Public Health Perspective on Large Population Studies of Human Genetic Variation, the Environment, and Common Disease

DHHS Secretary's Advisory Committee
on Genetics, Health, & Society

Bethesda, 1 March, 2005

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KEY COMPONENTS OF OUR VISION FOR GENETICS & PUBLIC HEALTH

- An avalanche of genomic information: validated SNPs, haplotype blocks, candidate genes/alleles associated with disease risk
- Effective linkages with better environmental and behavioral datasets for eco-genetic analyses
- Credible privacy and confidentiality protections for genetic and non-genetic information
- Breakthrough tests, vaccines, drugs, behaviors, and regulatory actions to reduce health risks and cost-effectively treat patients in the US and globally: “Saving lives millions at a time” (Hopkins)

IT'S A NEW WORLD

- New Biology---New Technology
- Genome Expression Microarrays
- Comparative Genomics
- Proteomics
- Bioinformatics & Computational Biology
- Mechanism & Evidence-Based Medicine:
  "What were you doing up to now?!"
- Predictive, personalized, preventive
  healthcare and community health services

Who Will Keep The Public Healthy?: Educating Public Health Professionals for the 21st Century, IOM, 2002

"With the arrival of the era in which we will have the ability to understand gene-environment interactions comes not only the era of genomic medicine, but of genomics-based public health. Understanding genomics, therefore, is essential for an effective public health workforce." (p.65)

CDC CENTERS

The Michigan Center for Genomics & Public Health seeks to integrate genomic discoveries into public health practice, with consideration of the ethical, legal, and social issues associated with the application of these discoveries, as well as the involvement of the community at large.

Training Tools

Six Weeks to Genomic Awareness

Genomics for Public Health Practitioners

Collaborative programs with UNC and U Washington Centers and the CDC Office of Genomics and Public Health

DEFINITIONS

- **Genetics** is the scientific study of genes and their roles in health and disease, physiology, and evolution.

- **Genomics** is a modern subset of the broader field of genetics, made feasible by remarkable advances in molecular biology, biotechnology, and computational sciences, to examine the entire complement of genes and their actions.

- Global analyses permit us and require us to go beyond the known “lamp-posts” of individual gene associations and effects.

- Proteins are the action molecules of the cell and the leading candidates for biomarkers—in tissues and in the blood.

  Proteins are coded for by genes.
- Proteomics is the global analysis of proteins in cells or body fluids. Techniques for global analysis of proteins are advancing rapidly, especially for discovery of biomarkers for diagnosis, treatment, and prevention.

Avalanche of Genomic Information

- The International HapMap Consortium aims to genotype 1 million SNPs from 270 individuals.
- Direct associations of individual SNP alleles with disease phenotypes (including linkage disequilibrium) are a more powerful method than linkage-based indirect association analyses.
- dbSNP has >8 million validated SNPs.
- Haplotype structures can be obtained via genome-wide LD, haplotype blocks (1 KB to 1 MB), and haplotype-tagging SNPs, respecting recombination hotspots and variable LD.

CDC/NCHS NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES 1999-2004)

Forty years of surveys and analyses

Impacts: removal of lead from gasoline, pediatric growth charts, prevalence estimates for cholesterol, BP, hepatitis C

Environmental exposure assays: Pb/EPP, Cd, Hg, As, VOC, acrylamide, 7 phthalates, 13 metals, latex allergy, 16 PAH, 8 phytoestrogens, dioxins, microbial.

Smoking history/ cotinine (ETS if non-smoker)

Osteoporosis/bone density, etc.

NIEHS Advisory Committee on Personalized Exposure Assessment

- Geograpic Information Systems, illustrated with NIEHS Children's Health Studies—GIS and wireless devices to track exposures to pesticides, validate diary entries, develop spatial models for households at risk for lead poisoning
- Bio-sensors and nanoscale devices with sensitive read-out
- Molecular signatures of exposure, early effect, variation in susceptibility [toxicogenomics]

Conceptual Strategy for Integrating Exposure Assessment Technologies in Human Environmental Health Research

- Identify priority diseases and plausible environmental factors
- Identify potential genetic determinants, pathways and model systems
- Identify target study populations
- Define genetic determinants of susceptibility
- Conduct targeted exposure assessment
- Identify & validate biomarkers
- Describe GxE interactions in exposure & disease

Technologies and Approaches

- Literature & databases (NPL)
- GIS coverages
- Computer-based pathway mapping/systems
- Body burden assays, macro-to-micro monitoring
- Genome screening/toxicogenomics
- Lab and human in vitro and in vivo sensors and biomarker studies

EPA Multimedia Integrated Modeling Systems (MIMS)

Simulate ambient airborne substances in urban settings at spatial scales ranging from <1 to10 km.

Aims: develop prototype, second-generation, and advanced human exposure modeling support tools for air pollution and homeland security.

Tools help bridge modeling gap between Eulerian chemical grid models and traditional Gaussian plume dispersion models (hybrids).

Models will capture temporal and spatial variability of ground-level concentrations of air toxics and hazardous releases, including “hot spots”.

Measuring Exposure to Environmental Pollution: from ambient to body burden

Ambient: criteria and hazardous air pollutants; disinfection byproducts from treated drinking water; heavy metals; radiation; biological agents

Personal: sensors/workplaces; community sampling

Biomonitoring: recognize bioaccumulation and metabolism; blood lead, mercury, cotinine; urine organophosphates. No information on source or pathway. E.g., CO: ETS, faulty gas stove, vehicle emissions.

National scale: establish reference ranges; CDC 1/03 data for 116 environmental chemicals

U.K. BioBank (1999--)

Wellcome Trust and MRC/UK: genetic databank with blood samples planned from 500,000 people. Researchers will apply to utilize the data and specimens.

Recruitment via general practices (500+), age 45-69, follow-up 10 yrs. Expect 1000+ deaths of illnesses for a wide range of cancers, heart attacks, heart disease, stroke, diabetes, hip Fx, RA, Parkinson's, and dementia.

Q for risks, lifestyle, 7d dietary diary; blood

Protocol issued 2/14/02

Expect to learn a lot from our colleagues today!

Statistical Power Estimates

>5000 cases/yr: DM, IHD, MI, CRC, BRCA

Detect RR for exposure (within genotypes) 1.5 and interaction ratio (IR) 1.4 for exposures and genotypes in 20-80% of participants (95% power, 0.1% significance)

1000-2000 cases/yr: RA, PD, HipFx, OvCA, Bladder CA, etc: RR 1.8-2.0, IR 1.7-2.0

Expect 40-50% of 6000-8000 patients/practice to enroll. Blood: EDTA-plasma, RT for up to 48 hr/4C.

Nested case-control and cross-sectional studies, including biochemical, proteomic, metabolomic measures and ancillary family-based studies

Technical & Ethical Criticisms of Design

- Cohort much too small to analyze complex multifactorial diseases; what about sib-pairs?
- Cohort age and medical record-keeping likely to compromise quality of environmental/behavior data vs genetic data
- Thus, likely to over-emphasize genetic factors, especially with targeted drugs vs diet/exercise
- Consent: to what? Secondary uses of data?
- Human Genetics Alert group opposes study of behavioural conditions; GeneWatch UK and Consumer's Action also engaged

Exposure Categories

Socioeconomic/demographic
Habits/lifestyle
Diet, including supplements and hot drinks
Reproductive history, including hormones
Medical Hx: injuries, radiation, OTC meds
Family history
Disability/impairment
Psychological profile
Early life (BW, weight)

Examples of Feasible Studies

Cigarette smoking/eNOS/ApoE4: IHD

Homocysteine/ApoE4: IHD

Adiposity/PPARG, etc: diabetes

Alcohol intake, smoking, Apo E4: dementia

Infections/HLA DRB1: RA

Exogenous hormones/BRCA1/2: BRCA

Endogenous testosterone/Androgen-R: PCa

Meat consumption/NAT-2: colon CA

Saturated fat/Apo E4: serum cholesterol values

Other Large-Scale Studies

National: Iceland [Estonia, Canada]

European Prospective Investigation into Cancer and Nutrition (EPIC): 370,000, age 40-74 at entry. Lacks entry clinical exam; does not capture all endpoints.

Note Women's Health Initiative in U.S. with 160,000 participants and many outcome and observational studies

PUBLIC HEALTH GENETICS (1)

- Bring together the digital code of inherited (genetic) information with “environmental cues” from nutrition, metabolism, lifestyle behaviors, pharmaceuticals and nutraceuticals, and chemical, physical, and infectious exposures

The result is “systems biology” at many levels, from proteins to eco-systems…

PUBLIC HEALTH GENETICS (2)

- Ecogenetics: environmental & occupational exposures and variation in susceptibility
- Chronic diseases: genetic predispositions, mutations (toxic effects) from exposures
- Unhealthful behaviors: smoking, alcohol
- Nutrition: hyperlipidemias, high BP, folic acid (high homocysteine), iron (hemochromatosis)

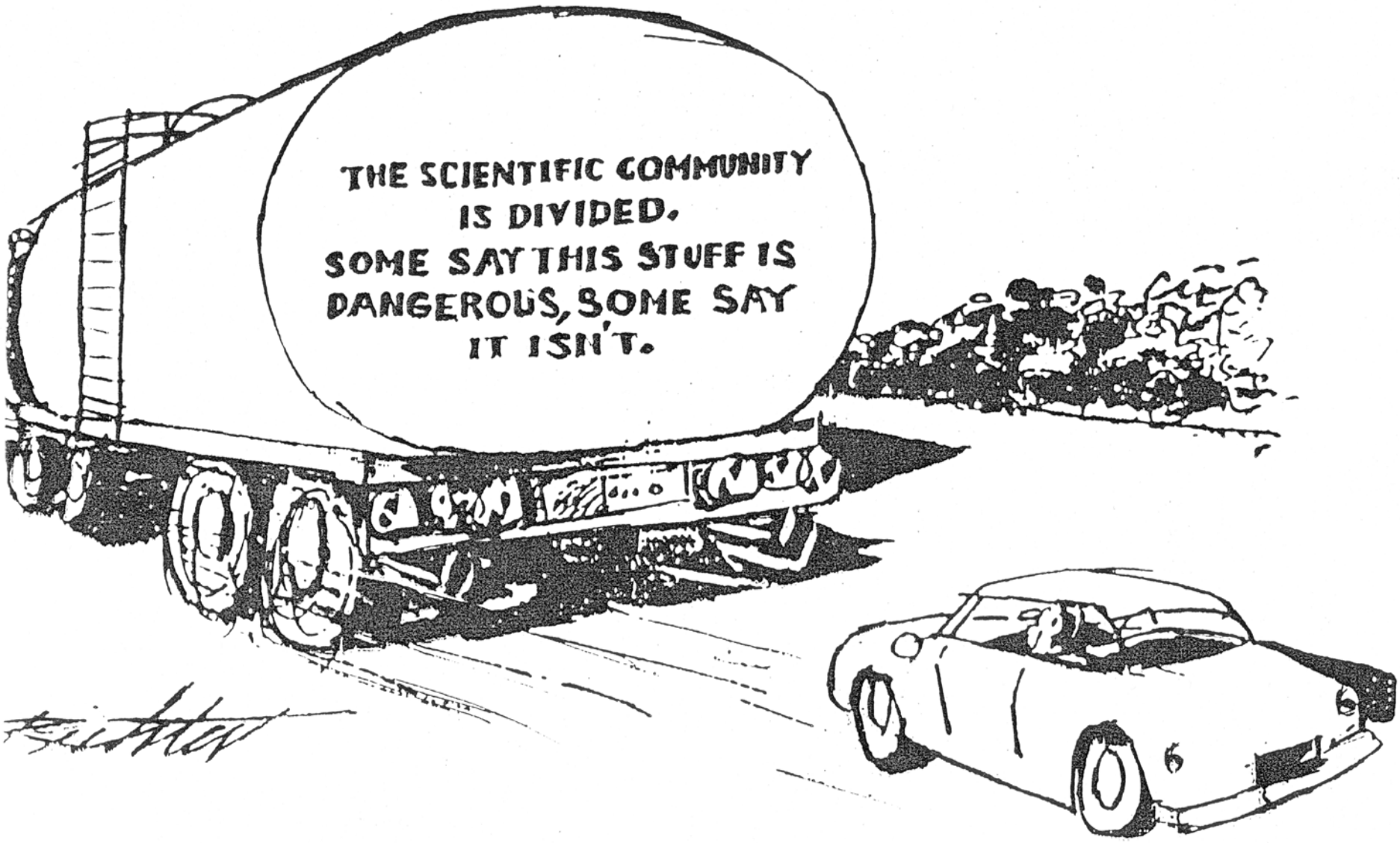
PUBLIC HEALTH GENETICS (3)

- Include genetics in protocols for health promotion/disease prevention research, e.g. host-pathogen interactions, risk factors for chronic diseases, and drug and vaccine development
- Integrate genetics into training and continuing education in every public health discipline: preventive medicine, epidemiology, biostatistics, EOH, health behavior and health education, pathobiology, policy and ethics

A Golden Age for the Public Health Sciences

Sequencing and analyzing the human genome is generating genetic information that must be linked with information about:

- **Nutrition and metabolism**
- **Lifestyle behaviors**
- **Diseases and medications**
- **Microbial, chemical, physical exposures**


THE SCIENTIFIC COMMUNITY IS DIVIDED.
SOME SAY THIS STUFF IS DANGEROUS, SOME SAY IT ISN'T.

Framework for Regulatory Decision-Making (OSTP, 1980)

Hazard Identification

- Epidemiology
- Lifetime rodent bioassays
- Short-term, in vitro/in vivo tests
- Structure / activity

Risk Characterization

- Potency (dose/response)
- Exposure analysis
- Variation in susceptibility

Risk Reduction

- Information
- Substitution
- Regulation / Prohibition

Toxicogenomics

Develop molecular signatures for effects of carcinogenic, mutagenic, teratogenic, and other toxic agents: NIEHS/NTP model compound is acetaminophen

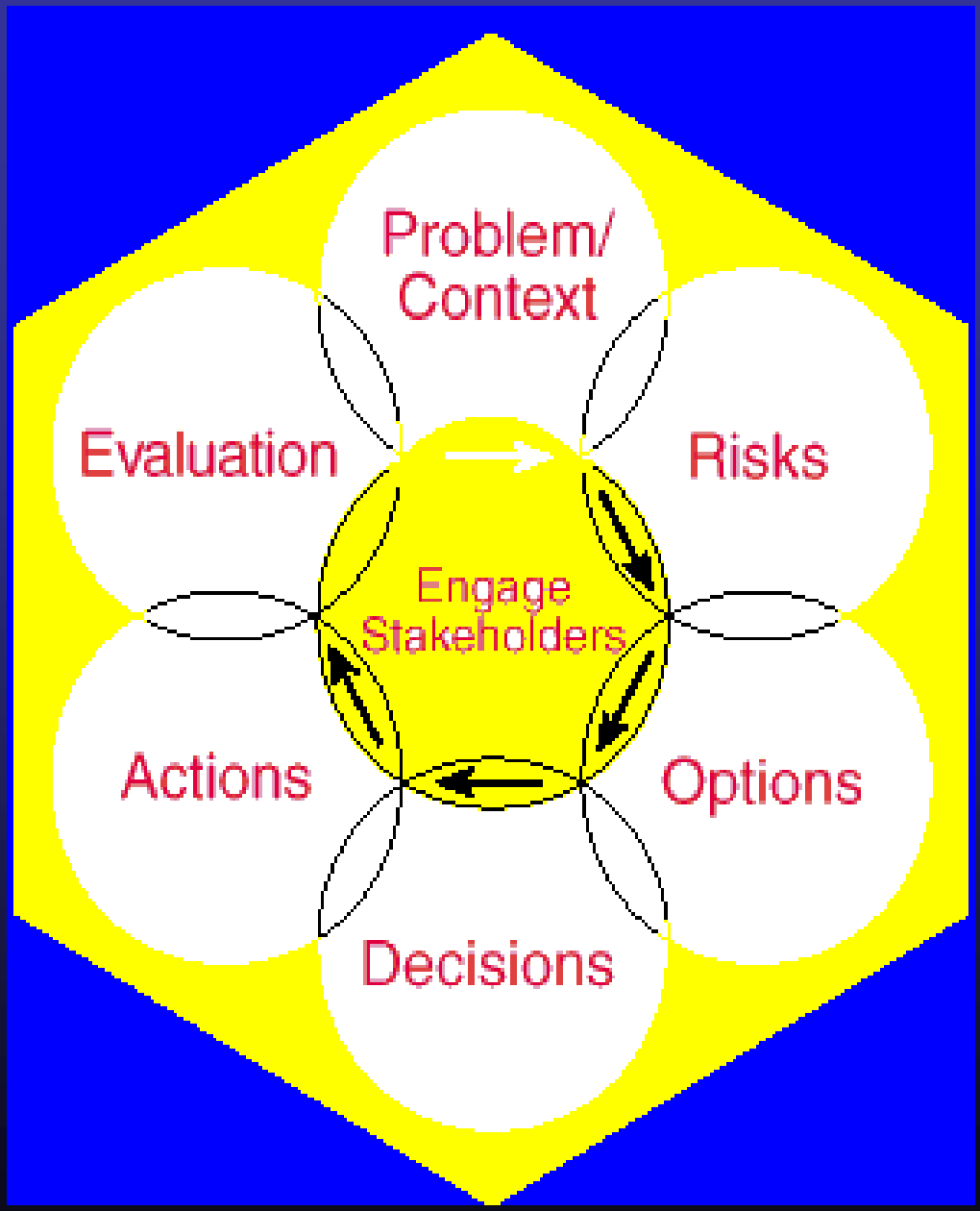
Test known carcinogens for distinctive patterns--benzidines, beta-naphthylamine, benzene, bis-chloromethyl ether, nitrosamines, asbestos, …in animal models

Test chemopreventive agents in animal models and organ and cell cultures

Framework for Risk Management from the Presidential/Congressional Commission on Risk Assessment and Risk Management (1997)

Note: CONTEXT

STAKEHOLDERS



Context

Move beyond one chemical, one environmental medium (air, water, soil, food), one health effect (cancer, birth defect…) at a time in risk assessment and risk management.

Requires multiple molecular signatures and biomarkers, and a comprehensive public health view.

Context for Applying Biomarkers

- Multiple sources of same agent
- Multiple media/pathways of exposure
- Multiple risks/effects of same agent
- Multiple agents causing same effects
- Public health: status / trends
- Ecological health
- Social, cultural, environmental justice considerations

HARNESSING GENETICS TO PREVENT DISEASE & IMPROVE HEALTH: A STATE POLICY GUIDE

Partnership for Prevention

Washington DC, 2003

www.prevent.org

AIMS OF THE PfP REPORT

Help state policymakers to:

- Protect consumers
- Monitor the implications of genetics for health, social, and environmental goals
- Assure genetic advances will be tapped not only to treat medical conditions, but also to prevent disease and improve health before people become ill.

KEY FINDINGS

- The greatest opportunity of the genomic era: personalized medicine and pharmacogenetics to prevent or better manage chronic diseases. Products and services will be diagnostic tests, drug therapies, and drug monitoring protocols.
- Genetics and genomics should be integrated into existing health, social, and environmental policies, rather than establishing stand-alone genetics programs.

AVOID “GENETIC EXCEPTIONALISM”

“At a time when many state policies were based on exceptionalism, the Michigan Governor’s Commission on Genetic Policy and Progress adopted an integration perspective and recommended that genetic issues be dealt with in the context of overall medical care values and principles”. (p.11)

THE CASE FOR INTEGRATION

- All health conditions have a genetic basis.
- Most common diseases result from gene-environment interactions, so genetic advances are likely to extend and expand, not supplant, current practices in medicine, public health, environmental protection
- Some genetic variations are associated with greater health risks than others; covering this wide range with one-size-fits- all policies is inappropriate.

THE CASE FOR INTEGRATION (cont'd)

Decisions about genetics policy involve complex issues about ethics, costs, benefits, and individual and societal interests. Medical care decisions should be linked with research, insurance, and broader public health policies.

The intersection between genetics and public policy is both immediate and long-term, warranting close monitoring and timely actions.

Limit genetic exceptionalism to prohibition of discrimination in insurance and employment.

PRINCIPLES OF COMMUNITY-BASED RESEARCH

University of Washington

- **Community partners should be involved from the earliest stages**
- **Community partners should have real influence on project**
- **Research processes and outcomes should benefit the community**
- **Community members should be part of the analysis/interpretation**
- **Productive partnerships should last beyond the project**
- **Community members should be empowered to initiate projects**

Omenn, in *Academic Medicine* (1998)

Additional Sources of Information

- CDC Office of Genomics and Disease Prevention
- Assn of State and Territorial Health Officers (ASTHO): Genomics Impact Newsletter, monthly.
- National Conference of State Legislatures: Genetic Technologies Project; www.ncsl.org

OUR GENETIC FUTURE

"Mapping the human genetic terrain may rank with the great expeditions of Lewis and Clark, Sir Edmund Hillary, and the Apollo Program."

--Francis Collins, Director

National Human Genome Research Institute, 1999

Next: Understand the dynamic proteomic compartments.

Link genetic variation with many kinds of non-genetic variables.