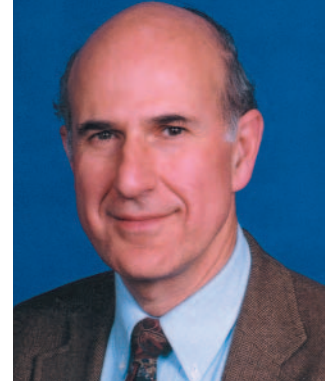


Most public health research on infectious disease and environmental chemical risks has paid little attention to inherited variation in susceptibility among people.



The Genomic Era: A Crucial Role for the Public Health Sciences

With the publication of the complete genomes of the yeast *Saccharomyces cerevisiae* (1), the worm *Caenorhabditis elegans* (2), and the fruitfly *Drosophila melanogaster* (3) and the expected completion of a substantially complete human genome sequence (4), scientists everywhere can turn their attention to understanding the significance of genetic variation within our species and across species. The NIEHS anticipated this period with the initiation in 1998 of the Environmental Genome Project (5), which focuses on identification of allelic variants (primarily single-nucleotide polymorphisms) of susceptibility genes for environmentally related diseases and population-based studies of gene-environment interactions. Salient genes include those for xenobiotic metabolism and detoxification, hormone metabolism, receptors, DNA repair, cell cycle, cell death, immune and inflammatory responses, nutritional pathways, oxidative processes, and signal transduction systems.

The concepts and methods of physiology, biostatistics and bioinformatics, epidemiology and population-based prevention trials, environmental and occupational health, and health behavior research are essential for interpreting the coming avalanche of data about genetic variation among people in health and disease (6-8). To understand the functions of genes and the significance of variation in patterns of thousands of genes, researchers need to learn how those genes and their gene products interact with exposures to various environmental chemical, physical, and infectious agents and with metabolic, nutritional, and behavioral factors, as well as with other genes (9). These ecogenetic interactions will be incorporated into databases through the process now called annotation (10).

More knowledge is needed about the heterogeneity of genetic predispositions, environmental exposures, and disease risks. Unfortunately, in most public health research on infectious disease and environmental chemical risks, little attention has been given to inherited variation in susceptibility among people; the focus has been only on the agents. Heterogeneity of subpopulations also has been neglected in epidemiologic studies in order to generate sufficient numbers to justify the analysis statistically. For quantitative traits, pharmacologists, toxicologists, and psychologists routinely emphasize means and standard errors of the means, disregarding potentially informative individuals with extreme responses. Nevertheless, genetics is now at the core of research on cancers, coronary heart disease, high blood pressure, neurologic and psychiatric disorders, and a host of other common clinical conditions, many influenced by environmental exposures. Properly conducted population studies are crucial to demonstrate the significance of environmental exposures to health risks by showing that technologic or behavioral reductions in levels of exposure will lead to a reduction in disease incidence overall, or in particular subpopulations. We can be confident that modern genetics—enhanced by genomics, proteomics, and bioinformatics—will contribute to a scientifically sound strategy for improving health and preventing disease, the overarching mission of public health.

If gene expression in microarray assays and protein expression in proteomic studies can be analyzed into well-differentiated patterns, such research will lead to vastly improved capabilities to address questions about low-level exposures. Such exposures to ionizing radiation and to chemicals are among the most controversial and uncertain aspects of environmental health and risk assessment (11). Extending the dose-response curve far downward to lower doses in toxicologic and epidemiologic studies will be very important. Cross-species comparisons of microarray and proteomics results in response to environmental hazards will become feasible in test animals and in people exposed in various settings. Additional risk modifiers from diet, concomitant exposures, aging, sex, hormonal and circadian cycles, pharmaceuticals, smoking, and alcohol can be incorporated in these detailed investigations.

The marriage of genetics and public health should usher in a golden age for the public health sciences and public health practice, particularly for environmental health. No longer do we view genetic predispositions to disease as immutable causes of disease; we seek ways to modify the gene expression or the many other factors that interact to influence the risk and severity of the disease (8). Thus, the conduct of studies to determine these interactions and effects is very much in the public interest.

Empowered by databases with useful information about genes and gene functions, researchers in the genomic era will establish linkages to databases that specify various environmental and occupational exposures, smoking behavior, dietary intakes, pharmaceutical and nutraceutical use, and medical and public health interventions and services for people in defined populations. Such studies require large cohorts of exposed populations with much improved measures of exposures. It is possible that substantial information may be accumulated in a single population study, like the National Health and Nutrition Examination Survey (NHANES) IV. However, links to air pollution, work site, hospital discharge, and many other kinds of data would still be necessary to conduct a comprehensive analysis to guide predictions of clinical outcomes for patients and environmental health risks for people in the community. More often, large university-based studies need to be collaborations, funded by multiple research project grants to consortia members or by a cooperative agreement or a center grant with subcontracts.

One crucial barrier could paralyze such studies: proposals in the U.S. Congress and in many state legislatures aimed at protecting individual privacy and the confidentiality of medical information may block the large population studies needed to answer questions from patients, families, communities, and policymakers about improving medical care and public health protection. A comprehen-

sive bill, originally introduced as “The Genetic Privacy Act of 1995,” lays out complex procedures for informed consent, review, and management of private records to permit research, especially clinical research with the patient and close relatives. In this bill, the information in one’s genetic code is characterized as a “coded probabilistic future diary because it describes an important part of a unique and personal future” (12). Its consent-based provisions for individuals may be impractical for population studies involving previously collected data on thousands of people. Other legislative proposals which focus primarily on genetic testing and care of individual patients mandate that all identifiers, both name and numbers, be removed from the records (personal medical records).

Another comprehensive effort was the 1999 Report from the Michigan Governor’s Commission on Genetic Privacy and Progress (13). Even though the mandate did not include research, the commission proposed that researchers have access to identifiable patient information for approved studies. Law and ethics are always seeking a balance between competing social demands, in this case demands for privacy and for scientific advances. Progress in human genetics, genetic epidemiology, and ecogenetics requires genetic linkage and association studies. Such studies cannot be conducted with anonymous databases. It is feasible for scientists to keep study information confidential and to destroy all identifying links (but not the primary data) once a particular study is concluded. To protect privacy, legislation can be crafted to allow the research, and still protect information about specific participants from discovery by third parties. Legislation could authorize analogues of the Certificates of Confidentiality issued by the federal government for alcohol and substance abuse studies. These certificates protect the research data from discovery, even in civil or criminal litigation.

Responsibilities and accountability procedures can be specified so that privacy and confidentiality are protected, and carefully approved and carefully monitored access to individual-level records can be

assured for ecogenetics studies that link data about multiple interacting risk factors. No area of the Human Genome Project needs such a balanced process more than the Environmental Genome Project.

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