INTRODUCTION TO THE OCCASION

This year, as we celebrate the 10th anniversary of Cancer Discovery, we are also celebrating the 50th anniversary of the National Cancer Act (NCA) of 1971 (1), which was established as a way to address the nation’s second-leading cause of death at that time. It gave overarching authority for the creation of national programs, in both the federal and private sectors, to establish such entities as the NCI, the National Cancer Advisory Board, and the President’s Cancer Panel. Over these past five decades, for better or worse, we have certainly seen the tremendous impact of this endeavor, with strategic appropriation of cancer research funding and establishment of cancer workforce training paradigms that have transformed our capacity to study cancer. The spirit and intention of the NCA was to give an unprecedented momentum to scientists and incentivize new concerted efforts toward understanding cancer “cells.” Curiously, this was an aspect of the disease that somehow eluded the brilliant scientists in medical research at that time. For in the previous decade, the scientific community had seen such medical advances as successful vaccines for infectious diseases and even major organ transplantations, yet the cancer death rate had more than doubled in the preceding three decades (2). The time was ripe for a “National Program for the Conquest of Cancer,” and so began the war on cancer.

At the start of this conquest, researchers did not even know the total number of genes in the human genome or the code that delineates gene structure. Therefore, this mandate to understand cancer at a cellular level had a steep learning curve. But researchers soon understood that cancer involved a type of deregulation of cell division related to the destabilization of nuclear DNA—a disease of the genes/genome.

Scientists were able to define the nature of accumulating mutations in key genes, cancer genes, and investigate the molecular consequences of these mutations, with BRCA1, TP53, and RB1 being key examples that are now deemed “Cancer Syndrome Genes,” given their propensity to drive cancer in multiple organ sites.

Fast-forwarding to present-day advances, we now have the fullness of the human genome sequence at our disposal, and the list of cancer genes now numbers in the hundreds which include various cellular functions. In fact, where the simple nature of cancer cells within a tumor was unknown at the beginning of the NCA, through advances in genomic science we can now interrogate each individual cell, every DNA strand in each cell, and all the genes expressed in each cell. We anticipate that integration of these data will identify the expression Quantitative Trait Loci (eQTL), or the genetic alterations, that regulate or modify gene expression in each individual cell. With the single-cell platforms, we can also utilize spatial genomics to define the interactions between these individual cells, defining how specific types of cells in the tumor microenvironment play an essential role in the trajectory of cancer disease course. Ultimately, we can even expand from knowledge of cellular tumor microenvironments to characterize the systemic host response, such as how immunologic responses are the key to staving off tumor growth. It is an amazing time to do cancer research, as each of these concepts, born out of investigating tumor cell biology, has blossomed into entirely new fields of genomic sciences that span the entire cancer continuum, starting with molecular epidemiology of cancer risk, to cancer theragnostics (therapy/diagnostics) for targeted treatments.

And yet, through all of these tremendous accomplishments, there remains a lingering question that becomes more palpable as advancements improve outcomes: why are there disparities in these improved outcomes across race and ethnic groups? The answer to this question is an age-old acknowledgment that marginalized minority populations have traditionally suffered unequal access to the healthcare that is required to survive a cancer diagnosis. And they suffer barriers to the wellness resources needed to even prevent a cancer diagnosis. These are complex issues that have evaded improvement across centuries. But on some transformative level, could basic science and genomics help to address underlying issues that evade these initiatives on the sociobehavioral front lines? The answer is a
resounding yes! It is the compounding issue of both clinical care and research gaps that drives racial disparities. As we take a brief glimpse of advancements in cancer research, through a lens of genomic science, we will reify the effectiveness of investing in concerted global research efforts and highlight new and ongoing opportunities to ensure equal benefit of genomic cancer research advancements to all populations.

**GENOMICS ACROSS THE CANCER CONTINUUM: THE POWER OF INCLUSION IN PRECISION MEDICINE**

**Risk Genomics**

Our cancer community is celebrating a well-earned steady decline in cancer incidence and cancer-related deaths, although certain populations are unfortunately left behind in that victory. The paucity of genomic data that have been generated for cancer risk, particularly genome-wide association studies (GWAS), has neglected to interrogate the majority of the world population (3, 4). Even when these populations are initially included in the test cohorts, the analysis “adjustments” would filter out any population-specific risk alleles by virtue of “controlling” for bias of allele frequencies in race groups, although we know that genetic risk can be distinct across ancestry groups, such as in breast cancer (5, 6). This has left us with the bleak realization that cancer genetic risk testing, largely powered by GWAS and other genetic risk heritability studies, results in a significantly higher frequency of identifying cancer gene mutations that are “variants of unknown significance” (40% in non-Hispanic Blacks vs. less than 15% in non-Hispanic Whites; ref. 7).

In addition, GWAS results have revealed a complexity that most traits are highly polygenic, particularly with regard to cancer risk (8). Through innovative methods, polygenic risk scores have become increasingly more relevant in genomic interrogations of risk; however, a prohibitive caveat is the lack of predictive power these scores have across ancestry groups. That is to say that a predictive polygenic score that was derived in a mostly European population, which is the reality of our current state of GWAS, will not perform well in other populations/individuals of other substantially different ancestry (9). Therefore, risk scores are systematically more predictive in non-Hispanic White patients, perpetuating the disparities across race groups.

The need for genetic screening tests across multiple cancer types will always be an ever-present goal, as the best way to survive cancer is to prevent the diagnosis through cancer prevention. Targeting high-risk patients for prevention efforts can be challenging without having an efficient way to identify them. Currently, two of the three CDC Tier 1–designated applications for genomic screening are cancer syndromes, including hereditary breast and ovarian cancer syndrome and Lynch syndrome. Although upward of 2% of the population at large are at high risk, the majority of these individuals may be unaware of their status. With the rapidly decreasing cost of genomic technology and implementation of ancestry-competent algorithms, development of genomic screening paradigms that are applicable to the broad diversity in global populations can realize the potential to prevent cancer more expediently. For this vision to manifest, perhaps the way forward is not to be constrained by prior knowledge of risk alleles that were based on limited populations. Rather, whole-exome and whole-genome sequencing to characterize novel pathogenic variants de novo, coupled with characterizing the resulting genome mutation signatures, could be a more direct method of screening for the propensity of cancer, rather than the indirect assessment of risk.

**Diagnostic Genomics**

Across the spectrum of cancer sites, we can appreciate the dynamics of each not being a singular disease, but specific subtypes of cancer/tumors. Our characterization of subtypes is due in large part to the integration of genomic signatures with clinical outcomes. Genomics has expanded the capacity of pathologic characterization to include signatures of hundreds of gene-expression patterns that delineate the molecular distinctions of tumor subtypes (10). This has been a tremendous asset for cancer research, yet we are still lagging on the clinical applications of these signatures to become standard of care. This lack of uptake is partly because these are cost-prohibitive assays and partly because they were biased in their definitions due to limited inclusion of diverse populations when they were defined. This limits their accuracy in the broad patient pool (11). For example, the gene signatures that define breast cancer subtypes have shaped our approaches to developing research for targeted therapies; however, we also find that gene signatures have significant variation across patient groups, underlying a bias in the incidence of specific subtypes within these patient groups. Specifically, we now know that triple-negative breast cancers (TNBC) are more prevalent in non-White populations (12) and that the subtypes of TNBC, defined by the genomic signature of hundreds of genes, also show significant bias among race groups (13). Yet, knowing this does not necessarily change the course of treatment. Recently, there has been increased attention to inclusion of minority patients in genomic studies that would derive a better understanding and application of the nuances in tumor biology. These are powered by partnerships between cohort studies that conduct targeted enrollment of minority groups. Most of these consortia are currently focused on African-American and/or Latin-American patients, but are exemplary models of how diversity in tumor biology research can lead to pivotal discoveries and produce clinical tools for improving patient outcomes. In addition, structural genomic phenotypes are increasingly relevant to cancer diagnosis and treatment decisions. For example, homologous recombination deficiency (HRD) is a consequence of loss-of-function mutations in DNA-repair genes. Specifically, HRD can be the result of BRCA1/2 mutations, and detection of HRD determines the probability of a patient’s cancer recurrence as a function of treatment responsiveness. These genomic phenotypes could eventually become key indicators for eligibility for targeted therapies as well. In particular, when minority patients are more likely to present with VUS mutations in these key cancer genes that have unknown pathogenic potential, having whole-genome data to detect the structural mutation patterns, such as HRD, can be the bridge that overcomes the gap in access to treatment. In this way, deploying whole-genome sequencing in cancer clinics can transform...
care and outcomes in minority patients, and differences in HRD have already come to light (14).

Treatment (Response) Genomics

Genomic advances have allowed researchers to tackle treatment obstacles with unprecedented efficiency and precision. From CRISPR gene editing to patient avatars using *ex vivo* and *in vivo* models, targeted therapies are truly customizable. Targeted therapies are effective because they are designed to exploit a dependency that is usually a result of genetic variation or gene expression specific to the tumor cells (i.e., gene fusions) or interactions occurring in the tumor microenvironment (i.e., immune suppression). In the case of gene-variant targeting, lung cancer therapies have gained an arsenal of targeted drugs against the EGFR pathway, but with varying sensitivities across the patient spectrum. Studies have revealed that racial differences in the frequency of ancestry-associated gene variants influence the eligibility of patients for certain treatments as well as the effectiveness of the drugs. Specifically, polymorphic variations of EGFR are directly related to sensitivity or insensitivity to mAb drugs, and these also appear to differ in frequency across race and ancestry groups, with specific implications across East Asian populations (15).

In addition, frequency of certain copy-number variations on chromosome 16 are higher in East Asian patients, compared with non-Hispanic White patients of European descent, leading to differential outcomes. Although specific examples of polymorphic variations influencing options and efficacy of treatment are limited, these are proof of concept that including diverse ancestry groups in clinical research will reveal opportunities to discern treatment options and make precision medicine more accurate across the diverse global patient populations.

**ADDRESSING DISPARITIES AS A MATTER OF ACCURACY: HOW PRECISE IS PRECISION MEDICINE?**

A lingering caveat of genomic science in cancer research is a matter of the ground truth, or reference, by which we draw most comparisons. Having the human genome sequenced was one of the most tremendous feats of consortium science to date. Meanwhile, the next phases of the Human Genome effort, including the Haplotype Mapping (HapMap) project and subsequently the 1000 Genomes project, revealed just how little we knew about complex diversity across the human population. Sequencing and comparing multiple genomes across distinct geographic populations has set the stage for assessing the continuous variation across the human diaspora, such that now in the context of identifying genomic variation related to cancer (or any disease) we recognize that the reference genome does not necessarily represent a healthy prototypical individual, which is extensively common among African-American and Latin-American populations, could create a foundation for yet untapped potential of characterizing ancestral allele interactions. This could lead to uncovering novel and more predictive sets of polygenic risk allele interactions.

The necessity of inclusion of diversity in this work is exemplified by recent studies that utilize whole-genome sequencing of non-White populations, including ancestral global populations, which have revealed novel genetic material, nearly the size of an additional chromosome worth of data, that were not included in the original reference genome (17). In fact, a significant proportion of this novel genomic data is expressed sequences that represent what are currently “unmapped reads” when conducting RNA-sequencing alignments to the current Human Genome Reference. This implies novel gene structure and expression that are yet uninterrogated. This revelation of bias in the reference genome also reveals how research can perpetuate our inability to effectively characterize the dynamic diversity of the genomic landscape and changes in gene networks at play in cancer etiology and progression. Indeed, these undefined genomic regions could also harbor the untapped potential of therapeutic targets as well. Once again, diversity in the subject populations for scientific interrogation unmasks a lack of rigor across relevant genetic ancestry backgrounds, which will remain a handicap in as long as we are complacent with the current standards.

There is a substantial investment to address these concerns within the National Human Genome Research Institute that is focused on increasing the representation of ethnic diversity in genomic research and the genomic research workforce, and on bringing genomic data forward into the clinical space. Specifically, in the area of cancer research, new initiatives funded by the NCI and its Center for Disparities are strategically addressing cancer disparities using genomics in comparative studies to define differences across ethnic ancestry groups. These studies are revealing novelities in tumor pathways involving metabolism, immunology, and tumor heterogeneity (10, 13). These exciting new findings, in the context of cancer disparities, reveal how diversity in research can expand our general knowledge of cancer biology. Without this diversity, we would never know the full complexity of cancer disease course or uncover novel treatment options to improve survival.

**CONCLUSIONS AND A CALL TO ACTION FOR HEALTH JUSTICE, USING GENOMICS TO ADDRESS DISPARITIES**

**Health Justice**

The unfortunate irony of cancer disparities is that the sacrifices of minority patients who suffer disparate outcomes have led to groundbreaking discoveries and transformative
therapies. For instance, HeLa cells were the first immortalized tumor cell line, derived from a non-Hispanic Black patient named Henrietta Lacks, and are among the most heavily used cells for cancer drug studies. Yet Black women are twice as likely to die from the same cancer. Without question, the past two decades alone have seen a tremendous benefit of strategic research across the cancer continuum. Between 1991 and 2018, the cancer death rate has fallen 31%, and that includes the largest ever one-year drop in the cancer death rate. However, among non-Hispanic Black patients, it was estimated that more than 200K new cancer cases and more than 73K cancer deaths were expected to occur in 2019. Indeed, non-Hispanic Black patients have the shortest survival of all race/ethnicity groups in most cancers. But progress is on the horizon. The overall cancer death rate is dropping faster in non-Hispanic Black patients, compared with non-Hispanic White patients, avoiding more than 460,000 cancer deaths in this population.

But without a persistent push forward, this trend will reach a plateau that is the ceiling of diversity in our understanding of tumor biology. As is the purpose of scientific growth, with the technological advancements of genomics, we have uncovered more questions to be answered, and we are now poised to characterize the dynamics of these cancer cell traits across diverse populations. Like a novel fourth dimension of time and fifth dimension of diversity, we are now able to model and predict the evolution of how cells change during the formation of cancer. This tumor evolution may be distinct across ancestry groups, and we need this knowledge to improve precision care. International consortia that harness ancestral genetic lineages in population genomics of cancer disparities are the best leap forward to refocus the lens of the ever-evolving and expanding potential of genomic research. And, in fact, these global partnerships were at the heart of our original NCA mandate and are our best shot to translate genomic research to benefit underserved populations.

**The Power of Inclusion: A Global Perspective**

Herein lies the next momentous opportunity to drive home a victory to cure cancer, but now instead of a conquest, we have a moonshot! The original NCA stated that a major goal was establishing global relationships and utilizing global oncology data to benefit Americans—all Americans. The Biden administration will undoubtedly expand upon the Cancer Moonshot initiative that was born in the Obama administration (18). Like the NCA, the Cancer Moonshot sought to harness all the potential of current scientific prowess to make major leaps of progress, funding high-risk, high-reward projects to ensure transformative impact through research. This can be a new era of progress that will not leave the underserved behind again but that changes the culture of deprioritization of minority patients. And so, with this moonshot opportunity, let us revisit the tenants of Health Justice in the Belmont Report.

The foundation of ethical Human Subjects research is the outcome of the Belmont Report (19), a historic document that was forged from the outrage of research misconduct, exploitation, and harm carried out in vulnerable populations—which led to a well-deserved mistrust of the scientific community. The three key principles of this report—respect, beneficence, and justice—are the benchmarks required for seeking approval to conduct research on humans. First, the tenet of respect clarifies that patient involvement is voluntary and patients should receive explanations of the research, and this is executed through informed consent. Second, the tenet of beneficence clarifies that research is purposed to be beneficial to patients and improve clinical outcomes, executed by the application of findings in the clinic space, the translation of the work. The last tenet, justice, is largely underdeveloped in our scientific arena. It simply states that there is fair treatment and distribution of the risks and the benefits of the research. This can be achieved only by the power of inclusion—inclusion of larger numbers of diverse minority ethnicities. But this requires voluntary participation. Indeed, to seek justice by way of health disparities research, acknowledging the wrongs of the past, in the context of how protections were erected in response to those injustices, may be the only way we can ever see better participation of minorities in genetic research initiatives.

Prioritizing the engagement, and follow-through, of diverse populations is also an aspect of respect and beneficence that would be extremely impactful in minority communities: engagement through targeted recruitment, with follow-through that includes their involvement in the study/research outcomes. Recent studies indicate that a large portion of minority patients make conscious decisions about participating in research based on whether they will receive the results of the study (20). One of the decision-driving factors of agreeing to genetic/genomic research was being informed of the results, indicating they wanted to know all the results of the study, including those that could not yet be interpreted. They felt that this knowledge would be a benefit to themselves and their families. Indeed, given the history of medical research abuse in minority groups, it is a logical consequence that these communities would require prior and post knowledge of the study goals and outcomes, that protections of their genomic data are not enough.

In conclusion, now that we know that the power of inclusion of diverse, global populations can be transformative to genomic research, throughout the entire cancer continuum, and that there is an ethical expectation to ensure that inclusion by way of Health Justice in our research advancements, let us not throw away our (Moon)shot!

**Author’s Disclosures**

M.B. Davis reports personal fees from QED Therapeutics and personal fees from Genentech outside the submitted work. No other disclosures were reported.

Published first April 2, 2021.

**REFERENCES**


Genomics and Cancer Disparities: The Justice and Power of Inclusion
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Cancer Discov 2021;11:805-809.