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Using Genetic Technologies To Reduce, Rather Than Widen, Health Disparities

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Abstract

Evidence shows that both biological and nonbiological factors contribute to health disparities. Genetics, in particular, plays a part in how common diseases manifest themselves. Today,

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unprecedented advances in genetically based diagnoses and treatments provide opportunities for personalized medicine. However, disadvantaged groups may lack access to these advances, and treatments based on research on non-Hispanic whites might not be generalizable to members of minority groups. Unless genetic technologies become universally accessible, existing disparities could be widened. Addressing this issue will require integrated strategies, including expanding genetic research, improving genetic literacy, and enhancing access to genetic technologies among minority populations in a way that avoids harms such as stigmatization.

Health disparities between whites and vulnerable social groups such as racial/ethnic minorities are often rooted in nonbiological factors, such as socio-economic status. Indeed, race is a sociocultural construct, not a biological category. However, genetics plays a part in how common diseases manifest themselves and is thus worth exploring from a health disparities perspective.

Approximately 60,000 years ago, small groups of people left Africa to populate the remaining continents.[1] Environmental forces encountered during thousands of years of migration (such as famine, climate, and disease) in some cases favored genetic differences that allowed certain people to live longer and reproduce more successfully than others.[2] The imprint of these evolutionary forces remains visible in human genes, and genetics can be used to detect, prevent, and treat disease in ways that recognize ancestral differences (that is, differences based on the continental origin of a person’s ancestors).

The past decade has seen major leaps forward in genetic technologies and medical therapies that are tailored to individuals. This has provided a foundation for the Precision Medicine Initiative, launched by President Barack Obama in 2015, which will collect and analyze information from a million volunteers and generate new understanding of how genetics, environment, and lifestyle contribute to disease.[3] However, new genetic technologies such as next-generation sequencing may be implemented in ways that perpetuate and even widen health disparities.

These technologies can detect mutations not only across the entire genome, but also in tumors themselves. The technologies have heightened awareness of the complexity and heterogeneity of diseases such as cancer and brought the promise of precision medicine closer to reality. Large-scale high-throughput technologies have also advanced the field of epigenetics, which describes chemical modifications to DNA that may alter gene expression without altering the DNA sequence itself. In contrast to genetic mutations, which remain fixed throughout a lifetime, epigenetic changes can be affected by lifestyle behaviors (such as diet, smoking, and physical activity). A growing body of research seeks to understand how socioeconomic status contributes to health disparities through epigenetic mechanisms.[4]

Despite the impressive leaps forward in genetics, not all groups are positioned to benefit from discoveries in the field. Breast cancer and chronic kidney disease represent two common diseases for which genetic and molecular knowledge have grown exponentially but for which racial and ethnic health disparities persist. In this article we illustrate how genetics has been used to combat breast cancer and kidney disease and discuss how to advance

genetic applications in health care in a way that reduces racial and ethnic disparities instead of widening them.

Using Genetics To Combat Disease

Hereditary Breast Cancer

The most common cause of hereditary breast cancer is hereditary breast and ovarian cancer syndrome, which is caused by mutations in the BRCA1 or BRCA2 genes. Eighty-five percent of women with the mutations (compared to 12 percent of women in the general public) will develop cancer, and 27–44 percent of women with the mutations (compared to 1.5 percent in the general public) will develop ovarian cancer. Women with the mutations can receive intensive cancer surveillance (for instance, having repeated screening by magnetic resonance imaging as well as mammography, and beginning mammography at a younger age than usual) and risk-reducing surgeries (such as mastectomies and removal of the ovaries). Among those who have the mutations, these surgeries have been shown to reduce cancer and mortality, compared to those who do not elect surgery.[5]

Studies indicate that African American and Hispanic women—including those with strong family histories of cancer—are much less likely than white women to receive genetic counseling or genetic testing for breast cancer.[6] Studies have reported that only 28 percent of at-risk African American women receive genetic counseling and testing, with low rates for Hispanic women as well.[7,8] National data from commercially insured patients with newly diagnosed early-onset breast cancer showed that only 30 percent of those diagnosed had received genetic testing.[8]

Because third-party insurance, Medicare, and some Medicaid plans cover testing for the BRCA1 and BRCA2 mutations, with costs waived for people with financial hardship, affordability does not appear to be the issue. Instead, the reasons for the disparities in genetic counseling and testing may be social and educational. In 2010 researchers from the Centers for Population Health and Health Disparities, a network of university-based research centers, documented that misconceptions about breast lumps—for example, that a nonpainful lump does not require medical evaluation—were more common among members of racial/ethnic minority groups and were associated with delays in seeking treatment.[9] In minority communities, low awareness of familial cancer risk and social and cultural beliefs, such as those that lead to stigma about hereditary cancer, also appear to contribute to disparities in the use of genetic services.[10]

In addition, evidence shows that one-third of African American women at high risk for hereditary breast cancer have not been referred for genetic counseling and testing, and physicians whose patients were mostly minorities were less likely than other physicians to order genetic tests.[9–12] Among women who do receive genetic counseling, members of minority groups are as likely to pursue genetic testing as whites are.[13] Education of both patients and health care providers may reduce culturally and racially based obstacles to genetic testing.

Genetics research aimed at reducing racial/ ethnic disparities should be built on a multilevel transdisciplinary foundation.[14] Within the Centers for Population Health and Health Disparities, investigators from the Partnership to Understand and Eliminate Disparate Outcomes (PUEDO) at the Fred Hutchinson Cancer Research Center are partnering with Mexican American women to explore the women's ancestry and breast cancer and the role of genetic testing in reducing breast cancer disparities between Mexican American and white women.[15]

PUEDO investigators found low levels of genetic literacy among rural Mexican Americans in the study, but the investigators suggested that community-based participatory research approaches could facilitate health awareness and improve the dissemination of genetic information.[15] In a linked project, investigators will examine the ancestral heterogeneity of study participants (with European, American Indian, and African ancestry) and test for relationships between the genetic markers that reflect ancestral origins and disease. Such research will inform individualized assessment of risk and facilitate health care that is more appropriate than current care.

> Consensus among genetic ethicists has discouraged the use of genetic tests that are not clinically useful.

Such studies may uncover new genetic sequences that are not yet recognized as risk markers for breast cancer. The genetic databases on which clinical decisions about treating breast cancer rely are incomplete for minority groups, which severely undermines the quality of genetic testing in those who do receive it. The "normal" genetic sequence of the BRCA1 and BRCA2 genes was determined based on information about women of European or Ashkenazi descent, in whom risk is often determined based on a small, well-defined group of mutations. In contrast, it is not always possible to distinguish normal versus abnormal sequences in women from racial/ ethnic minority groups. Such women are more likely than white women to receive ambiguous results from genetic testing for breast cancer.[16] This situation perpetuates disparities in personalized health care based on genetic information.

Sporadic Breast Cancer

Although hereditary breast cancer has achieved a high level of public visibility, up to 90 percent of breast cancers are considered "sporadic"—that is, without known family history. For sporadic breast cancer, many recent clinical breakthroughs have emerged based on new knowledge of genetic markers, which have dramatically changed the landscape of breast cancer treatment over the past decade.

Sporadic breast cancer is the most common cancer among women, and, compared to white women, minority women tend to be diagnosed with more advanced disease and to experience worse five-year survival rates with sporadic breast cancer.[17–19] Genetic approaches and tools hold great promise for understanding and addressing the roots of these disparities. Moreover, understanding epigenetics may shed light on how the genetic control of cell division becomes deregulated and causes cancer.

Based on analyses of genetic data and tumor markers, breast cancer is increasingly recognized as a heterogeneous disease with multiple subtypes. Differences in tumor biology

—or, more appropriately, tumor aggressiveness—contribute strongly to the observed racial/ethnic disparities in breast cancer stage at diagnosis and survival rates.[20,21] A study by Javaid Iqbal and coauthors[22] supports the concept of a racial/ ethnic disparity in tumor aggressiveness, which refers to the higher prevalence of certain types of breast cancer in non-Hispanic black women than in non-Hispanic white women.[23–26] Aggressive tumors lack common therapeutically targetable proteins—the estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2, known as HER2.[27] Tumors lacking all three proteins are called “triple negative” tumors, and they are less amenable to treatment and are associated with worse prognosis, compared to tumors that contain these proteins.

The reasons for the greater prevalence of tumors that lack the estrogen receptor and those that lack the progesterone receptor, as well as of triple negative tumors, in non-Hispanic black women, compared to non-Hispanic white women, are a focus of ongoing research. Previous studies have suggested that socioeconomic status might account for these disparities.[28,29] However, a large nationwide survey showed that, compared to non-Hispanic white women, non-Hispanic black women had odds that were about twice as high of being diagnosed with triple negative tumors, regardless of socioeconomic status.[30] Furthermore, a recent study of racial variation in breast tumor methylation (a type of epigenetic change) suggested that methylation patterns of breast tumors, particularly the more aggressive ones, may differ depending on whether the patient’s ancestry is African or European, and that the racial differences could also contribute to cancer risk.[31]

A more complete understanding of the triple-negative breast cancer subtype, in particular, is needed to expand treatment options. One of the most promising research efforts comes from the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC), which developed more refined tumor classification schemes that better reflect the range of breast cancer subtypes, compared to previous schemes. By integrating genomic and gene expression data across cancers, METABRIC was able to classify cancers into ten integrative clusters.[32,33] The clusters can be mapped to distinct clinical outcomes, such as more or less aggressive tumors, and may therefore expand our understanding of the underlying biology and molecular drivers of breast cancer.

For example, cluster 10 includes high-grade triple-negative tumors that afflict young women and identifies a characteristic group of mutations. High-grade cancers are often faster growing, frequently metastasize, and are more likely than other cancers to recur after treatment. There is a greater prevalence of high-grade triple-negative tumors in non-Hispanic black women than in white women, but unfortunately few data exist on the prevalence of these integrative clusters in the former population.

Data are also lacking on how women who are genetically at risk for cancer might prevent the occurrence of triple-negative tumors through lifestyle changes or by avoiding certain environmental exposures. Data from a research consortium suggested that women who have not breastfed infants are at increased risk of these tumors and that promotion of lactation may be effective in reducing these types of cancers.[34] In a large analysis of the impact of lifestyle factors on breast cancer, a woman’s age at the birth of her first child appeared to be

the only factor associated with risk in women with mutations in the BRCA1 gene—with older maternal age being associated with less risk.[35]

Many promising markers and signatures from molecular, genomic, and epigenetic databases have the potential to explain the racial/ethnic disparity in tumor aggressiveness in sporadic breast cancer. Epigenetic markers may be especially informative about groups that are exposed to environmental risks, such as food deserts, unsafe streets, stress, and pollution. However, the small samples of tumors from minority women available for study, insufficient details about patient and tumor characteristics in the data, and limited follow-up information on minority women continue to limit translation of genetic knowledge into clinical benefits for all individuals.

Chronic Kidney Disease

As noted above, health disparities can arise biologically from the selection of genetic variants that were advantageous for survival at certain stages in humans' evolutionary history. Several genetic variants that protect against deadly infectious diseases have also been shown to contribute to racial and ethnic disparities in risk for chronic kidney disease. For instance, genetic variants in the APOL1 gene are protective against African trypanosomiasis (sleeping sickness), but they are also associated with kidney disease.[36]

As early as 1977 African Americans were known to have nearly four times the risk of end-stage renal disease as European Americans. This disparity is likely driven by the faster progression of kidney disease in African Americans than in European Americans and cannot be explained solely by traditional risk factors, such as hypertension, diabetes, and socioeconomic status.[37–41]

> One of the clearest messages from genetic studies is that cancer is much more biologically heterogeneous than originally recognized.

The advent of DNA microarray technology, which makes it possible to examine thousands of genetic variants at once, led to what is known as admixture mapping to facilitate the understanding of relationships among continental ancestral origins, genetics, and disease.[42] Admixture mapping takes advantage of the small proportion of genetic variants that differ in frequency across populations. Two years after the initial admixture mapping studies for renal disease began in the early 2000s, the APOL1 gene was identified as being associated with renal disease risk, and the risk genotypes were established.[36,43]

Researchers determined that high-risk genotypes of APOL1 exist in up to one of six individuals of African ancestry (16.6 percent) but are extremely rare in European Americans.[44] Having these genotypes can increase a person's risk of kidney disease by up to seven times, compared to someone without the genotypes.[36]

However, the molecular mechanisms by which APOL1 genotypes increase kidney disease risk are unknown, and thus treatments that specifically target individuals with high-risk genotypes—including lifestyle interventions to reduce disease risk—have not yet been identified. Whether testing individuals for these high-risk APOL1 genotypes and communicating the test results to physicians and patients would improve kidney disease

outcomes is an area of intense research interest. For instance, the Genetic Testing to Understand and Address Renal Disease Disparities (GUARDD) trial is recruiting patients to investigate the impact of knowing whether or not a patient has the APOL1 genotype on prevention and treatment of chronic kidney disease.[45]

Ethical Considerations

> Providers and patients must be educated to understand the risks, benefits, and limitations of genomic, epigenetic, and molecular research.

Despite the promise of genetic and molecular technologies in understanding the emergence of disparities in the prevalence, severity, treatment, and survival rates of certain diseases, substantial obstacles—including incomplete genetic databases, inadequate treatment options, and poorly understood disease mechanisms—limit the clinical application of genetic knowledge to all groups. Even if disparities in access to genetic counseling and testing could be overcome, understudied minority communities might still be less likely than whites to benefit from current and emerging genetic technologies.

In addition, there are a number of ethical concerns involved in identifying genetic contributions to disease risk that are more common in, or largely confined to, certain populations or groups with particular ancestries. For instance, linking health disparities to genetic causes may make those disparities seem less amenable to public health intervention. That would not only risk stigmatization of the individuals and populations at highest risk but would also neglect significant socioeconomic or environmental contributors to health disparities.

Additionally, genetic or molecular testing might reveal a condition for which treatment is limited, and for which prognosis is likely to be poor. Consensus among genetic ethicists has discouraged the use of genetic tests that are not clinically useful, such as testing for certain genotypes of the APOE gene to predict the risk of Alzheimer’s disease. Genetic research should focus less on diagnostics and more on targeting treatments to people who are most at risk. Only then will the anticipated reduction in health disparities be realized.

Policy Recommendations

For genetic technologies to deliver on their promise of facilitating the use of precision medicine for everyone and reducing health disparities, efforts are needed inside and outside of the scientific arena. We highlight our policy recommendations below.

Minority-Focused Genetic Research

People of non-European ancestry are underrepresented in the genetic databases on which genetic studies rely. Genetic research requires the enrollment and retention of sufficient numbers of individuals to assess the impact of genetic variability on complex diseases such as cancer and kidney disease. Large-scale databases are necessary for differentiating between genetic variants that are protective or neutral and those that increase risk, understanding disease mechanisms, and treating disease based on genetic information. More

research should be dedicated to identifying and understanding the full range of genetic diversity in all people, and more funding is needed for minority-focused genetics research.

Community-Based Participatory Research

Certain forms of research have had greater success than others at recruiting and retaining minority participants. One relatively successful form is community-based participatory research,[46] which engages study participants in the research process to promote trust and transparency. Community-based participatory research programs and interventions have been shown to be effective and sustainable and to create partnerships with community members that offer opportunities to promote genetic literacy.[47] The PUEDO study,[15] for instance, used a community-based research approach.

Research On Gene-Environment Interactions

A person's environment, as created through lifestyle behaviors, can exacerbate or ameliorate his or her genetic risk of disease, but the understanding of how environmental factors can best prevent disease is especially limited. One of the clearest messages from genetic studies is that cancer is much more biologically heterogeneous than originally recognized and that genetics is key to understanding this heterogeneity.

Similarly, the impact of a person's environment on disease—for example, through dietary or lifestyle changes—may differ among individuals with different genetic backgrounds. Genetic information could be used, for example, to inform tailored, population-level health interventions that target lifestyle behaviors or to understand how genetic variation modulates individual response to lifestyle interventions, such as a change in diet. Epigenetics research and, more broadly, research on the interactions between genes and one's environment should be funded.

Education

The application of genetic technologies to reducing health disparities cannot be achieved solely by improving the scientific knowledge base. Health care providers and patients must also be educated to understand the risks, benefits, and limitations of genomic, epigenetic, and molecular research. Educational challenges for both patients and providers may be greater in community health settings than in academic or research medical centers, because of resource constraints. Given that most people obtain health care services in community settings, support for education in these environments is especially critical.

Conclusion

Genetic technologies have dramatically expanded the understanding of common diseases and thereby increased the ability to prevent, diagnose, and treat them. However, people with non-European ancestries are underrepresented in genetic databases, which limits the ability to apply genetic knowledge to reduce disease in these groups. Failing to adequately fund minority-focused genetic research runs the risk of widening existing disparities on an ever-increasing scale. This risk is best addressed by greater support for minority-focused research, community-based participatory research, and studies of gene-environment

interactions. Ideally, these targeted efforts will help narrow, rather than widen, genetically influenced health disparities.

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