery
Melanoma / Pancreatic Cancer	*p16*	General population	Predictive testing/risk assessment
Myeloproliferative disorders	*JAK2*	Individuals with clinical suspicion of myeloproliferative disorders	Confirm diagnosis
Pain Management	*CYP450*	Individuals treated for chronic or acute pain	Treatment with codeine and derivative drugs
Parkinson disease	*LRRK2*	Individuals with clinical suspicion or family history of Parkinson's disease	Diagnosis and treatment of individuals and family members
Periodontal disease	*IL-1*	General population	Population screening

Disorder/Effect	Test to be Used*	Clinical Scenario	
		Target Population	Indication
Prostate Cancer	*uPM3*	General adult male population	Population screening
Retinitis pigmentosa (RP)	*ARRP1*	Individuals with clinical suspicion or family history of RP	Diagnosis and carrier testing
Thrombophilia	*F5, F2*	Individuals with family history or clinical suspicion of thrombophilia	Prevention and management
Thrombophilia	*VKORC1, CYP2C9*	Individuals prior to treatment for thrombophilia	Treatment with warfarin

*variants or mutations in the identified gene or genes

Annex 6: Example Analytic Framework and Key Questions

Analytic Framework from the evidence report: *Testing for Cytochrome P450 Polymorphisms in Adults With Non-Psychotic Depression Treated With Selective Serotonin Reuptake Inhibitors (SSRIs)*. Numbers refer to the Key Questions shown below.



Key Questions

Question 1: (overarching question): Does testing for cytochrome P450 (CYP450) polymorphisms in adults entering selective serotonin reuptake inhibitor (SSRI) treatment for non-psychotic depression lead to improvement in outcomes, or are testing results useful in medical, personal, or public health decision making?

Question 2: What is the analytic validity of tests that identify key CYP450 polymorphisms?

Question 3a: How well do particular CYP450 genotypes predict metabolism of particular SSRIs? Do factors such as race/ethnicity, diet, or other medications, affect this association?

Question 3b: How well does CYP450 testing predict drug efficacy? Do factors such as race/ethnicity, diet, or other medications, affect this association?

Question 3c: How well does CYP450 testing predict adverse drug reactions? Do factors such as race/ethnicity, diet, or other medications, affect this association?

Question 4a: Does CYP450 testing influence depression management decisions by patients and providers in ways that could improve or worsen outcomes?

Question 4b: Does the identification of the CYP450 genotypes in adults entering SSRI treatment for non-psychotic depression lead to improved clinical outcomes compared to not testing?

Question 4c: Are the testing results useful in medical, personal or public health decision making?

Question 5: What are the harms associated with testing for CYP450 polymorphisms and subsequent management options?

Family History Public Health Initiative

Family History Public Health Initiative At A Glance

2002:
- NOPHG launched the Family History Public Health Initiative
- A national, multi-disciplinary team was formed to develop a research agenda and make recommendations for the development of a new family history tool, Family Healthware™

2003:
- A 10-article theme issue of the *American Journal of Preventive Medicine* was published from the 2002 Family History Workshop
- A contract was awarded to develop Family Healthware™

2004:
- NOPHG awarded funding to three research centers to evaluate Family Healthware™
- NOPHG partnered with DHHS on the Surgeon General's Family History Initiative to make Thanksgiving National Family History Day and to develop My Family Health Portrait, a simplified version of Family Healthware™

2005:
- Family Healthware™ tool was completed
- NOPHG hosted a workshop on tools and strategies for collecting family history for common diseases
- First patients enrolled in the Family Healthware™ evaluation study
- NOPHG launched a family history resource section on its website
- As part of the Surgeon General's Family History Initiative, NOPHG developed and mailed family history resource materials to health departments in all states and U.S. territories

2006:
- NOPHG started a project to develop guidelines on the legal and privacy issues affecting the use of family history information
- NOPHG facilitated a family history session at CDC's 2006 National Health Promotion Conference that highlighted family history activities in states
- Patent filed for Family Healtware™

2007:
- Family Healthware™ evaluation study ends (October)
- Modfications are made to Family Healthware™
- Family Healthware™ is made available for pilot studies and further research
- NOPHG is collaborating with NIH to merge Family Healthware™ and My Family Health Portrait

Family history is known to be a risk factor for many chronic diseases—including coronary heart disease, cancer, and diabetes—but its use in preventive medicine has not been emphasized compared with modifiable risk factors such as smoking and diet. Although clinicians are trained to collect family health history, they often fail to do so because of lack of time, inadequate reimbursement, and a lack of skill in interpreting family history information. Using data from the U.S. Healthstyles 2004 survey, we reported that 96% of Americans believe that knowing their family history is important to their health, yet only 30% have ever tried to gather and organize their family health history.

Most common diseases result from the interactions of multiple environmental factors in complex patterns that, despite progress in sequencing the human genome, are unlikely to be understood fully in the near future. In the meantime, family health history can be used as a low-cost, low-tech "genomic tool" to capture the interaction of genetic, environmental, and behavioral factors in determining disease risk.

Family History Public Health Initiative

Recognizing the potential of family history for disease prevention and health promotion, NOPHG started the Family History Public Health Initiative in 2002. The purpose of this initiative is to ensure that family history is recognized as an important risk factor for common chronic diseases such as cancer and diabetes, and to promote its use in programs aimed at reducing the burden of these diseases in the U.S. population. Activities of this initiative include:

- Studies to assess the validity and utility of using family health history as a public health strategy,
- Collaborations with federal, state and local public health agencies, universities, and private and not-for-profit organizations to develop and implement campaigns to increase public awareness about the public health importance of family history and to improve and facilitate the use of family history information by health professionals, and
- Development and dissemination of family history resources and tools through the CDC website, printed publications, news media, conferences, meetings, workshops, and other venues.

Key Accomplishments

Development of Family Healthware™

One of the objectives of the national multi-disciplinary Working Group formed by NOPHG was to conduct an extensive

review of existing family history tools and to develop criteria for the development of a new tool called Family Healthware™. This group consisted of experts in clinical genetics, behavioral science, health communication, preventive medicine, and epidemiology from the CDC, NIH, and other federal agencies, state public health programs, academia, and the health care community. Family Healthware™ would be used for assessing several levels of familial risk for common chronic diseases and to provide health advice according to risk level. The Working Group developed the following criteria for including diseases in the tool:

- Substantial public health burden,
- A clear case definition,
- High awareness of disease status among relatives,
- Accurately reported by relatives,
- Family history found to be an established risk factor,
- Population prevalence of family history as a risk factor can be estimated,
- Effective interventions exist for primary and secondary prevention, and
- Different recommendations according to familial risk groups may be possible.

The Working Group selected six diseases (coronary heart disease, stroke, diabetes, and colorectal, breast, and ovarian cancer), and worked with a major commercial communications firm and a software development company to develop the data collection instrument, risk algorithms, and patient report for Family Healthware™.

Family Healthware™ was completed in September 2005. This web-based tool provides users with a familial risk assessment and a "prevention plan" containing personalized recommendations for lifestyle changes and screening recommendations. The tool collects data from the users on health behaviors (e.g., smoking and exercise), screening tests (e.g., blood cholesterol and mammography), and disease history of first- and second-degree relatives. A first set of algorithms assesses the familial risk for each disease. A second set of algorithms uses the familial risk combined with self-reported data on health behaviors and screening results to generate personalized prevention messages.

The goal was to gather the minimum amount of information to classify people into risk groups. The current underlying scheme classifies individuals into 3 risk groups – average, moderate, and high. These categories are determined mainly by the number and type of relatives affected as well as their age at disease onset (Scheuner MT, et al. Am J Med Genet 1997; 71: 315-324.) The risk classification can be used to guide and inform prevention activities. People at average risk would be encouraged to adhere to standard public health recommendations for maintaining good health. People with an increased risk (high or moderate) could be given more personalized prevention recommendations such as more intense lifestyle changes or the adoption of early detection strategies. People at high risk could also be referred to a genetic counselor or other appropriate specialist.

Evaluation Study of the Family Healthware™ Tool

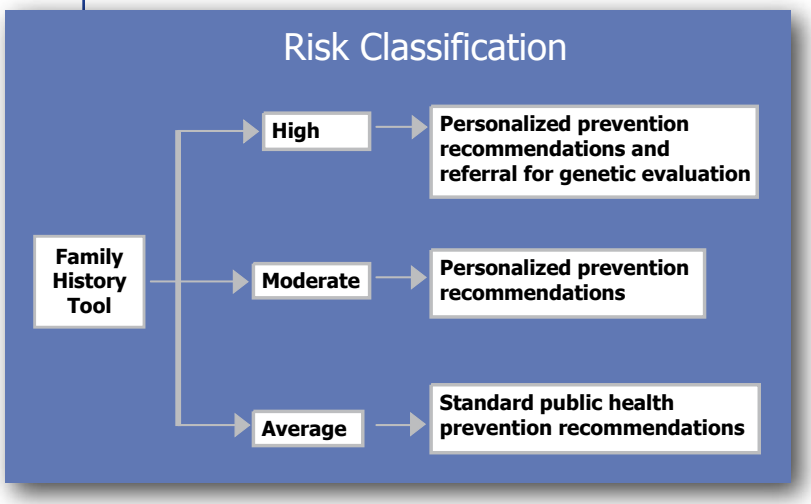
In 2005, NOPHG awarded funding to three research centers at the University of Michigan School of Medicine, Evanston Northwestern Healthcare Research Institute, and Case Western Reserve University School of Medicine to evaluate the clinical utility of the Family Healthware™ tool. These universities are working with a network of primary care practices to determine if personalized prevention messages according to familial risk will motivate people at risk to change their lifestyle or screening behaviors within six months of using Family Healthware™. The study began enrolling patients in December 2005, and data collection was completed in fall 2007.

Campaign for National Family History Day

NOPHG collaborated with DHHS on the Surgeon General's Family History Initiative, which is a national campaign that marked Thanksgiving as National Family History Day and included the development of a web-based tool called "My Family Health Portrait"— a simplified version of CDC's Family Healthware™. CDC delivered packets of family history resource materials to chronic disease and genetics experts in health departments of every U.S. state and territory. These materials were designed to assist local health departments in their efforts to educate people about the importance of collecting their family health history. In addition, CDC developed a family history website for the public, at http://www.cdc.gov/genomics/public/famhist.htm, that includes fact sheets, presentations, case studies, news articles, relevant links, and other resources.

Family History Products

CDC collaborated with the American Academy of Family Physicians (AAFP) to develop web-based modules on family history for the Annual Clinical Focus (ACF) on Genomics.



NOPHG developed a brochure on family history of diabetes. The brochure was developed at a 6th-8th grade literacy level and is available in English and Spanish. The brochure is accessible through NOPHG's website: http://www.cdc.gov/genomics/public/famhix/fs.htm.

Current Activities

- The evaluation of Family Healthware™ is currently in its final stages (data editing and reporting of baseline results, collection of follow-up data). Six manuscripts are in preparation, one of which will cover the methodology and design of the study. The other

manuscripts will cover health risk perceptions according to family history for the chronic conditions included in Family Healthware™.

- The Family History Initiative will use NHANES data to assess the contribution of family history to the risk of some chronic diseases in the U.S. population. A manuscript on family history and risk of diabetes in the U.S. population has been accepted for publication and a manuscript on osteoporosis is under CDC clearance. Basically, the common method in these manuscripts is to stratify the U.S. population in three levels of familial risk (average, moderate, and high) and then test the association of this stratification with the prevalence of the disease. In diabetes, for example, a high familial risk is highly associated with a high prevalence of diabetes.
- A methods paper on the development of Family Healthware™ is being completed.
- The Family History Team, in collaboration with the Michigan Center for Public Health and Community Genetics, developed the Family History Project to analyze the legal and privacy issues affecting the use of family history information by clinicians, public health practitioners, and the general public. A guide addressing these issues for consumers and health care providers and a manuscript are in progress.

Next Steps

In the immediate future, the Family History Initiative will focus on 1) continuing the examination of familial risk for common chronic diseases in the U.S. population; 2) publishing and disseminating the results of the evaluation of the Family Healthware™ tool; 3) promoting the inclusion of more detailed family history questions in large health surveys routinely conducted by CDC and other entities; 4) collaborating with other CDC and HHS units for the inclusion of family history as another risk factor to consider in public health campaigns aimed at reducing the burden of disease.

Long-term plans for the Family History Initiative are to promote 1) the use of Family Healthware™ in research, public health practice, and primary care settings; 2) a more general use of family history in the assessment of risk for chronic diseases (for example, by improving the algorithms currently used to assess risk for diabetes, heart disease, and cancer); 3) a more formal use of family history in the health care system (for example, making family history part of electronic medical records).

Selected Publications

1. Yoon PW, Scheuner MT, et al. Can family history be used as a tool for public health and preventive medicine? *Genet Med* 2002; 4(4):304-310.
2. Yoon PW, Scheuner MT, Khoury MJ. Research priorities for evaluating family history in the prevention of common chronic diseases. *Am J Prev Med* 2003;24(2):128-135.
3. Hunt SC, Gwinn M, Adams TD. Family History Assessment : Strategies for Prevention of Cardiovascular Disease. *Am J Prev Med* 2003;24:136-142.
4. McCusker ME, Yoon PW, Gwinn M, et al. Family History and Cardiovascular Disease Risk-Reducing Behaviors. *Genet Med* 2004;6(3):153-158.
5. Yoon PW, Scheuner MT, Gwinn M, et al. Awareness of family health history as a risk factor for disease, United States, 2004. *MMWR* 2004; 53:1044-1047.
6. Hariri S, Yoon PW, Qureshi N, et al. Family history of type 2 diabetes: a population-based screening tool for prevention? *Genet Med* 2006 Feb;8(2):102-8.
7. Ramsey SD, Yoon PW, Moonesinghe R , et al. Population-based Study of the Prevalence of Family History of Cancer: Implications for Cancer Screening and Prevention. *Genet Med* 2006 Sep;8(9):571-5.
8. Scheuner MT, Whitworth WC, McGruder H, Yoon PW, et al. Expanding the definition of a positive family history for early-onset coronary heart disease. *Genet Med* 2006;8(8):491-501.
9. Scheuner MT, Whitworth WC, McGruder H, Yoon PW, et al. Familial risk assessment for early-onset coronary heart disease. *Genet Med* 2006;8(80:525-31.
10. Hariri S, Yoon PW, Moonesinghe R, et al. Evaluation of family history as a risk factor and screening tool

for detecting undiagnosed diabetes in a nationally representative survey population. *Genet Med.* 2006 Dec;8(12):752-759.
11. Valdez R, Greenlund K, Yoon PW. Is family history a useful tool to detect children at risk for chronic disease and to enrich prevention campaigns aimed at the pediatric population? *Pediatrics* (in press).
12. Scheuner MT and Yoon PW. The use of family history in clinical medicine and public health. In: Handbook of Genomic Medicine. Willard H, Ginsburg G, eds. New York: *ELSEVIER* (in press).
13. Valdez R, Yoon PW, Liu T, Khoury MJ. Family history and prevalence of diabetes in the U.S. population: 6-year results from the National Health and Nutrition Examination Survey (NHANES, 1999-2004). Diabetes Care (in press).

Public Health Genomics Capacity Building

State Health Departments

State and local health departments serve an essential and unique role in disease prevention and health promotion in the U.S. These crucial entities have a legal mandate for infectious disease control and prevention, and are responsible for core public health functions, such as surveillance, epidemiology, laboratory services, and environmental sciences. Their strong foundation in establishing public, private, and government partnerships and coordinating activities allows them to reach a broad range of audiences to directly address health problems. Given their scope and capacity-development orientation, health departments are well-suited to provide leadership and coordination for integrating genomics knowledge and tools into public health programs for disease prevention and health promotion.

In July 2003, cooperative agreements were established with state health departments, which included seven separate funding components (tobacco; nutrition, physical activity, and obesity; WISEWOMAN; oral disease; arthritis; BRFSS; and genomics). The cooperative agreements were implemented with a five-year funding period. Four awardees were selected: Michigan, Minnesota, Oregon, and Utah. A major focus of the cooperative agreements to date has been the integration of genetic risk factors and family history into core chronic disease prevention programs and state public health functions.

NOPHG provides specific technical and administrative assistance to the four states in developing and expanding their public health genomics capacity. State activities focus on building infrastructure and partnerships, training the public health workforce, educating the general public, using surveillance surveys to assess genomics integration, and promoting genomics screening tools.

Genomics Programs

Michigan Department of Community Health

The Public Health Genomics Program of the Michigan Department of Community Health (MDCH) is located in the Division of Genomics, Perinatal Health, and Chronic Disease Epidemiology in the Bureau of Epidemiology, and is responsible for implementing Michigan's State Genetics Plan, which was established in 2002. The goals of this plan are to 1) increase genetic literacy in the State of Michigan, 2) assess the public health impact of heritable conditions and the utilization of genetic services, 3) improve access to genetic information, prevention strategies and services, 4) promote early identification and treatment of individuals with birth defects, heritable disorders or genetic susceptibilities, throughout the life cycle, 5) identify best practices and promote a policy framework to assure high quality services, and 6) promote appropriate public health responses to advances in genomic medicine and technology. The objectives of the cooperative agreement fall under these goals.

The Michigan Genomics program is comprised of 19 staff from the newborn screening and public health genomics units. Four of these staff work full-time on the objectives of the cooperative agreement. Also included among the staff are a program manager, genomics epidemiologist, genomics educator, and gene-environmental specialist, who have diverse backgrounds in genetic counseling, epidemiology, public health, environmental sciences, and education.

In addition to the cooperative agreement, the Michigan Genomics program also receives funding from the Genetic Services Branch of the Health Resources and Services Administration (HRSA). Support is also provided by partners within the state health department and external organizations.

Partnerships

The Michigan Genomics program has close partnerships with the chronic disease prevention programs within the state health department, including arthritis, cancer, cardiovascular disease, dementia, diabetes, osteoporosis, and tobacco. The program also works collaboratively with the state laboratories, vital records, epidemiology, immunization, infectious disease, environmental health, and maternal and child health; Children's Special Health Care Services (CSHCS); School Health; Office of the Surgeon General; Medicaid; and Women, Infants, and Children (WIC). Examples of genomics integration include:

- **Cardiovascular disease**: 1) Since 2004, the Michigan Genomics program has been developing a new project to address sudden cardiac death (SCD) of the young in Michigan. The goal of this project is to identify public health and medical system changes, and family-based interventions to increase awareness, screening, and treatment for relatives potentially at risk. 2) MDCH receives CDC funds to implement the WISEWOMAN program in Michigan, which focuses on reducing the burden of cardiovascular disease in women of low socioeconomic status and low health insurance coverage. The Michigan genomics program collaborates with the WISEWOMAN program by integrating family history into risk assessments and educational materials on cardiovascular disease.

- **Diabetes:** 1) The Michigan Genomics program has developed two educational design modules for diabetes and genetics and family history. The first module includes information on genetics and genomics, and the role of genomics and family history in diabetes. The second module includes the same information as the first module, and also resources on genomics and family history in relation to diabetes, and discusses the importance of well-controlled diabetes for women of reproductive age, and the use of informed consent and genetic technology for diabetes. 2) The program collaborates with three diabetes programs called Healthy Hair, Dodge the Punch, and Healthy Families Start with You, which were initiated by the National Kidney Foundation of Michigan. The goal of these programs is to prevent kidney disease among African Americans by raising awareness of diabetes and high blood pressure and risk factors, including genetics and family history, and encouraging individuals to take action.

- **Newborn screening program:** The Michigan Genomics program and the Newborn Screening Program are leading a new project to develop a repository of neonatal specimens collected from the general population in Michigan from 1978 to 1999 (21½ years). Main collaborators of this project are the University of Michigan and Michigan State University. Potential analyses of this repository include examining specimens for associations between chemical contaminants and health outcomes and linking data with public health registries in the state (e.g., birth defects, cancer, BRFSS).

The Michigan Genomics program also partners with a broad range of organizations throughout the state, including hospitals, health plans, local public health departments, faith-based groups, health care providers, K-12 schools and universities, research groups, mental health groups, policy makers, media, private sector, and support and advocacy groups. The Michigan Genomics program has ongoing activities with the following partners: Michigan Cancer Consortium, University of Michigan Center for Public Health and Community Genomics, Michigan Cancer Genetics Alliance, Oakwood Health Systems, and Michigan State University. Some of these activities include improving health care provider tools for collecting family history information, integrating family history risk assessments into disease detection programs, developing a model for implementing genomics programs in other state health departments, developing educational materials on chronic diseases and genetics and family history, conducting community outreach, and planning and implementing scientific conferences.

Surveillance and Other Data Collection Activities

Since 2004, the Michigan Behavioral Risk Factor Surveillance System (BRFSS) has included genomics questions. These include: four questions on family history in 2004, seven questions on family history (general health, and specific to colon and rectal cancer) in 2005, questions on direct-to-consumer marketing (DTC) in 2006; and two questions on sudden cardiac death of the young in 2007. The Michigan Genomics program plans to submit a manuscript on the results of colorectal cancer and family history to MMWR this summer.

In 2005, the Michigan Genomics program collaborated with the Michigan Cancer Registry to conduct medical chart reviews in 23 clinics randomly selected throughout the state. 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. Based on the findings, 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 collect and record their family history information routinely and to share this information with their physicians.

The Michigan Genomics program, in collaboration with an insurance provider, conducted another medical chart review project in 2005, which included 250 medical charts from 50 physicians. These charts showed similar findings on the presence or absence of family history information. Another chart review was conducted in 2006, using a revised data collection tool which had been expanded to include questions about physician referrals for genetic services, use of folic acid, and birth defects.

Minnesota Department of Health

The Chronic Disease Genomics Project of the Minnesota Department of Health (MDH) is located within the Division of Health Promotion and Chronic Disease. One full-time person, with experience and educational background in genetic counseling and public health, works exclusively on activities of the genomics project. Part-time student interns from the University of Minnesota and health educators and web designers in the state health department also provide support.

The primary source of funding for the Minnesota Genomics program is through the cooperative agreement. Support is also provided by partners within the state health department and external organizations. To strengthen the efforts of the genomics program, contracts have been established, using cooperative agreement funds, with the Center for Public Health Education and Outreach at the University of Minnesota (UMN) to develop educational materials and websites and organize workshops and meetings.

Partnerships

The Minnesota Genomics program partners with various chronic disease prevention programs within the state health department, including arthritis, asthma, cancer, cardiovascular disease, and diabetes. Some examples of collaborative activities include:

- **Cardiovascular disease:** The Minnesota Genomics program collaborates with the WISEWOMAN program by integrating family history into risk assessments and educational materials on cardiovascular disease. It also provides a "hotline" for women who have questions about family history and genetics.

- **Cancer:** The Sage Screening Program is a statewide, comprehensive prevention program for breast and cervical cancer among women who are 40 years old or older and have low socioeconomic status and

limited or no health insurance coverage. The Minnesota Genomics program collaborates with SAGE by integrating family history into its educational activities, and publishes articles on cancer and family history in the newsletter SAGE Advice, which is written for clinicians.

The Minnesota Genomics program successfully facilitated the integration of genomics into the comprehensive state cancer control plan, which provides recommendations to policy makers, planners, providers, and advocates.

A key external partnership of the Minnesota Genomics program is the Center for Public Health Education and Outreach at the University of Minnesota (UMN). In 2006 and 2007, Minnesota Genomics staff collaborated with UMN on the planning and implementation of the annual Summer Public Health Institute, which included courses on public health genomics. The 2007 Institute also included a roundtable discussion featuring keynote speaker Muin Khoury, MD, PhD, director of NOPHG, and other experts in public health genomics. More than 300 participants from 28 states and four countries enrolled in over 50 courses offered by the Institute.

Data Collection Activities

In 2006, the Minnesota Genomics program collaborated with a local health plan to conduct a review of 12,263 electronic medical charts to evaluate the quality of family history data concerning four types of cancer (breast, colon, prostate, and ovarian) captured from January 2004 to October 2005. More than 40% of the charts documented family history. Of charts with family history, 39% included documentation for cancer. For the four cancers, less than 4% included any information on age of onset and death.

In 2006, the Minnesota Genomics program led a project to systematically review established guidelines (e.g., by the U.S. Preventive Services Taskforce, the American Cancer Society, and other organizations) and to analyze research studies that summarized epidemiological data on the relationship between modifiable and non-modifiable risk factors (e.g., family history) and chronic diseases (e.g., asthma, cardiovascular disease, cancer, diabetes). This information was used to develop fact sheets on chronic diseases and family history for the public, which were disseminated widely and adopted by the chronic disease program in MDH and in other state genomics programs. The Minnesota Genomics program plans to submit the findings of this review for publication in peer-reviewed journals.

Oregon Department of Human Services

The Genomics Program of the Oregon Department of Human Services (ODHS) is located in the Office of Family Health in the Public Health Division. The goal of the program is to implement the goals of the Oregon strategic plan for genetics and public health, which include reducing morbidity and mortality from inherited conditions and birth defects, improving quality of life for individuals and families impacted by inherited conditions and birth defects, and empowering people to make informed decisions about genetics and health.

The Oregon Genomics program is comprised of five part-time staff, with experience and education in genetic counseling, public health, epidemiology, policy, and graphic and information design. The program also receives support from the Oregon Health and Science University and other institutions. The primary source of funding for the Oregon Genomics program is from the cooperative agreement with NOPHG. Support is also provided by partners within the Oregon state health department and external organizations.

Partnerships

The Oregon Genomics program is engaged in activities with various chronic disease prevention programs within

the state health department, including asthma, cancer, and diabetes. Some examples of collaborative activities include:

- **Diabetes:** Over the past year, the Oregon Genomics program has actively worked with the state chronic disease prevention programs to incorporate genomics into existing public health surveillance surveys. For example, family history questions for diabetes were included in BRFSS, and family history questions for asthma were included in PRAMS II. The Oregon Genomics program and the state chronic disease prevention programs have published articles in peer-reviewed journals and other publications, and presented posters on the results of these surveys.

- **Cancer:** The Oregon Genomics program facilitated the inclusion of genomics into Oregon's Comprehensive Cancer Control Plan. The plan includes genomics goals for the state, and the priorities of the Oregon genomics program to achieve these goals. Specific objectives fall under prevention, such as "Increase the proportion of Oregonians who are aware of genetic factors that increase individual cancer risk." Indicators for this objective are: 1) number of health care provider training sessions, and 2) type and number of participants. Information collected from the family history project, conducted in collaboration with the Kaiser Permanente Northwest and with primary-care providers, will be used to achieve the genomics objective for the Comprehensive Cancer Control Plan.

The Oregon Genomics program also collaborates with external partners, such as the Oregon Partnership for Cancer Control, Cystic Fibrosis Newborn Screening, and clinical genetic providers.

Surveillance and Other Data Collection Activities

Since 2005, the Oregon Genomics program has routinely included genomics questions in BRFSS. The 2005 survey questions inquired about health care provider practices and family history and perceived risk. In 2006, questions on diabetes screening among non-diabetics, genetics knowledge, and direct-to-consumer marketing were included. In 2007, questions will focus on family history of cardiovascular disease versus diabetes, and direct-to-consumer marketing. The genomics program also included questions in the PRAMS II survey inquiring about health care provider practices and family history, diabetes, and asthma.

In 2005, the Oregon Genomics program conducted the "Provider Family History Project" with Kaiser Permanente Northwest (KPNW) to learn about primary-care provider practices for collecting and using family history of patients, and to assess the use of CDC's family history tool. The results of this project were presented to NOPHG and other partners, and a manuscript is currently being developed for a peer-reviewed publication. The Oregon Genomics program intends to follow up with the primary-care providers involved in this project, and identify needs and areas for improving the collection and use of family history information.

Utah Department of Health

The Chronic Disease Genomics Program of the Utah Department of Health (UDOH) is located in the Division of Community and Family Health Services in the Bureau of Health Promotion. A part-time program manager, a full-time genomics educator, and a part-time epidemiologist work on program activities. An external advisory group provides direction for genomics strategies and activities in Utah.

In February 2006, the Utah Genomics program started the Family Health History Taskforce to position Utah as a leader in family history. This Taskforce is made up of 65 individuals with backgrounds in genealogy, genetic epidemiology, academics and research, and also community members, and other individuals interested in family history. Members participate in committees (e.g., public awareness, clinical applications, methodology

and research, etc.). The Taskforce meets quarterly, and the committees meet monthly.

The primary source of funding for the Utah Genomics program is through the cooperative agreement with CDC. Other offices in the bureau share resources with the Utah genomics program on communications and contract management.

Partnerships

The Utah Genomics program is engaged in activities with various chronic disease prevention programs within the state health department, including asthma, cancer, and diabetes. Some examples of collaborative activities include:

- **Asthma:** In April 2006, the Utah Genomics program participated in a workshop with the asthma program to develop genomics priorities and activities for asthma, which included pharmacogenomics, family history, and ethical, legal, and social issues. Activities focused on: 1) identifying partners, 2) developing fact sheets on genetics, genomics, and pharmacogenomics, 3) offering genomics workshops, 4) developing public awareness campaigns, and 5) developing surveys. These priorities and activities were included in the new five-year Utah Asthma Plan to be released in 2007.

- **Cancer:** The Utah Genomics program successfully integrated genomics into the early detection and prevention component of the state Cancer Plan. The objective is to increase the number of families and providers who appropriately utilize family health histories. Strategies to achieve this objective are: 1) public education on family history, 2) provider education on family history, 3) address issues of discrimination and confidentiality, 4) identify moderate and high risk populations, and 5) increase moderate and high risk individuals who obtain appropriate screening and referral to genetic services. To support continued efforts at genomics integration, the program participates in routine cancer coordination meetings.

The Utah Genomics program also has key partnerships with external organizations, such as Intermountain Health Care and the Genetic Science Learning Center.

Surveillance and Other Data Collection Activities

Since 2005, genomics questions have been included in the BRFSS. In 2006, genomics questions focused on asthma, and in 2007, questions focused on diabetes and family history. In 2005, the Utah Genomics program included questions in the Youth Risk Behavior Surveillance System (YRBSS). This survey is conducted every other year, and it includes national, state, and local school-based surveys of representative samples of 9th through 12th grade students.

Centers for Genomics and Public Health

To address the need to build public health genomics capacity in chronic disease prevention and health promotion programs, NOPHG collaborated with the Association of Schools of Public Health to establish the first Centers for Genomics and Public Health in 2001. These centers were located in the schools of public health at the Universities of Michigan, North Carolina, and Washington. The goal was to establish regional hubs of expertise in genomics and population health that built on and complimented existing university programs and developed partnerships with state and local health departments and other agencies and organizations. These partnerships would provide a foundation for a national network of resource centers that could develop the capacity for responding to future needs and opportunities related to genomics.

In 2005, NOPHG awarded funding to two of the centers (Universities of Michigan and Washington) to

continue their work in public health genomics for a four-year cooperative agreement period. The cooperative agreements are for non-research activities according to CDC policies. The centers' activities focus on:

- Providing technical assistance to regional, state, and local public health agencies and other public health organizations,
- Providing competency-based training for the public health workforce, focusing on practical applications of genomics in population health,
- Identifying and responding to opportunities to serve as credible and impartial providers of information on genomics and population health for the health community, policy makers, and general public,
- Participating in collaborative activities with CDC and other partners, and
- Evaluating processes, achievements, and impact of the centers' activities.

University of Michigan

The Center for Public Health and Community Genomics was established at the University of Michigan School of Public Health, in collaboration with the University of Michigan Medical School and the Michigan Department of Community Health. The Center has nine part-time staff.

Michigan's Center has three broad goals, with an underlying emphasis on the ethical, legal, and social issues associated with the application of genomics to public health, as well as the importance of engaging the community at large in the development and implementation of public health genetics programs. These goals are to:

- Increase the genomics and public health knowledge base, with a special focus on cardiovascular disease,
- Provide technical assistance to state, regional, and local public health entities in the integration of genomics into public health practice, and
- Train members of the current and future workforce in genomics.

In addition to the funds from NOPHG, the Center also receives funds from the Life Sciences Values and Society Program for projects that examine the ethical, legal, and social issues associated with the application of genomics in public health practice. In 2006, the Center was awarded a contract by NIH's National Human Genome Research Institute to develop and implement the Mid-West Community Genetics Forum in 2007.

Key Accomplishments and Current Activities

Family History Law Project: In partnership with NOPHG, Michigan's Center conducted a comprehensive literature review of clinical genomics, family history, genetic risk, and the ethical, legal, and social implications of family history; an assessment of the guidance materials that have already been developed; a review of family history tools currently in use; and an analysis of laws and ethical principles affecting the use of family history. Information about this project was presented at the Statewide Symposium of Family History in Primary Care Practice in September 2006. Two guidebooks (one for primary care physicians and one for patients) were written to facilitate the use of family history as a part of the clinical encounter. A series of manuscripts, which will explore the legal and ethical aspects of family history in more depth, are under development.

Community-based models: In partnership with MDCH, the Center developed a community-based model of an intersectoral approach to the use and dissemination of family history.

State public health genomics model: The Center is developing a model for other state health departments to use in creating their own public health genomics programs. This model will include strategies, best practices, and a database of training tools.

Academic/practice partnerships: The Center developed a survey which will look at the aspects that make up a partnership model. This survey, as well as a series of interviews that will follow it, will serve as a catalyst to further academic/practice partnerships in the Midwest region.

Genetics/genomics curriculum: The Center developed a new curriculum addressing molecular genetics and genomics which is in being used in public high schools in Flint and Detroit. A parallel series of activities engages parents and other community members in helping to shape the curriculum to ensure relevance to the lives of the students and their parents; improve the awareness and appreciation of the community of genomic science and research; and strengthen student learning and interest in science through joint activities of students and their parents.

SAGE: The Center collaborated with NOPHG to develop and convene a Stakeholders' Advisory Group on EGAPP (SAGE) and assessed the role of stakeholders in implementing evidence-based practice standards.

Michigan neonatal biotrust: The Center is partnering with the Michigan Department of Community Health and the Life, Sciences, and Society Program to develop policy and community engagement background materials and recommendations.

Public health genomics APHA forum: The Center led the successful effort to establish a Public Health Genomics Forum within the American Public Health Association (APHA). The forum will bring together academics, practitioners, and community partners who desire to further genomics in public health; express public health principles in genomic research, practices, and teaching; and sponsor scientific sessions at APHA.

Conferences and meetings: In April 2008, the Michigan Center will host three meetings: an annual States, Centers and NOPHG meeting, a Public Health Genomics Grand Rounds, and a Regional Genomics Conference. The Grand Rounds will focus on new and emerging genomic tools and applications for public health practice. This event will be web cast throughout the U.S. and internationally. The Regional Genomics Conference will involve public health agencies and universities from the Region V states (Michigan, Illinois, Indiana, Ohio, Minnesota, and Wisconsin) and other states and focus on facilitating partnerships to further genomics in public health practice and in university-based public health education.

University of Washington

The Center for Genomics and Public Health at the University of Washington has one full time and seven part time staff members. The primary goal of the Center is to integrate advances in genetic technology into public health practice and offer research and educational opportunities for public health students and professionals.

University of Washington
Center for Genomics
and Public Health

Key Accomplishments and Current Activities

Family history: 1) Washington's Center integrated family history questions into the Washington STEPS program and into a new project focused on preterm birth in Washington. 2) Center staff has developed several publications focused on family history, including diabetes and asthma. Several additional manuscripts are in process, including a cost-utility analysis using family history information, sensitivity and specificity of relatives' reports of family history information, and social-cultural issues in collecting

family history information in Pacific Islanders and Japanese Americans. 3) Staff assisted in developing and reviewing family history questions and fact sheets for several state genomics programs, including BRFSS and PRAMS.

Educating the public health workforce: 1) The Center developed a Web-based CME module for physicians on colorectal cancer in collaboration with the Center for Health Care Education. 2) The center director frequently makes keynote addresses and give talks at professional conferences, meetings, and seminars. Topics have included family history, obesity, genomics and public health, genetics in diabetes, genetic testing and public health policy, and genetic epidemiology. 3) Eight students working on masters or doctoral degrees work part time at the Center. Center-trained students now hold positions in the Washington State Department of Health, Washington State Disability and Health Program, Puget Sound Health Alliance, and Washington State Newborn Screening Program.

Publications and reviews: Center staff members have worked with several partners to develop and submit abstracts and manuscripts based on collaborative work, including the Oregon genomics program's work focused on the Stages of Change Model as it relates to integrating genomics into public health practice; Academic-Practice Partnerships; and Asthma Genomics: Implications of Public Health. They have also published three HuGE reviews and have three more in process. Several products focused on obesity have been produced. Two additional manuscripts are in process, one of which evaluates the influence of socioeconomic factors in response to a genetic testing direct-to-consumer marketing campaign in collaboration with CDC; the other focuses on ethical issues in newborn screening.

***Spotlight* newsletter:** The Center produces and distributes a newsletter called *Spotlight.* The first issue on family history was distributed statewide in Michigan and used by the Minnesota Department of Health in a press release on family history activities. Locally, the Center distributes this newsletter at 16 city libraries and a large medical practice that has eight clinical sites.

Meetings: The Center hosted a strategic planning retreat in April 2007 for the four CDC-funded States, the Michigan Center, and NOPHG to discuss priority activities and plans for the upcoming year. One of the significant outcomes of the retreat is a plan for publication of several individual state and collaborative articles in peer-reviewed journals and *Morbidity and Mortality Weekly Report* (*MMWR*) on public health genomics. The Center will coordinate a large part of this work over the next year.

Next Steps

NOPHG will continue funding the four state health departments through their final year of funding, which ends in June 2008. NOPHG will also continue to support the two Centers through their final year of funding, which ends in September 2008. In this last year of funding, the States, Centers, and NOPHG will collaborate on writing publications on the results of the states' surveillance and health care provider activities. Two publications on BRFSS data on family history will be submitted to *MMWR* this winter.

For April 2008, the States, Centers, and NOPHG are planning an annual meeting, which will be hosted by the Michigan Center. This meeting will be in conjunction with two other meetings: a Public Health Genomics Grand Rounds and Regional Genomics Conference, also to be hosted by the Michigan Center.

3.0 Vision for the Next 10 Years of Public Health Genomics at CDC

Advances in genomics have led to mounting expectations for the translation of genomic research into applications for health care and disease prevention. A comprehensive agenda for translation research and surveillance is needed to move human genome discoveries into health practice in a way that maximizes health benefits and minimizes harm to individuals and populations. Currently, hundreds of thousands of genetic variants are being evaluated for association with common, chronic diseases. Research is accelerating the use of new biomarkers derived from gene expression, proteomic, and other "omic" technologies. The number of genetic tests used in clinical practice and research is increasing. In addition, family medical history is receiving renewed attention as a genomic and public health tool for disease detection and prevention.

As we look forward to the next decade of public health genomics at CDC, we should consider current challenges, formulate a clear vision for where we want to go, and develop and expand collaborative initiatives that can advance the vision.

Current Challenges in Public Health Genomics

In the past decade, NOPHG has established public health genomics as an interdisciplinary field and developed strong collaborations to begin closing the gap between gene discoveries and population health benefits. This endeavor still faces important challenges, including the following:

1. The "investment gap": Currently, most of the federal investment in genomics is in basic science, with far less dedicated to translating research findings into population health benefits.
2. The public health role: Skeptics have argued that except for newborn screening, public health has very little to do with genomics, which belongs squarely in the clinical domain. The emergence of public health genomics worldwide over the past decade has helped demonstrate the value of a population health perspective in weighing the benefits and harms of new technologies. Important roles for public health genomics include: assessing and assuring the delivery of validated genomics technologies and services to all segments of the population; and assessing the value added by genomics to current approaches to disease prevention and health promotion.
3. Genetic diseases vs. genetic information: The traditional medical genetics model focuses on the management of rare, single-gene disorders. Collectively, these genetic diseases are estimated to account for perhaps 5% of the burden of human disease; however, genetic information is relevant to a wide variety of common chronic diseases, as well as illness due to infectious or environmental exposures. A major challenge for public health is to translate the complexity of information on gene-environment interactions into preventive interventions.
4. Slow progress in health applications of genomics: In spite of recent excitement about genetic discoveries using genome-wide association studies, the genomics field has not matured to a point where health applications can be based on solid scientific evidence. Between 2001 and 2006, fewer than 3% of all published human genomics research has focused on translation. During the same time period, the U.S. Preventive Services Task Force has developed only two evidence-based guidelines related to genomic applications.
5. Public health workforce: The past decade has revealed major gaps in the knowledge base and training of the public health workforce in genomics, including those at CDC. Most schools of public health do not have special requirements for genomics training, despite recommendations by the Institute of Medicine for training public health professionals in the 21st century. If we are to succeed in the integration of genomics into public health programs, research and policies, public health professionals at CDC and at the national, state, and local levels need to become more competent in understanding genomic

information.

6. Public health capacity: To be able to evaluate potential applications of genomics for population health, CDC needs to improve its capacity in laboratory genomics, informatics, genetic epidemiology, and health services research.

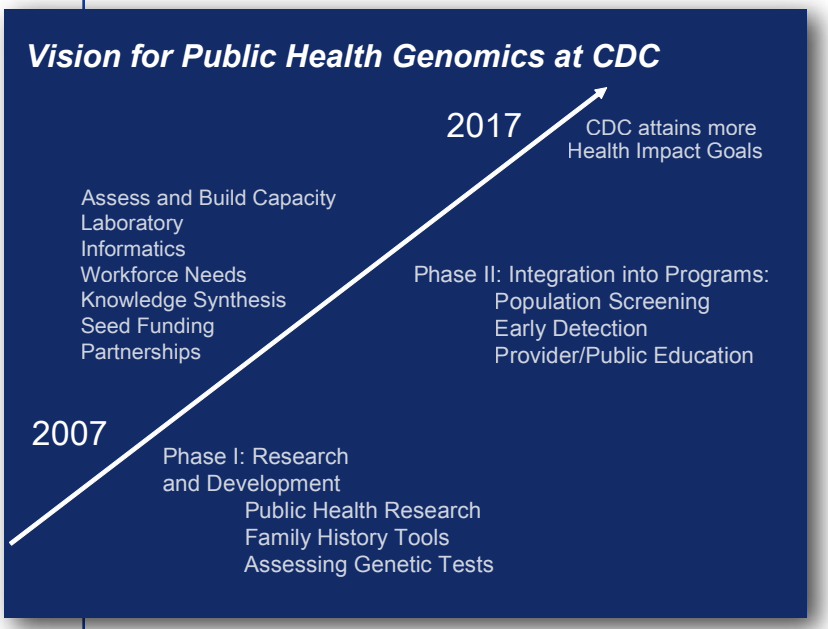
NOPHG Vision for the Next Decade

Our vision for public health genomics at CDC in the next decade is to accelerate the evaluation and appropriate integration of new genomic knowledge into CDC goals and actions. During the past two years, CDC has developed new goals for achieving greater health impact in the U.S. These goals are framed in the context of life stages, places, preparedness, and global health.

Progress toward this vision will be accomplished in two overlapping phases:

Phase I: During the next five years, NOPHG plans to accelerate the research and development of new information and tools for use by the public and the health care community. Specific approaches and products will include a human genome profile of the U.S. population, family history tools, genetic test evaluations, and dissemination of translational materials to the public and providers. CDC will fund intramural and extramural research on genomics and population health.

Phase II: During the following five years, NOPHG envisions a phased approach for integrating genomic information into public health programs that promote health and prevent disease. When evidence-based recommendations are developed, NOPHG will work to integrate them into activities conducted by CDC and its partners in the public health and clinical communities.



NOPHG will spearhead an ongoing assessment of CDC's public health genomics capacity (laboratory, informatics, training, etc.) With additional resources, we will try to build gaps in infrastructure in order to meet the challenge of public health genomics in the next decade.

Expansion of Collaborative NOPHG Initiatives

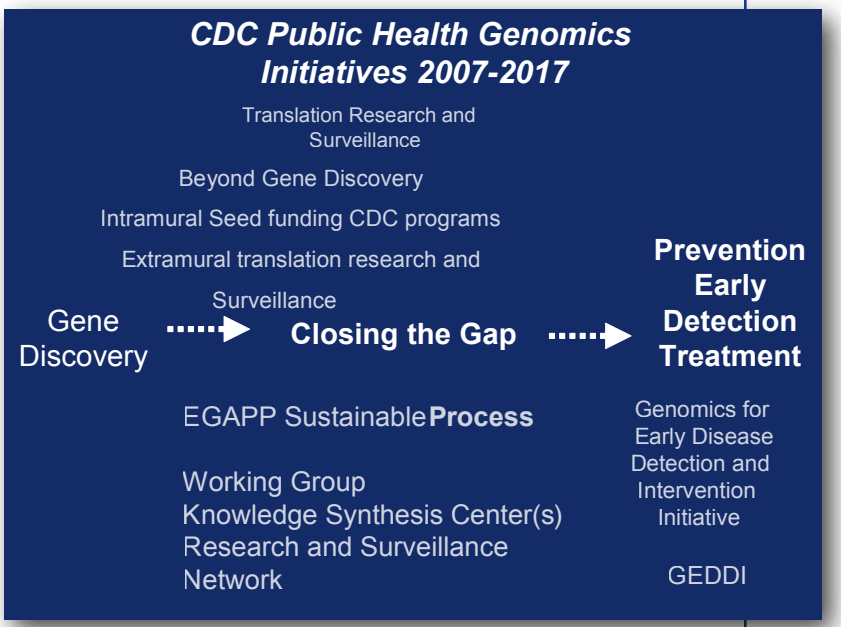
The next 10 years of public health genomics at CDC will focus on:

- accelerating the process of translation to close the widening gap between basic research and application,
- synthesizing and integrating knowledge for better decision making,
- engaging, educating, and empowering consumers and providers,
- expanding and leveraging partnerships to enhance the integration of genomics across all areas of health and health care, and
- expanding international collaborations in public health genomics.

The following section describes proposed NOPHG collaborative initiatives for the next 10 years that build on

the success and achievements of ongoing projects. The diagram on the next page shows how these initiatives are designed to begin to close the gap between gene discoveries and population health.

1. **Beyond Gene Discovery (BGD)**
   With the completion of the Human Genome Project and the emerging availability of genomic technologies to measure human genetic variation, CDC and the CDC Foundation are launching a new initiative, Beyond Gene Discovery (BGD). In collaboration with public, private, and academic partners, the initiative 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. NHANES provides a 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 studies (about 7,000 participants in NHANES III from 1991 to 1994 and 8,000 participants in NHANES from 1999 to 2002). 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 interviews, laboratory tests, and direct examinations is also available to the NHANES participants. BGD is the first large-scale effort in the U.S. to support 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 has the following overarching, three-year goals:

   - Produce the first comprehensive report of the "Genome Profile of the United States" population, a summary of the prevalence of common genetic variants in the U.S., including racial and ethnic population groups.
   - Support the development of a searchable, online information system of human genome variation (allele, genotype and haplotype frequencies at individual and multiple genetic loci) that is readily accessible to researchers, health care providers and policy makers. Access to these data will comply with federal requirements that ensure the protection of survey participant confidentiality.
   - Develop and disseminate a comprehensive agenda for population research to fill the gaps between gene discoveries and health benefits of genetic information. The agenda will identify potentially fruitful analyses to be conducted by researchers on genotype-phenotype correlation, gene-gene and gene-environment interaction and various health outcomes.
   - Enhance CDC's informatics and analytic capacity to develop research datasets that link relevant genetic test results and NHANES interview, examination, and laboratory measurements. Such an

enhanced capacity is needed for data management, review, quality control, editing, documentation, production of research datasets, developing access modalities that protect confidentiality, support of proposed research activities, and disclosure review to maintain confidentiality of NHANES participants.

2. **Accelerate Translation Research and Surveillance**
   NOPHG will continue to develop its portfolio for translation research and surveillance activities that will advance knowledge about the validity, utility, utilization and population health impact of genomic applications and family history for improving health and preventing disease in well defined populations or practice settings. The objective is to address key questions along the translation continuum, from 1) the initial development and evaluation of candidate genomic applications, to 2) thorough evaluation of the genomic applications and development of evidence-based clinical practice guidelines for the use of those applications, to 3) the dissemination and implementation of recommended applications in clinical and public health practice, to 4) the evaluation of the extent and fidelity with which recommended applications are implemented in community settings and the effect of implementation on population health.

3. **Intramural Seed Funding for Public Health Genomics Research**
   To build on the successes of the current seed funding projects, NOPHG intends to accelerate the process of integrating genomics into public health investigations (e.g., infectious, environmental, occupational, injury, MCH and chronic diseases) by funding additional projects through CDC and its partners. These projects will demonstrate the utility of public health genomics research throughout CDC programs and will help plant the seeds of growth and development across these programs.

4. **Sustainable EGAPP Process**
   To adapt EGAPP to meet the growing challenges of evidence based synthesis and information dissemination, NOPHG plans to evolve the EGAPP Working Group to enhance partnerships and collaborations with similar efforts around the country and globally. One goal is to make EGAPP products more timely yet authoritative by enhancing interactions with other groups and developing and disseminating methods for such synthesis through one or more new EGAPP knowledge synthesis centers. Through the translation research and surveillance research cooperative agreement discussed above, we plan to form a network of investigators, EGAPPNet, to meet regularly to share methods and findings and to identify gaps suggesting additional research and surveillance activities. This network will also interact synergistically with the EGAPP Working Group and the EGAPP knowledge synthesis centers to advance our knowledge and dissemination of genomic applications for population health.

5. **Genomics for Early Disease Detection and Intervention Initiative (GEDDI)**
   NOPHG will work with CDC programs and other partners 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 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 – e.g., by using genetic markers in early identification of cancer, or targeting therapies based on genotype that optimize response and avoid adverse drug reactions. We can expect increasingly rapid development of new genetic tests – including those that test multiple genetic markers concurrently using microarray technologies (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, genomic applications already being used in clinical medicine can be evaluated at the population level for assessing disease risk, influencing early disease detection, and providing 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 contribute to improved population health.

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. 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 health care 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.

Under the GEDDI initiative, NOPHG will take results of translation research and evidence based synthesis and use validated information across public health programs. NOPHG 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.

4.0 Genomics Workforce Competencies

Genomic competencies for the public health workforce at any level in any program

A public health worker should be able to:

- Demonstrate basic knowledge of the role that genomics plays in the development of disease
- Identify the limits of his/her genomic expertise
- Make appropriate referrals to those with more genomic expertise

Genomic competencies for ALL public health professionals

A public health professional within his/her professional field and program should be able to:

- Apply the basic public health sciences, (including behavioral and social sciences, biostatistics, epidemiology, informatics, environmental health) to genomic issues and studies and genetic testing, using the genomic vocabulary to attain the goal of disease prevention
- Identify ethical and medical limitations to genetic testing, including uses that don't benefit the individual
- Maintain up-to-date knowledge on the development of genetic advances and technologies relevant to his/her specialty or field of expertise and learn the uses of genomics as a tool for achieving public health goals related to his/her field or area of practice
- Identify the role of cultural, social, behavioral, environmental and genetic factors in the development of disease, disease prevention, and health promoting behaviors; and their impact on medical service organization and delivery of services to maximize wellness and prevent disease
- Participate in strategic policy planning and development related to genetic testing or genomic programs
- Collaborate with existing and emerging health agencies and organizations, academic, research, private and commercial enterprises, including genomic-related businesses, agencies and organizations and community partnerships to identify and solve genomic-related problems
- Participate in the evaluation of program effectiveness, accessibility, cost benefit, cost effectiveness and quality of personal and population-based genomic services in public health
- Develop protocols to ensure informed consent and human subject protection in research

Genomic competencies for ALL public health leaders/administrators

A public health leader/administrator as appropriate to a specific agency or program should be able to:

- Communicate the role of genomics in public health to policy makers, community members and staff
- Develop a clear understanding of the different perspectives of various community stakeholders that may use or apply genetic information beyond the individual and/or family
- Identify the political, legal, social, ethical and economic issues associated with integrating genomics into public health
- Effectively integrate genomic issues into policies and programs
- Assure that current science and research are used in all planning for and delivery of genomic services
- Include genomic competencies in staffing plans to ensure adequate capacity and infrastructure building
- Assure that all workers develop appropriate genomic competencies and can appropriately apply genomic knowledge and tools within the parameters of their professional duties
- Manage genomic program fiscal and human resources, including cost analysis of genetic tests or services, and strategies for developing budget priorities and proposals for funding from external sources to ensure

equal access
- Promote a legislative agenda, public policies, statutes, and regulations that effectively address genomic issues to ensure appropriate use of genetic tests, adequate services for all, and adequate funding avenues

Genomic competencies for public health professionals in clinical services evaluating individuals and families

The public health clinician, as appropriate to discipline, agency or program, should be able to:

- Apply basic genomic concepts, including patterns of inheritance, gene-environment interactions, role of genes in health and disease, and implications for health promotion programs to relevant clinical services
- Demonstrate understanding of the indications for, components of, and resources for genetic testing and/or genomic-based interventions
- Describe ethical, legal, social, and financial issues related to genetic testing and recording of genomic information
- Explain basic concepts of probability and risk and benefits of genomics in health and disease assessment in the context of the clinical practice
- Deliver genomic information, recommendations, and care without patient or family coercion within an appropriate informed-consent process

Genomic competencies for public health professionals in epidemiology and data management

The public health epidemiologist and/or data manager, as appropriate to discipline, agency or program, should be able to:

- Apply basic epidemiologic skills to genomic situations on an individual and population basis, including surveillance for diseases, community wide population-based genomic research and follow-up studies
- Identify the underlying scientific principles and evaluate strength of evidence from genomic literature, including applicable interventions and effectiveness
- Accurately describe the sensitivity and specificity of genetic tests to audiences
- Provide appropriate baseline and other applicable data to develop and support genomic policies and intervention plans
- Employ appropriate information systems and coordinate information from multiple sources to integrate genomics into health policies and programs
- Protect confidentiality of genomic information through applicable confidentiality rules and data management systems
- Evaluate effectiveness, accessibility, cost benefit and effectiveness, and quality of individual and population-based genomic services in public health
- Evaluate the utility of diagnostic testing and screening programs, including structure, function, and transmission of genes and gene/environmental interactions in public health
- Conduct genomic epidemiology and data management public and professional education programs within limits of personal educational background

Genomic competencies for public health professionals in population-based health education

Anyone providing education in a public health program, as appropriate to discipline, agency, or program, should be able to:

- Translate health-related information about social and cultural environments, (including community needs

and interests and societal value systems) for use in population-based scientifically sound genomic health education programs
- Determine the factors such as learning styles, literacy, learning environment, and barriers that influence learning about genomics
- Differentiate between genomic education and genetic counseling
- Facilitate genomic education for agency staff, administrators, volunteers, community groups and other interested personnel
- Utilize social marketing to develop a plan for incorporating genomics into health education services by working with community organizations, genomic experts, and other resource people for support and assistance in program planning
- Provide a critical analysis of current and future community genomic education needs
- Advocate genomic education programs and/or integration of genomic components into education programs

Genomic competencies for public health professionals in laboratory sciences

The public health laboratory professional, as appropriate to discipline, agency or program, should be able to:

- Perform genetic assays with appropriate validation studies
- Establish basic analytical and quality assurance performance criteria (sensitivity, specificity) for genetic tests
- Participate in development of new test methodologies and standards for genetic testing to optimize test performance and efficiency and meet public health genomic program goals
- Utilize evidence-based research to incorporate emerging genomic technology into public health laboratory practice
- Communicate results of genetic tests, test limitations, complexities and implications, and relevant inferences from laboratory data to the public, policy makers, legislators, media, and health care providers in appropriate and concise language
- Advocate laboratory participation in genomic policy and regulatory development
- Participate in external validation studies of genetic testing with the larger clinical laboratory community to ensure appropriate introduction, application, interpretation and use

Genomic competencies for public health professionals in environmental health

The public health environmental professional, as appropriate to discipline, agency or program, should be able to:

- Describe how environmental factors and genes can interact with each other in disease development
- Apply methods to evaluate genetic susceptibilities in a population and use that information to direct environmental sampling activities, biological testing programs and other public health activities
- Apply risk communication principles and genomic knowledge associated with exposures accurately in environmental programs
- Describe how genomic information may affect public policy and zoning, environmental regulation, development, and planning
- Advocate the environmental perspective in genomic policy and regulatory development
- Describe where and how to acquire accurate and practical genomic information and advice impacting environmental programs

5.0 Bibliography of NOPHG Publications

This section provides a bibliography of publications written by staff in CDC's National Office of Public Health Genomics (NOPHG) from 1997 to 2008. Publications are organized by year.

Scientific Articles, Book Chapters, Selected Published Abstracts

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6.0 NOPHG Conferences and Meetings

This section provides a list of conferences, meetings, seminars and workshops organized by CDC's National Office of Public Health Genomics (NOPHG) and its partners.

1998

- 1st Annual Conference on Genetics and Public Health (May ~ Atlanta, GA)

1999

- 2nd Annual Conference on Genetics and Public Health: Integrating genetics into public health research, policy and practice highlights (December ~ Baltimore, MD)

2000

- 3rd National Conference on Genetics and Disease Prevention: Genetics and Public Health Practice: Connecting Research, Education, Practice, and Community Highlights (September ~ Ann Arbor, MI)

2001

- HuGE Meeting: Guidelines For Evaluating Human Genome Epidemiology Studies (January ~ Atlanta, GA)
- Applying Genetic and Public Health Strategies to Primary Immunodeficiency Diseases Synopsis (November ~ Atlanta, GA)

2002

- Genomics and Chronic Disease Summit (January ~ Atlanta, GA)
- Family History as a Tool for Public Health and Preventive Medicine (May ~ Atlanta, GA)
- Applying New Biotechnologies to the Study of Occupational Cancer (May ~ Washington, DC)
- HuGE Workshop: Scientific Foundation for Using Genetic Information to Improve Health and Prevent Disease (July ~ Cambridge, U.K.)
- Family Health Tree Genomics Centers Meeting (August ~ Salt Lake City, UT)
- Banking Newborn Blood Spots for Public Health (September ~ Atlanta, GA)
- Role of Human Genetics in Infectious Diseases & Public Health - NCID HuGE Course (November ~ Atlanta, GA)

2003

- Genomics Day 2003: Public Health Genomics at CDC (January ~ Atlanta, GA)
- ACCE/Genetic Testing Meeting (February ~ Atlanta, GA)
- Family History Workshop (April ~ Atlanta, GA)
- Genomics and the Future of Public Health Symposium Presentations (May ~ Atlanta, GA)
- HuGE Workshop: Introducing the Concepts of Human Genome Epidemiology (May ~ Atlanta, GA)
- Genomics and Asthma: Implications for Public Health (September ~ Seattle, WA)
- Newborn Screening for Cystic Fibrosis (November ~ Atlanta, GA)

2004

- Public Health Assessment of Genetic Tests for Screening and Prevention (September ~ Atlanta, GA)
- HuGENet™ Systematic Review Methodology Workshop (November ~ Cambridge, U.K.)

2005

- Expert Meeting on Evidence-Based Review of Genomic Applications (January ~ Atlanta, GA)

- Genomics Day 2005: Public Health Genomics at CDC (January ~ Atlanta, GA)
- International Biobank and Cohort Studies Meeting: Developing a Harmonious Approach (February ~ Atlanta, GA)
- Annual Meeting of Funded States and Centers - Genomics and Chronic Disease Prevention Programs (March ~ Atlanta, GA)
- Genome based Research and Population Health (April ~ Bellagio, Italy)
- EGAPP Working Group Meeting (May ~ Atlanta, GA)
- HuGENet™ Methodological Challenges in the Meta-analysis of Genetic Association Studies Meeting (May ~ Leicester, U.K.)
- EGAPP Working Group Meeting (July ~ Atlanta, GA)
- HuGENet™ Network of Networks Workshop (October ~ Cambridge, U.K.)
- EGAPP Working Group Meeting (October ~ Atlanta, GA)
- Family History Workshop (November ~ Atlanta, GA)

2006

- Use of Family History Information in Pediatric Primary Care and Public Health (February ~ Atlanta, GA)
- EGAPP Working Group Meeting (February ~ Atlanta, GA)
- Inaugural Meeting of the CDC Public Health Genomics Collaboration (March ~ Atlanta, GA)
- EGAPP Working Group Meeting (June ~ Atlanta, GA)
- STrengthening the REporting of Genetic Associations (STREGA): an international HuGE workshop (June ~ Ottawa, Canada)
- EGAPP Working Group Meeting (September ~ Atlanta, GA)
- Annual Meeting of Funded States - Genomics and Chronic Disease Prevention Programs (September ~ Atlanta, GA)
- HuGENet™ Short Course (November ~ Cambridge, U.K.)
- HuGENet™ Workshop on the Assessment of Cumulative Evidence on Genetic Associations (November ~ Venice, Italy)

2007

- EGAPP Working Group Meeting (January ~ Atlanta, GA)
- 2nd CDC Public Health Genomics Collaboration (March ~ Atlanta, GA)
- Annual Meeting of Funded States and Centers - Genomics and Chronic Disease Prevention Programs (April ~ Ann Arbor, MI)
- EGAPP Working Group Meeting (April ~ Atlanta, GA)
- EGAPP Working Group Meeting (August ~ Atlanta, GA)
- 3rd CDC Public Health Genomics Collaboration (October ~ Atlanta, GA)
- Public Health Genomics Monthly Seminar Series: "Closing the Gap Between Human Genome Discoveries and Population Health" (Rockville, MD)

2008

- 10th Anniversary of Public Health Genomics at CDC Meeting (January ~ Atlanta, GA)
- HuGE Workshop (January ~ Atlanta, GA)
- EGAPP Stakeholders' Group Meeting (January ~ Houston, TX)
- EGAPP Working Group Meeting (February ~ Atlanta, GA)
- EGAPP Steering Committee Meeting (February ~ Atlanta, GA)
- Beyond Gene Discovery Meeting (March ~ Atlanta, GA)
- Public Health Genomics Institute: A Scientific Foundation for Closing the Gap Between Human Genome Discoveries and Population Health (June ~ Atlanta, GA)