From Genes to Public Health: The Applications of Genetic Technology in Disease Prevention

Muin J. Khoury, MD, PhD, and the Genetics Working Group

ABSTRACT

Objectives. With advances in the Human Genome Project, the implications of genetic technology in disease prevention should be assessed.

Methods. The paradigm suggested in *The Future of Public Health*—assessment, policy development, and assurance—was used to examine the continuum from genetic technology to public health practice.

Results. First, important public health functions are to (1) assess the impact of genes and their interactions with modifiable disease risk factors on the health status of the population and (2) assess the impact and safety of genetic testing on the population. Second, given the many implications of genetic testing, the public health community should participate in policy development related to the timing and use of genetic testing in disease prevention. Third, whenever appropriate, the public health community needs to ensure the development of public health genetics programs (e.g. newborn screening) and evaluate the quality and effectiveness of the use of genetic testing in disease prevention.

Conclusions. Although most current genetic tests are not ready for disease prevention, there is an important role for the public health community in translating genetic technology into disease prevention. (*Am J Public Health.* 1996;86:1717–1722)

Introduction

During the past decade, there have been tremendous advances in molecular genetic technology. These advances have led to the Human Genome Project, a long-term initiative to map and sequence the human genome. In the next decade, most if not all human genes will be mapped and sequenced.[1–3] Relatively simple technology such as the polymerase chain reaction is now available to examine genetic variation at many gene loci by using small amounts of human tissue (e.g., blood spots and cheek swabs).[4] This emergence of genetic technology is accompanied by increasing concern regarding the use and misuse of genetic information in society.[5–8]

Despite the advances in molecular genetics and their implications in disease prevention,[9,10] it is not entirely clear when and how genetics can be applied in this regard. As genetic tests are proliferating in the US population, their appropriate usage in the public health setting needs careful scrutiny. In its evaluation of the future of public health in the United States, the Institute of Medicine defined the core functions of public health agencies as assessment, policy development, and assurance[11] (Table 1). In this commentary, we discuss the potential applications of genetics in the context of these core public health functions.

From Gene Identification to Public Health Applications

The Human Genome Project is targeting our estimated 50 000 to 100 000 human genes, only a small fraction of which have been identified so far.[12,13] Many identified human genes are associated with relatively uncommon disorders, such as phenylketonuria and hemophilia. Also, there are disease genes that account for a small fraction of the more common chronic diseases, such as α_1-antitrypsin deficiency in pulmonary emphysema.[14] Furthermore, genes play important roles in the etiology of most, if not all, human diseases ranging from cancer to coronary heart disease.[15] The roles that genes play differ greatly, ranging from genes that completely determine the disease state (i.e., disease genes) to genes that interact with other genes and environmental factors in causing disease (i.e., susceptibility genes). These genetic risk factors include numerous polymorphic traits and enzyme systems involved in the metabolism of drugs and carcinogens.[16–18]

Molecular technology is allowing research applications in family studies to identify disease and susceptibility genes. These studies, which are mostly based on high-risk families with multiple affected individuals, rely on the use of genetic analysis methods such as linkage and segregation analyses.[10] A notable example is the intense search for breast cancer genes in high-risk families. Using linkage analysis[19] and, more recently, direct sequencing of the gene,[20,21] investigators have identified a gene on chromosome 17 (BRCA1). Women who inherit BRCA1 mutation(s) may have a 90% lifetime risk of developing either breast or ovarian cancer.[22] The application of the identifica-

The authors are with the Centers for Disease Control and Prevention, Atlanta, Ga. See the Acknowledgments for a complete listing of the members of the group.

Requests for reprints should be sent to Muin J. Khoury, MD, PhD, Birth Defects and Genetics Diseases Branch, National Center for Environmental Health, Centers for Disease Control and Prevention, Mailstop F45, Atlanta, GA 30341-3724.

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TABLE 1—Public Health Core Functions in Applying Genetic Technology to Disease Prevention

Step	Description of Activities	Disease/Gene Examples
Assessment	Epidemiological studies (assess risks and attributable fractions; gene–environment interactions)	Rheumatoid arthritis, Alzheimer's disease, breast cancer
Policy development	When and how genetic tests are to be applied in disease prevention programs	Testing for various genes
Assurance	Development of public health genetic programs, evaluation of prevention effectiveness, quality assurance	Newborn screening for sickle cell disease, proficiency testing for newborn screening

tion of such genes has been in the context of genetic counseling and the delivery of preventive medical health care to individuals in high-risk families. However, the only available means of primary prevention thus far has been prophylactic mastectomy, which may not provide full protection against the development of breast cancer[23,24] and which raises important issues regarding widespread genetic testing for BRCA1. In addition, the contribution of the apparently numerous BRCA1 mutation(s) to the overall risk of breast and ovarian cancer in the population needs further evaluation.

Genetics and the Levels of Disease Prevention

Prevention strategies include primary, secondary, or tertiary interventions. Primary interventions seek to prevent disease before it occurs. For rare, fully penetrant, and lethal single-gene and chromosomal disorders, medical and community-based interventions thus far have focused on carrier detection and premarital counseling, as well as on prenatal diagnosis and pregnancy termination. (This last may not be considered primary prevention.) Such approaches have been applied for several single-gene conditions such as Tay-Sachs disease[25] and for chromosomal disorders such as Down's syndrome.[26,27]

Primary prevention will have an important role in genetically influenced disorders other than the rare and lethal single-gene disorders, an excellent example being neural tube defects. A promising avenue for primary prevention is the discovery that maternal periconceptional folic acid use reduces both the risk of recurrence of neural tube defects among women with a previously affected pregnancy, as well as the risk of first-time occurrence of neural tube defects in the population.[28] A recent analysis of the relationship between folate levels and neural tube defects suggests that food fortification with folic acid may be the most cost-effective way to reach women of reproductive age.[29,30]

Secondary prevention targets clinical manifestations of disease by early detection and intervention during the preclinical phase of the disease. A classic example in public health genetics is newborn screening for metabolic disorders such as phenylketonuria and galactosemia,[31] with resulting early intervention.

Tertiary intervention minimizes the effects of disease by preventing complications and deterioration. One example of a tertiary prevention effort for a genetic disease is that of antibiotic prophylaxis and immunization for individuals with sickle cell anemia to prevent life-threatening bacterial infections.[32] Another example is the identification of factor VIII gene mutations and associated HLA genotypes that predispose hemophilia A patients to develop factor VIII inhibitors.[33,34] Early identification of this propensity can provide an opportunity for intervention with an immune tolerance program to prevent life-threatening bleeding complications of hemophilia.

Nevertheless, most chronic diseases are etiologically heterogeneous; no single gene is likely to account for a significant attributable fraction of cases. Furthermore, not all persons with a susceptibility genotype will develop the disease. Since most nongenetic risk factors for chronic diseases usually have low predictive value for these diseases,[35] the use of genetic tests is likely to improve the disease predictive value of environmental risk factors.[36] Therefore, a new paradigm of the primary prevention of many chronic diseases could be the identification and interruption of environmental cofactors that lead to clinical disease among persons with susceptibility genotypes.[36] For most diseases and genetic risk factors, such cofactors are poorly understood, and much work is needed before the results of basic genetic research and findings in high-risk families can be translated into population-based interventions.[37]

Core Public Health Functions in Genetics

Assessment

The Institute of Medicine has recommended that "every public health agency regularly and systematically collect, assemble, analyze and make available information on the health of the community, including statistics on health status, community health needs, and epidemiologic and other studies of health problems."[11(p 7)] If the public health applications of the Human Genome Project are to be widespread, the impact of genes in the population at large has to be carefully evaluated through epidemiological studies. Such studies quantify the impact of susceptibility alleles on disease incidence and prevalence. Population-based cohort, cross-sectional case–control studies are needed to estimate relative and absolute risks (positive and negative predictive values) associated with each allele, as well as the population-attributable fraction for the disease of interest.[10] The case–control method, which compares the frequency of specific alleles between affected and unaffected individuals drawn from the same population, has great appeal since DNA studies provide biological markers for susceptibility that do not change over time.[38] Also, multiple genes can be assessed in case–control studies as independent factors in epidemiological analyses. Case–control approaches also provide an important way to look for effect modification and to illuminate biological interaction between genes and nongenetic risk factors (such as occupational exposures and diet and lifestyle factors).[38] The study of gene–environment interaction can provide an important basis for refining the predictive value of traditional epidemiological risk factors and for targeting intervention and preven-

tion activities for individuals in high-risk groups.[10]

One example of a population-based study is the evaluation of the association between the HLA system and rheumatoid arthritis. The contribution of this genetic system to the genetic etiology of rheumatoid arthritis is estimated to be on the order of 30% of the total risk.[39] The immune response *HLA-DR4* allele (*DRB*0401*) is associated with up to a sixfold relative risk of disease. Among Whites, it is also associated with a more severe form of rheumatoid arthritis, in which a gene dosage effect is observed.[40] Screening for *HLA-DR4* among patients with rheumatoid arthritis may therefore be useful in disease management. Although no single environmental factor or infectious agent has been associated with rheumatoid arthritis, it is interesting that *HLA-DR4* is also associated with an increased risk of chronic Lyme arthritis (*Borrelia burgdorferi* infection).[41] Other genes, such as T-cell receptor sequences, may also be involved in rheumatoid arthritis etiology.

Another example of a population-based study is the evaluation of the association between Alzheimer's disease and the apolipoprotein E *E4* allele. Mounting evidence suggests that the apolipoprotein E *E4* allele is strongly associated with both late-onset familial Alzheimer's disease and the more common sporadic Alzheimer's disease.[42–44] Among families at high risk of late-onset Alzheimer's disease, disease risk has been shown to increase with the number of *E4* alleles; 47% of people heterozygous for the *E4* allele and 91% of people homozygous for the *E4* allele were shown to be affected.[42] Risk ratios for heterozygotes and homozygotes were 2.8 and 8.1, respectively.

Public Health Policy Development

The Institute of Medicine has recommended that public health agencies use the scientific knowledge base obtained from an assessment of the health of the population in the decision making and formulation of public health policy. In the arena of genetics, one goal is the use of genetic testing in medical practice as well as in population programs designed to reduce morbidity and mortality associated with disease and susceptibility genes. In any formulation of sound public health genetic policy, however, several issues need to be considered before genetic tests can be applied in population-based prevention programs (Table 2).

The avalanche of genomic information expected to accrue over the next decade has already led to concerns regarding the potential misuse of such information.[5–8] Holtzman[6] argues that there is a great need to "proceed with caution" in applying genetic testing in human populations because (1) society's use of genetics has, in the past, led to human rights abuses; (2) an accelerating trend toward commercialization of DNA technology and motivation for profit could lead to differential development of testing for certain diseases but not for others; (3) indiscriminate application of genetic tests could occur without an understanding of the limitations in interpreting their results; and (4) our ability to detect susceptibility genes will outpace our ability to provide effective intervention after these genes are detected. Nevertheless, the detection of disease susceptibility genes provides the exciting possibility of learning about gene functions and could open entirely new approaches for treatment as well as prevention.

One example of the ethical questions involved in genetic testing is the use of DNA testing in detecting a predisposition to cancer. Despite the recent successes in identifying breast and colon cancer genes, the National Advisory Council for Human Genome Research recently concluded that "it is premature to offer testing of either high-risk families or the general population as part of general medical practice."[45 (p785)]

Another ethical issue has involved genetic testing in the workplace for use in job placement, relocation, and the targeting of medical surveillance.[47–50] The objectives of such testing could include differential diagnosis in cases with clinical symptoms, monitoring for toxic effects, and screening for susceptibility to the effects of chemicals.

Steps and safeguards have been suggested to deal with ethical issues surrounding genetic testing. These include protection of individual autonomy and the right to decide based on a proper informed-consent process, preservation of the confidentiality of results of genetic testing, limitation of genetic testing in the workplace and by insurance companies, careful scientific evaluation of the ability of genetic tests to measure the underlying susceptible genotype, and education of the medical profession and the general public.[6] There are definite concerns regarding employment discrimination against individuals with specific genotypes. At present, genetic tests are not generally recommended because of a lack of information on their predictive value. This suggests that applied epidemiological studies are necessary to evaluate genetic tests both within and outside the workplace. Increasingly, many people will belong in one or more subgroups that are genetically sensitive to the effects of exposure. There are currently no good models for dealing with genetic variation in environmental and occupational regulations.

TABLE 2—Issues to Consider in Using Genetic Testing in Disease Prevention

1. Public health impact of disease: incidence, prevalence, morbidity, mortality
2. Prevalence of genotype
3. Laboratory quality issues: analytic sensitivity, specificity, and predictive values of genetic test
4. Magnitude of association between genotype and disease: relative, absolute, and attributable risks
5. Interaction with known modifiable risk factors for the disease
6. Available intervention or prevention methods
7. Cost of test
8. Ethical, legal, and social issues

Furthermore, as the genetic basis for complex behavioral disorders continues to unravel,[51–53] ethical issues will become prominent in potential applications of genetic testing for predispositions to behavioral patterns and psychiatric disorders. Discussions about these issues should be ongoing before any genetic tests are applied in medicine and public health.

Finally, it seems prudent to enact new laws that serve as guidelines or restrictions for applying genetics in public health programs as current regulations do not adequately protect an individual's privacy regarding genetic information. Detailed discussion of these issues is beyond the scope of this article.

Assurance

Assurance can be viewed in the context of the three overlapping strategies for disease prevention: behavior prevention, environmental prevention, and clinical prevention.[54]

The behavior prevention strategy requires the ability to educate individuals regarding the risks for diseases in them, their progeny, and their relatives based on the unique combination of their genetic

background and their lifetime experiences. Although human gene therapy trials are in progress for a multitude of single-gene disorders, it is unlikely that this form of intervention will be readily available for common human diseases in the near future. Thus, while genotypes of individuals remain unchanged, environments can be modified at the level of either individuals or populations, and behavior prevention efforts could be targeted toward elimination, reduction, or change of the environmental exposures to individuals. Education and behavior modification can sometimes be most effective in population groups at highest risk for the disease in question (e.g., HIV infection[55]). In genetics, the basic premise is that education and behavior modification can be targeted toward individuals with differential genetic susceptibilities to specific environmental factors in order to reduce the risks for specific diseases.

The environmental prevention strategy is oriented toward reducing exposures in the workplace and in the home, and reducing disease risks by supplementing food or water with certain essential nutrients. For example, water fluoridation programs have contributed to the tremendous decline of dental caries in many countries. Environmental strategies for intervention are geared toward the population as a whole and do not inherently address genetic differences among individuals. Sometimes, global programs such as food supplementation, while beneficial to most people, may be deleterious to a relatively small fraction of genetically susceptible individuals who could be more sensitive to adverse effects from this intervention (such as deleterious effects of iron supplementation for persons with hereditary hemochromatosis).

The clinical prevention strategy emphasizes preventive medicine in the health care setting. This is the traditional method of family-based intervention through genetic counseling. In an era of health care reform and cost control, the delivery of high-quality preventive care is essential. Although new medical technologies can be expensive, the appropriate use of molecular genetic technology is likely to improve the cost-effectiveness of screening and intervention strategies by targeting prevention strategies to persons at high risk of developing diseases. This is true for several reasons. First, procedures used to amplify DNA obtained from blood samples and to identify specific disease-related alleles are becoming increasingly automated and refined. As a result, the cost of DNA-based testing will continue to decrease dramatically. Second, many traditional methods used to identify persons at increased risk of disease, such as a family history of cancer or heart disease, analysis of blood lipids, dietary assessment, and blood pressure measurement, are often weak predictors of disease risk and frequently result in either a false-positive or a false-negative classification of an individual's risk status. Thus, the improved ability of molecular genetic techniques to classify risk factor status accurately can reduce the costs as well as increase the effectiveness of intervention strategies.

One essential public health function is to translate research into practice. Although research efforts can identify the efficacy of specific interventions, the effectiveness of such interventions needs to be carefully evaluated in population settings. Thus, an important public health application of genetics is to evaluate the effectiveness of population-based programs (e.g., follow-up after newborn screening) and to ensure the quality of genetic testing in the population.

For example, sickle cell disease is an autosomal recessive disorder affecting about 1 in 400 African-American newborns. Affected children have long been known to be at increased risk for morbidity and mortality because of complications such as septicemia, especially between the ages of 1 and 3 years.[56] Using a randomized controlled clinical trial, researchers have shown that the early institution of penicillin prophylaxis is highly effective in reducing morbidity and mortality among infants and children with sickle cell disease,[32] so penicillin prophylaxis is now used widely in the comprehensive primary care of children with this disease. This has led, in part, to the initiation of pilot newborn hemoglobinopathy screening programs in the 1970s. A National Institutes of Health Consensus Conference concluded that screening newborns for sickle cell disease could reduce morbidity and mortality.[57] By 1993, more than 40 states had responded with programs for screening at least selected newborns.[57] But despite the well-documented beneficial effects of early medical intervention for sickle cell disease, no population-based national data are yet available with which to assess and track the effectiveness of preventing morbidity and mortality among infants with sickle cell disease ascertained through newborn screening. In particular, more information is needed regarding determinants of morbidity and mortality among such infants.

Finally, an important component of assurance is the quality assurance of genetic testing. For more than 17 years, the Centers for Disease Control and Prevention has conducted research on material development and has assisted laboratories with the quality assurance for newborn dried-blood-spots screening tests. These quality assurance services primarily support newborn screening tests (e.g., for congenital hypothyroidism, phenylketonuria, and hemoglobinopathies) performed by state laboratories. The quality assurance program enables screening laboratories to achieve high levels of technical proficiency and continuity that transcend changes in commercial assay reagents. In addition, the program provides laboratories with quarterly panels of blind-coded dried blood specimens and gives them an independent external assessment of their performance.

Laboratories that perform genetic tests and report those test results back to patients must comply with the regulations put forth by the Clinical Laboratory Improvement Act of 1988.[58] Prior to reporting test results, laboratories must establish for each method the performance specifications for the accuracy, precision, analytical sensitivity and specificity, and reportable range of patient test results; the reference range of normal values; and any other applicable performance characteristics. These regulations, which ensure that genetic tests can have high sensitivity, specificity, and predictive value for the genotype they are measuring, have obvious implications not only in clinical medicine but also in public health programs (e.g., newborn screening).

Concluding Remarks

If the Human Genome Project is to have widespread applications in disease prevention, population-based epidemiological studies are needed to assess the role of genes in specific diseases, and the interaction with known and modifiable disease risk factors. Such studies provide the scientific foundation for validating genetic tests in the population. At the same time, ethical, legal, and social issues need to be carefully evaluated before any genetic tests can be used for disease prevention. Finally, it is essential that public health agencies evaluate the effectiveness of genetic testing programs and ensure the quality of genetic testing in the US population. □

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Members of the Genetics Working Group, by their affiliation within the Centers for Disease Control and Prevention or elsewhere:

National Center for Environmental Health: Myron Adams, Vicki Brown, Andrew T. L. Chen, J. David Erickson, William Hannon, Joanne Mei, Cynthia Moore, Patricia Mueller, Godfrey Oakley, Richard Olney, Chin-Yih Ou, John A. Reidy, Karen Steinberg, Nedra Whitehead.

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National Institute for Occupational Safety and Health: Paul Schulte.

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