Genomic Medicine and Racial/Ethnic Health Disparities: Promises, Perils, and the Challenges for Health Care and Public Health Policy

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INTRODUCTION

For more than a century, public policy decisions spurred by scientific discoveries regarding evolution, heredity, human variation, genetics and eugenics have been surrounded by controversy, optimism, fear, and human tragedy. In the last half-century, since the discovery of the DNA double helix, humans have been both attracted to, and frightened by, the notion that medical science might someday be capable of enormous advances in medical treatments centered on genetic characteristics. Through the Human Genome Project and other scientific efforts, researchers have mapped the entire human genome (ie, the sequence of chemical components of DNA). Scientific and policy debates following new genetic discoveries have been intense and emotional in all spheres of human life and public discourse. The controversies have been intractable and the debates have been intense and emotional when they have involved questions about the causes of, and solutions for, racial and ethnic health disparities in the United States.  

Disparities in health status and health care in the United States are well known and in fact increased within the last 50 years. We use the terms racial and ethnic health disparities as they are used in statistical reports published by the US government. A large body of research shows that a significant cause of some disparities is long-standing, pervasive racial and ethnic discrimination. Additionally, several authors have explored the newer area of genetic research and its potential utility in explaining at least part of the burden of racial and ethnic health disparities not explained by discrimination or other causes.  

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Reporting genetic findings in health disparities research has sometimes led to intense controversy. For example, Palmar et al found a persistent increase in risk of pre-maturity in infants born to White mother-Black father pregnancies after adjustment for many sociodemographic and medical risk factors in a very large population-based cohort, and attributed the differences to genetics. Letters sent to the journal editors by others lamented what they claimed to be the inappropriateness of the application of the construct of race by the authors to suggest that Black fathers’ genetic contribution was the primary reason for this increase in risk. In their response, the authors defended their conclusions but acknowledged that they were controversial. Many researchers have concluded that environmental and behavioral factors tend to have a stronger influence on summary measures of population health (eg, life expectancy) than genetic factors or access to medical care. Taking a somewhat different approach, other researchers have concluded that most diseases, including single gene and multiple gene disorders, arise from the

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complex interactions between genes and the environment as a function of the age or stage of development of the individual. However, whatever the differences are in the two approaches, it must be emphasized that most genetic researchers are well aware of the importance of environmental causes of health disparities. Very few would contend that genetic research alone is likely to be the key to the alleviation of racial and ethnic disparities in health status.

Extensive genetic research on common complex diseases using genome-wide association studies has led to many novel genetic risk loci, as well as opportunities for research to improve health care. However, translating genomic-based research for public health has raised new issues such as evidence of utility, economic implications, equal access, and public perspective.

The aims of this article are: 1) to show how developments in genomic medicine may increase the potential for a higher degree of disparities in screening and treating populations; 2) to illustrate the validity problems in, and limited utility of, current genetic testing; 3) to consider how public health agencies should respond to developments in genetic research, both to improve its validity and reliability, and to ensure more equitable access to more accurate and useful technologies as they develop; and 4) to examine the possibility that advances in genomics might contribute to a better understanding of, and the possible future elimination of, racial and ethnic health disparities, which in turn will depend on how effectively research is conducted and interpreted, and the extent to which valid and useful findings are effectively applied to improve health policies and practices.

**Advances in Genetic Medicine**

Genetic medicine is already beginning to enter the realms of primary care through the availability of testing for predisposition to certain cancers and carrier screening and diagnostic tests for common recessive disorders such as cystic fibrosis and hereditary haemochromatosis. In pharmacogenetics, researchers study the effects of variation in the genetic makeup of patients on the risk of some diseases and responses to treatment with particular drugs. For example, variation in the gene that controls the production of apolipoprotein E in the human body, affects the response to lipid lowering drugs and the risk of Alzheimer’s disease.

Recently, FDA approved diagnostic tests to detect two critical genes that control drug metabolism, CYP2D6 and CYP2C19, using the AmpliChip microarray assay. The approval of AmpliChip by FDA is limited to analytic validity and clinical feasibility, and does not include any claims of clinical validity or utility for specific pharmacogenomic applications.

Some researchers have speculated that the identification of these two genotypes might help clinicians to predict how patients would metabolize some drugs based on enzyme activity and allow genetic testing to tailor drug treatment for each patient. Individualized therapy may assist patients by reducing adverse drug reactions and minimizing drug dose requirements.

The differences in prevalence of diseases, allele frequency and genotype frequency among racial/ethnic groups are well known. Population genetic studies have revealed large genetic variations across the five racial subpopulations that map to continental history. The Third National Health and Nutrition Examination Survey (NHANES III) conducted by the National Center for Health Statistics is the first nationally representative survey of the United States population to provide genetic data. Linkage of the NHANES III phenotype data with this genetic information provides the opportunity to conduct a vast array of outcome studies designed to investigate the association of a wide variety of health factors with genetic variation. Researchers who analyzed the survey data by racial/ethnic groups (non-Hispanic whites, non-Hispanic blacks and Mexican Americans) found significant differences in allele frequency (in 88 of 90 genetic variants) and genotype prevalence (in 87 of 90 genetic variants).

Researchers analyzing NHANES III survey data found that genetic variants are differentially associated with disease outcomes in different racial and ethnic groups. A candidate gene study of the association of five genetic variants with metabolic syndrome using dominant and additive models showed that the significance of the associations between the polymorphisms and metabolic syndrome differed markedly between the three racial/ethnic groups. Another study of the association between genetic variants and chronic kidney disease (CKD) using multivariate analysis showed association of different genetic variants among the three racial/ethnic groups.

If studies of optimal power were available, we hypothesize the strength (“effect sizes” or the odds ratios) and direction of associations among multiple genetic variants and specific disorders would vary across categories of race/ethnicity, especially when data are available for all racial/ethnic categories.

The differences in disease prevalence, genotype frequencies, and the odds ratios of association between the disease and the genotype have an impact on predictive genetic testing for diseases for different racial/ethnic groups. An important consideration for genetic susceptibility testing is the concept of genomic profiling – using genetic variants at multiple loci that are weak risk factors individually for a complex disease but collectively may better predict future disease. The genomic profiles for individuals who are not identical twins would be different for different individuals; and often the
variation of genomic profiles might be higher within racial/ethnic groups than between racial/ethnic groups. However, the genomic profile for a given disease could have different genetic variants for different racial/ethnic groups.

WHAT ARE THE IMPLICATIONS FOR HEALTH SCIENCE AND HEALTH CARE?

There is heated debate over what implications can be drawn from the developing research. Do the results indicate that we have to consider different genetic tests and different genomic medicine for different racial/ethnic groups? If we do this, will it reduce or add to the current racial, ethnic and class disparities in health care services in the United States?

At least 29 medicines (or combinations of medicines) have been claimed in peer-reviewed scientific or medical journals to have differences in either safety, or more commonly efficacy, among racial or ethnic groups. However, these claims are sometimes highly controversial. The US Food and Drug administration approved the heart failure drug, isosorbide dinitrate and hydralazine hydrochloride (BiDi®), aimed at Black patients in 2005 and this is the first time that the agency has approved a drug for a specific racial group.

Genetics as well as confounded environmental factors probably contribute to many of the reported differences in gene-disease associations between different racial or ethnic groups. Furthermore, the results of studies vary with the analytic role (confounder, effect modifier, or stratification variable) assigned to race/ethnicity by the investigator. The case of beta blockers illustrates this problem. Researchers at Washington University and the University of Maryland recently reported that a significant number of Black heart patients had a gene alteration that resulted in the patients “making what amounts to their own version of beta blockers all the time.” This, the researchers concluded, might explain previous research that had shown that many Black patients with heart failure seemed to receive little additional clinical benefit from taking beta blockers. The research estimated that 40% of Blacks, but only 2% of Whites, have this gene variant. But this apparently large difference does not necessarily provide a clear indication of how clinical practice should change if at all.

According to the research, a clear majority of Black patients still benefit from beta blockers, as do the overwhelming majority of White patients. A physician who wants to change his prescribing practices in light of this research will have to order a genetic test for each Black patient before making a decision about the use of beta blockers for the particular patient. Even if only 2% of White patients have the gene variant, should White patients also be screened because they are White? Should treatment be personalized to the patient’s genetic characteristics and other personal lifestyle and health-related characteristics instead of being race-based? And what is the cost-effectiveness of this preliminary screening? Often significant differences by racial category do not provide a reliable guide when it comes to any particular individual. Race, whether imposed or self-identified, is a weak surrogate for various genetic and non-genetic factors in correlation with health status.

Advancing pharmacogenomic science should lead to a greater capability to identify the molecular basis of drug response. This should in turn reduce and then eliminate the need to rely upon relatively crude racial classifications for purposes of drug therapy selection. Some researchers contend that a focus on race is clinically misleading and socially dangerous, since it reinforces a concept of division that has created enormous injustice throughout history. In contrast, other researchers strongly argue that race clearly does matter, given the current state of genetic research and diagnosis, and it would be clinically and ethically wrong to ignore measurable differences and treat the concept of race as an unmentionable taboo. In our view, race is a social construct with a terrible history of scientific misuse. However, despite the past misuse of race in science, the subject certainly is not taboo or too controversial to be examined in empirical genomic studies.

Nevertheless, even if racial stereotyping and discrimination do not increase in the course of advancing genetic medicine, disparities may arise from the differential access by race/ethnicity to the application of personalized diagnosis and treatment. If it becomes possible to determine the unique genetic profile of an individual, clinicians should then be able to treat each individual for his or her own genetic susceptibilities. This suggests a future in which accurate predictive medicine, based on one’s individual genetic profile, would promote healthier lives and a better ability to manage interactions with the environmental factors. However, in the increasingly private and market-oriented health care system of the United States, the more personalized healthcare testing and treatment stemming from genomics may significantly increase the already substantial health disparities seen in the population. Currently, genetic testing is costly, and its cost-effectiveness has not been satisfactorily demonstrated to many payers. At present, therefore, most genetic testing is paid for directly by the patient out of pocket. In the absence of public initiatives to extend genetic testing coverage requirements for health insurance, lower income (and many middle income) citizens will not benefit from the advancing research. If that happens, genomic medicine will be added to a potentially long list of valuable medical technologies that will
be rationed by cost, and ability to pay, rather than need or clinical effectiveness.\textsuperscript{39}

Less access to, and utilization of, genetic counseling and cancer predisposition testing among the underserved of all racial/ethnic groups, as well as with racial and ethnic minorities compared with the White population, has led to growing healthcare disparities in clinical cancer genetics that are only beginning to be addressed.\textsuperscript{40} Deficiencies in the utility of genetic testing in underserved populations as a result of the limited testing experience, and in the effectiveness of risk-reducing interventions, compound access and knowledge-base disparities.\textsuperscript{40}

Ironically, one factor mitigating the adverse impacts of these developments on US health equity is the still rudimentary level of genetic testing and medicine. Research may have uncovered the human genome, but there are not many developed medical applications for the knowledge at present. Individuals are paying for personal genome analyses and going to their physicians with the results, only to find that the information has currently very limited practical use. Until more genetic testing and applications of genomic medicine become clinically valid and useful, differential access to these innovations by race/ethnicity might be less harmful to the disadvantaged.

Most current genetic tests appear to be analytically valid (accurately and reliably measuring a given genotype). However, their clinical validity is very modest, given the current science. More fundamentally, the clinical utility of most genetic tests is unknown. “If a patient is found to be at risk for a disease, what can be done about it? This is the arena in which there are virtually no data available on the health impact of genome-wide analysis.”\textsuperscript{41,44}

There is very little existing research that can show how human genome discoveries can be translated into health care and disease prevention. One estimate is that only 3% of published genomic medical research focuses on the value of genomic applications for health practice, the subsequent development of evidence-based guidelines, the use of guidelines in health practice, and/or the real world health outcomes of genomic applications. Genomic research findings are often reported sensationaly in the news media, but are often not clearly connected to possible changes in current clinical practice.\textsuperscript{42}

**DISCUSSION**

Current advances in genetic medicine are promising but the promise will not be fulfilled easily. A great deal of additional research must be done to move genetic medical findings into clinical practice. We must also consider the possible impact of these findings on health disparities and how the benefits of genomic medicine can be extended to everyone, not just those who can pay the often high price. Faced with these issues, what should public health policymakers do?

The development and growing applications of genomic medicine have raised a number of policy implications and issues that public health policymakers and professionals are considering now. These must be clarified and resolved in the near future if genetic medicine is to be a valid and reliable technology for all citizens regardless of wealth, race/ethnicity, or other determinant of social disadvantage. Below, we offer four implications for public health policies and professionals.

**Implication 1**

Health policymakers must continue efforts to ensure that genetic research findings are not employed to invade the privacy of individuals, and damage their ability to find employment and health insurance.\textsuperscript{44} After 13 years of legislative struggle, the Genetic Information Non-discrimination Act of 2008 was enacted. It provides a foundation for further necessary policymaking in order to prevent the use of genetic information to maintain or establish social disparities and individual privacy violations.\textsuperscript{20}

It is clear that much more public and clinical education is needed on the potential benefits and limitations of genomics. As noted earlier, those purchasing individualized genetics diagnostics often have an unrealistic expectation of the health benefits that they will receive, above and beyond following tried and true positive health behaviors, such as controlling calorie and alcohol intake, avoiding tobacco products, engaging in regular exercise and the like.\textsuperscript{41,44}

Public health professionals and organizations can, and increasingly do, play an important role in educating the public as to the benefits and limitations of marketed genomics products. For example, the Departments of Public Health for the states of Connecticut, Massachusetts and New York have worked together to formulate a response to a direct-to-consumer (DTC) marketing campaign for BRCA 1 and BRCA 2 testing. The objective is to ensure that citizens, particularly potential customers for the testing, are aware of the various demographic factors, including personal and family histories of breast and ovarian cancer that might make the test worthwhile. The states also want to provide accurate and unbiased information about the BRCA 1 and BRCA 2 testing processes and outcomes to providers, the general public and those who are truly at high risk for developing cancer.\textsuperscript{45}
Implication 2

The public health community, and its researchers, must increase their commitment to and involvement in genomics research and its applications.\(^6\) In an era where health care is increasingly marketed as an individual economic commodity, at price levels that exclude many citizens, it is important that genomics and other technologies be developed and implemented to benefit community health.\(^7\) The Centers for Disease Control and Prevention (CDC) have already begun funding public health genomics research and training, both at the national and state level.\(^8\) The EGAPP initiative by CDC has been established to develop an evidence-based process by which genomic technologies can be assessed for their potential transfer to clinical practice.\(^9\)

These research efforts need to be collaborative, involving private and public sectors, and all relevant areas of health research. They also need to be sustained and expanded throughout the United States and internationally. One group of researchers has called for “an interdisciplinary knowledge integration process under the rubric of a field variously dubbed public health genomics or public health genomics, which is poised to address these challenges, [and] the development of an international initiative to promote a collaborative approach to harness genome-based knowledge for the benefit of worldwide population health.”\(^50\) Here as elsewhere, population health must ultimately include global health.

Implication 3

A major challenge for researchers, practitioners, and policy makers alike is to be mindful that race is a social construct with a terrible history of scientific misuse. They must also always remember that racial categories are neither determined by, nor exclusively associated with, bad disease genes. Genetic and genomic research questions, treatment options, and policy objectives should be framed in ways that do not encourage eugenic ideologies or facilitate illegal discrimination based on race/ethnicity, socio-economic status, or other social determinants of disadvantage or health disparities.

Implication 4

Finally, and most importantly, the US public health community must work with others to widen public access to valid and cost-effective generic medicine, but also to remind the nation and world what generic medicine can and cannot do. Genomics encompasses a potentially valuable set of present and future technologies that can save and improve many lives. But, in the US, these technologies now lie within a larger health care system that reflects a society containing large health and other social disparities.

Whatever benefits genetic technologies bring to health care and public health — and they might be quite substantial — the realization of those benefits depend on the development of a national public health and health care system that guarantee everyone access to necessary health services and an equal opportunity to be healthy. That is the only way that we can truly respond to the national tragedy of health disparities.

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478 Ethnicity & Disease, Volume 19, Autumn 2009