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Integrating the Genetics of Race and Ethnicity Into Cancer Research:

Trailing Jane and John Q. Public

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Variations in cancer burden associated with racial/ethnic identity are well documented in the United States; of these, increased cancer mortality rates among African American individuals are arguably the most alarming. Are these disparities in cancer outcomes caused by socioeconomic inequities or variation in tumor biology and/or genetics? Health care access barriers created by socioeconomic disadvantages are more prevalent in the African American community compared with white American groups, and this undoubtedly contributes to disparities. But other factors might be involved as well. It is debatable whether the existing racial/ethnic categories have any relevant biologic significance or if they simply represent sociopolitical constructs. Genomics, proteomics, and other "-omic" technologies continue to revolutionize the treatment of cancer; these tools can also be used to characterize genetic components of race/ethnicity. This leads to a second question: why does cancer research continue to rely on self-reported racial/ethnic identity when we have the capability to clarify associations between race and disease risk through less ambiguous measures of heritage?

The general public has welcomed opportunities to obtain genetic racial/ethnic information. Consumer responses to commercial germline testing services through enterprises such as 23 and Me and Ancestry DNA has been robust. While cost is clearly a factor in access to these products, several million of these packages have been purchased. Each generates reports of the ancestral background of an individual using DNA extracted from saliva specimens. The resulting pattern of genetic ancestry informative markers (AIMs), which are single-nucleotide polymorphisms that occur in populations of various racial/ethnic origins to differing extents, quantifies the heritage contributed to an individual by ancestors from distinct demographics and/or diverse geographic regions around the globe.

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The United States populace represents a true melting pot of genetic mixture from the Native Americans, Europeans, Africans, and Asians who have populated North America over the past several centuries. Despite varying degrees of admixture, individuals self-identify (or are categorized by others) as being white, black/African American, Hispanic/Latino, Asian, or Native American based on familial ties, physical attributes, culture, language, and/or geography. These commonalities often yield population subsets that choose to reside together in shared neighborhoods, resulting in cohesive communities with similar interests and perspectives. To the extent that diet, lifestyle, and environment contribute to cancer risk, these sociocultural aspects of race/ethnicity are indeed relevant to cancer research and cancer control. A tragic reality is that these groupings have also served as the basis for discriminatory employment practices and educational prospects—the cornerstones of social injustice and wealth inequality. This harsh consequence substantiates the philosophy that racial/ethnic identities are sociopolitical constructs.

However, if we focus on this sociopolitical construct with a tunnel vision that precludes consideration of geographically defined ancestry, we jeopardize an opportunity to fully understand the influence of genetics on cancer risk. The clinical relevance of ancestral background is readily apparent in individuals of Ashkenazi Jewish heritage (Table). This Eastern/Central European Jewish population has retained substantial genetic homogeneity over several generations, despite transcontinental migration. Consequently, 1% to 2.5% of Ashkenazi Jews harbor 1 of 3 deleterious *BRCA1* and *BRCA2* founder mutations.[1] Ashkenazi Jewish patients with breast and/or ovarian cancer are therefore promptly referred for genetic counseling. Ashkenazi background can also influence personalized screening recommendations (eg, mammography initiation at younger ages and consideration of magnetic resonance imaging of the breast) because of suspected hereditary susceptibility.

In populations of mixed racial/ethnic heritage, genotyping of AIMs can be a powerful strategy to clarify ancestral heritage that might affect cancer risk. For example, in children with acute lymphoblastic leukemia, higher relapse rates are associated with Native American ancestry as assessed by AIMs testing, even in participants self-reporting as white.[4] However, Native American ancestry established by genetic testing in Hispanic/Latina women (who are may be of mixed European, Native American, and/or African American ancestry) is associated with a reduced lifetime risk of breast cancer.[3] This genetic pattern may contribute to the lower population-based breast cancer incidence rates documented for Hispanic/Latina and Native American women compared with white Americans (Table).

Self-reported African American identity correlates closely with predominant African ancestry, but several centuries of genetic admixture have yielded individuals who are categorized as African American despite having substantial non-African ancestry.[6] Furthermore, the continent of Africa is expansive and diverse; existing data indicate that women from western sub-Saharan Africa have an increased prevalence of estrogen-receptor-negative breast cancer[7] as well as triple-negative breast cancer,[8] while the phenotype distribution of East Africans is more similar to that of European and white American women. The colonial-era trans-Atlantic slave trade brought Africans from mostly the western regions of sub-Saharan Africa to the Americas, while the East African slave trade and other economic, political, and cultural circumstances over several centuries resulted in

complex patterns of forced and voluntary migration to the Middle East and Asia. The 2-fold higher population-based incidence of triple-negative breast cancer observed among African American women compared with white American women might therefore be explained by the contribution of West African ancestry to the heritage of contemporary self-reported African Americans. Genetic admixture among African Americans is increasing; US census data document that nearly 2 million Americans now report being biracial (black and white), a 134% increase from 2000 to 2010. AIMs genotyping is a promising strategy to add precision to the characterization of individual cancer risk associated with ancestral background.

Despite the prospect of AIMs genotyping unravelling factors that confound understanding of the cancer risk associated with African heritage, integration of this strategy into research has occurred relatively slowly. It is possible that fears of being perceived as promoting something akin to “race medicine” (the rationale for the horrific Tuskegee experiments, which left syphilis untreated in African American men from 1932 to 1972) has hindered integration of AIMs genotyping into mainstream cancer research.

However, some notable exceptions do exist, including the Annual Symposium on the Biology of Cancer Disparities by the American Association for Cancer Research, which regularly features AIMs research, as well as a 2016 consortium that pooled African American patients and has the potential to robustly define the role of AIMs in breast cancer research.[9] In addition, this genotyping tool might be able to clarify outcome disparities that have been reported in cancer clinical trials research. For example, a pooled analysis of the Southwest Oncology Group adjuvant therapy trials[10] (Table) demonstrated that tightly regulated clinical trial mechanisms can achieve delivery of equitable care and equal outcomes to diverse patients with most cancers, but not hormonally driven malignant conditions. African American patients enrolled in breast and prostate cancer clinical trials experienced statistically significant outcome disadvantages. This finding implies that explanations for disparities associated with race/ethnicity are multifactorial, with tumor biology, genetics, and socioeconomic factors contributing to varying degrees depending on the primary disease type. Adoption of AIMs analyses can disentangle some of these confounding factors.

Many in the general public have accepted opportunities for elucidating geographically defined ancestral background, apparently seeing this technology as a celebration of our diversity on both an individual and a community level. The oncology research community should set aside sensitivities that may impede sound scientific endeavors. AIMs genotyping is simply 1 more device in the molecular and genetic epidemiology toolbox; we should follow the lead of the general public and use this tool to understand and conquer the cancer burden of our diverse patient population.

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Table.

Examples of Ancestry Associated With Cancer Risk

Ancestral Component (Characterization Mechanism)	Cancer Risk
Ashkenazi (Eastern/Central European) Jewish heritage[1] (self-reported)	Increased risk of *BRCA 1* and *BRCA 2* mutations
Afro-Caribbean heritage[2] (self-reported)	Increased risk of *BRCA 1* and *BRCA 2* mutations
Variable extents of Native American ancestry in mixed-heritage Hispanic/Latina women[3] (ancestry informative marker genotyping)	Reduced risk of breast cancer associated with greater extent of Native American ancestry
Variable extents of Native American ancestry in mixed-heritage children with admixed heritage[4] (ancestry informative marker genotyping)	Higher rates of relapse in children with acute lymphoblastic leukemia associated with greater extent of Native American ancestry
African ancestry in African American women with mixed heritage[5] (ancestry informative marker genotyping)	Novel estrogen receptor–negative breast cancer susceptibility locus