Addressing health disparities in cancer with genomics

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Incorporating genomics more widely into cancer screening and management will help to tackle the mortality gap between Black and white patients with cancer. Here, we emphasize the role of genomics as a tool to promote health equity in cancer.

> “recruiting a diverse study population will be key”

With the initiation of the Human Genome Project in 1990, the era of precision oncology seemed just within reach. By assessing the tumour genome, oncologists would have the ability to select (or omit) therapies best suited to optimize each individual's likelihood of disease control and survival. Several projects, such as the 1000 Genomes Project, endeavoured to catalogue the spectrum of genetic variation among the human population. Thirty years later, we have made significant progress but are yet to harness the full potential of genomics in oncology. Health inequities persist in the cancer community; in particular, stark differences in survival outcomes among Black and white patients have been evident for decades. In this article, we use Black and white to refer to individuals of primarily African and European ancestry, respectively. Among patients with any of the four most common malignancies in the United States, Black patients are consistently more likely to die than white patients, with the exception of women with lung cancer[1]. Black women have lower incidence rates of breast cancer yet have a 40% higher mortality rate. Prostate and colorectal cancers are more often diagnosed among Black individuals, and Black men have prostate cancer mortality rates that are more than double that of their white counterparts.

Proposed solutions for addressing these inequities typically include diversifying clinical trial enrolment[2], recruiting an oncology workforce that reflects the national population[3] and improving access to quality oncological care for all individuals, especially the most impoverished in our communities[4]. Genetics and genomics research should also be perceived as a tool within the armamentarium needed to address the mortality gap between Black and white patients with cancer. These investigations can pinpoint genetic mutations and epigenetic mechanisms that contribute to the higher incidence and mortality rates among Black patients with cancer[5]. Moreover, genomics can help identify novel targets for therapies, a principal goal of precision oncology. Traditionally, genomic research has been used to identify mutations that will guide the selection (or omission) of chemotherapy, targeted therapies or immunotherapy. Yet, it has been woefully underutilized to tailor screening, surgical and radiotherapy recommendations. We highlight opportunities to incorporate genomics more widely into oncological care as well as a few existing initiatives that apply genomics innovatively in cancer management to promote health equity.

At present, the scope of genomic-guided screening is limited, but genomics has the potential to more widely influence screening recommendations. For instance, controversy surrounding mammographic screening has focused on the recommended age at initiation (40 years versus 50 years) as well as the frequency of mammography (annual versus biennial). These arguments mire the discussions in a false dichotomy from which we need to evolve. This is precisely what the Women Informed to Screen Depending On Measures of risk (WISDOM) Study seeks to accomplish. In this randomized controlled trial, women will be randomized to standard annual mammography versus a risk-based algorithm for screening. Risk assessment will integrate clinical risk prediction models, polygenic risk scores representing the effects of multiple single-nucleotide polymorphisms (SNPs), including ethnicity-specific SNPs, and genetic testing for high- and moderate-penetrance breast cancer gene mutations. The resulting risk estimates will determine screening parameters such as age at initiation and termination, frequency, and imaging modality. By incorporating genomics into the algorithm that determines when to screen and how often, we can elucidate which subsets of women may be best served by annual imaging and those who are safe to undergo biennial screening, especially within Black and Hispanic communities. Most importantly, women at high risk of aggressive interval cancers can be identified and offered the opportunity for intensive surveillance using dynamic contrast-enhanced MRI every 6 months[6,7]. Waiting to begin screening at 40 years could disadvantage underserved women who are at risk of young-onset breast cancer due to inherited mutations in *BRCA1*, *BRCA2* or *PALB2*.

There are several opportunities to apply a similar approach to colorectal cancer or lung cancer screening and post-treatment surveillance imaging. Owing to the rising incidence of colorectal cancer among individuals under 50 years old, guidelines have been modified

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> Reimagining the bounds of genomics in oncological care

to begin colonoscopy at 45 years old. However, African American individuals are about 20% more likely to get colorectal cancer and about 40% more likely to die from it than most other racial groups. Although some of this disease burden can be attributed to lack of screening, access to healthy food and systemic racism when seeking care, the genetic underpinnings of early disease onset and aggressiveness are still being clarified. Investing in screening trials that incorporate genomic sequencing and adequately recruit individuals of African ancestry can guide the formation of tailored screening guidelines rather than our current model of 'one size fits all'.

Expanding the role of genomic profiling in surgical and radiotherapy treatment recommendations for patients with curable rectal cancer could identify subsets for whom radiotherapy can be safely omitted following neoadjuvant chemoradiotherapy. At present, the decision to observe patients with rectal cancer achieving complete clinical response is based on physical and endoscopic exam with or without MRI of the pelvis[8]. The risk of local regrowth is ~20%, but defining the genomic signatures associated with regrowth in diverse populations could improve overall outcomes for the 'wait and watch' approach. The PORTEC-4a/4b trials have embraced the value of incorporating tumour-specific data into treatment decisions and will determine whether molecular profiles can better guide adjuvant therapy decisions in high-to-intermediate-risk endometrial cancer. This is especially important for Black women, who have a higher risk of developing serous and carcinosarcoma subtypes that are associated with a worse prognosis. Genomic tests such as Oncotype and MammaPrint have been used primarily to direct omission or incorporation of chemotherapy in patients with early-stage breast cancer. However, Oncotype scores >18 have also been associated with triple the risk of locoregional recurrence on multivariable analysis. The ongoing Tailor RT trial randomizes women with either pT3N0 disease or 1–3 positive lymph nodes and an Oncotype score ≤25 to standard nodal irradiation or omits nodal treatment. Of note, genomic assays may have lower prognostic value in understudied and underserved minority populations[9]; therefore, recruiting a diverse study population will be key to ensuring the generalizability of clinical trial results.

Reimagining the bounds of genomics in oncological care, as outlined above, will require investment in innovative and coordinated means of accessing and analysing large-scale genetic and genomic data. At present, the American Society of Clinical Oncology (ASCO) oversees CancerLinQ, a database that houses information from the medical records of 1.5 million patients. An analysis of patients with ovarian cancer within the CancerLinQ database revealed a 17.2% *BRCA1* or *BRCA2* mutation rate[10], suggesting that there is opportunity to conduct genetic analyses, albeit likely limited in scope. Access to CancerLinQ and prioritization of genetic studies will generate hypotheses that can inform additional inquiries and trials aimed at promoting health equity.

Populations of African ancestry have long been denied opportunities to engage in research because of systemic racism, but they are the ones most likely to benefit from innovative technologies that accelerate progress against the most aggressive cancers. The proposed Health Advanced Research Projects Agency (HARPA) has the potential to accelerate the application of genetics and genomic data to solutions for health equity. This new agency focused on funding innovative, risk-taking projects should support international collaborations that strategically recruit samples from a wide swath of the global community, especially groups with a disproportionate cancer burden. The Polyethnic-1000 project, sponsored by the New York Genome Center, is studying the genetic and genomic data of racial and ethnic minorities across seven different malignancies. Although its scope is limited to New York City residents, this paradigm should be emulated on a national and international level to produce actionable findings. Moreover, HARPA should invest in expanding access to at-home genetic testing, as the ease of at-home testing combined with affordability of kits would democratize access to genomic testing and improve the diversity of genomic data.

Simply devising and conducting genetic or genomic studies will be insufficient, given the perception of science in the general population. Training a workforce capable of meeting the health needs of racial and ethnic minorities as well as economically disadvantaged patients with cancer will be of paramount importance in successfully executing the next generation of biomarker-informed oncology clinical trials. Beginning with public education and investments in undergraduate medical education, we must address the shortcomings in prior research and begin integrating strategies for engaging racial and ethnic minorities in research. At this pivotal moment in history, the scientific community can build on a worldwide push to change the status quo and bring about real and lasting change in our health systems. If the COVID-19 pandemic has taught us anything, it is that humans can come together across disciplines, countries and continents to work collaboratively to reduce the global burden of disease.

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Competing interests
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