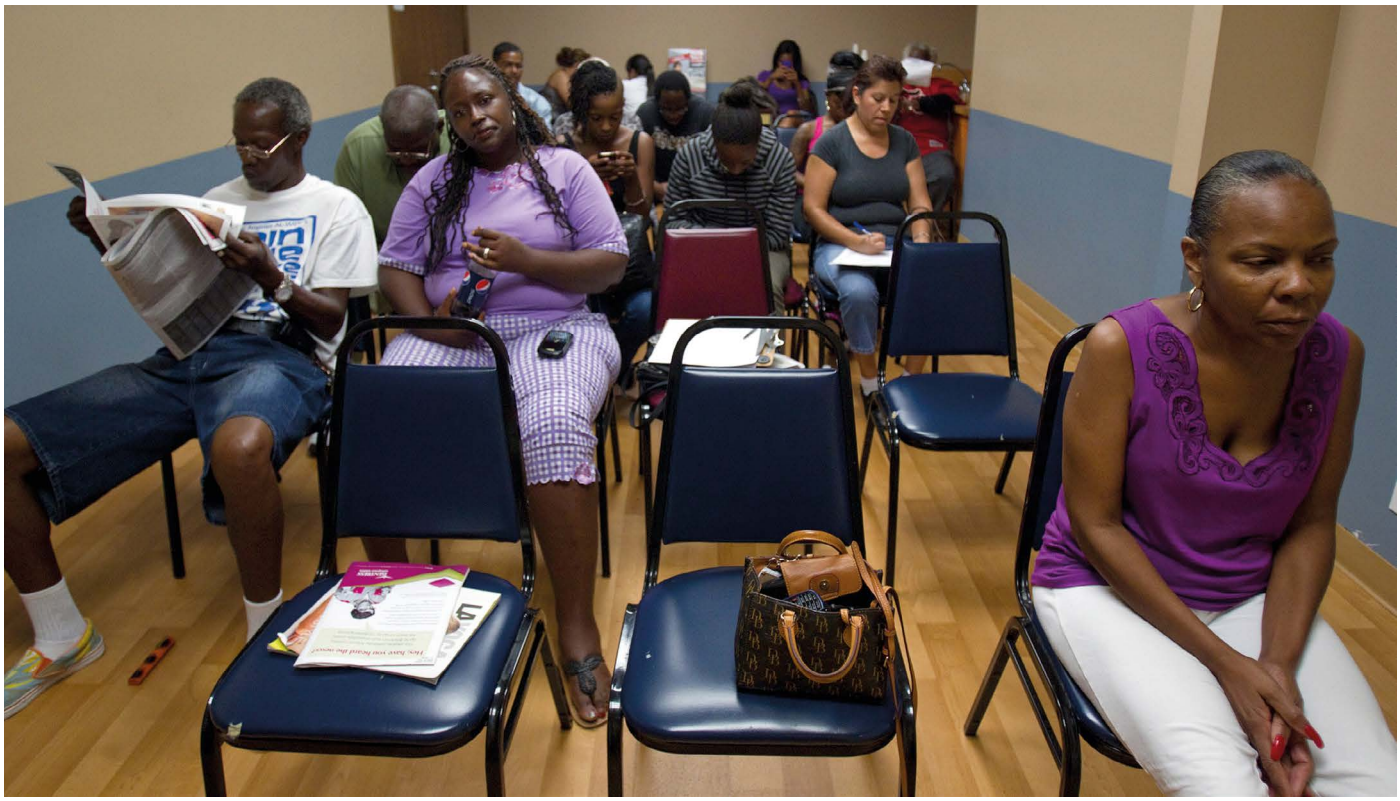


GINA FERAZZI/LOS ANGELES TIMES VIA GETTY

Databases that fail to include sufficient data from people of colour risk widening health-care inequalities.

Divided by precision

Efforts to optimize cancer care are likely to worsen existing health-care disparities, and might even introduce new inequalities. **By Jyoti Madhusoodanan**

The legacy of a woman who died of cervical cancer in 1951 epitomizes, in principle, the promise of precision oncology. Researchers extracted cells from her tumour and cultured them. After her death, they scrutinized her cells' genomes for cancer-causing mutations, and used them to test drugs that could target those genetic variants. This paved the way for the first genetically targeted cancer treatments.

The woman's name was Henrietta Lacks, and her tumour cells — the first human cell line able to survive indefinitely in a laboratory — have been the foundation for many genetic studies. But despite the wealth of information that has been gleaned from her cells, if Lacks — who was Black — was diagnosed today, she would be twice as likely to die of her disease as a white person with the same cancer. The reason for her abysmal odds lies not in her genes, but her race.

Racial disparities in cancer are well documented. Black people in the United States are around twice as likely to die of prostate or stomach cancer as their white counterparts. Black and Hispanic people are diagnosed younger and with more aggressive types of breast cancer than white people. Across most cancer types, death rates are higher for Black people than they are for other groups. It is hoped that precision oncology, an approach that uses a tumour's molecular signature to identify the most effective therapies for an individual, will improve outcomes for all people with cancer. But researchers and clinicians worry that it will deepen existing inequality.

The concerns are rooted in both genomic and socioeconomic biases. Precision oncology relies on large databases that curate genetic and molecular features gathered from genome-wide association studies and tumour-sequencing efforts. Lacks was Black, but subsequent genomic-sequencing efforts overwhelmingly represent people of European descent. As a result, any genetic variants that increase cancer risk are likely to be missed if they cluster only in populations of people of colour, says radiation oncologist Daniel Spratt at the University of Michigan in Ann Arbor.

Researchers use these data to identify biomarkers associated with clinical features such as severe symptoms and fast progression. These disease-linked biomarkers are then used by clinicians to select therapeutic strategies, or by drug manufacturers to develop medications that target tumour-linked variants. Each step is a part of precision oncology. And each one only benefits people represented in the databases — not the minority ethnic groups whose data aren't included.

In 2015, the US National Institutes of Health (NIH) launched an initiative, called All of Us, that aims to close this gap, in part, by prioritizing efforts to collect data from ethnically

diverse populations. But achieving equity in cancer care requires more than just documenting genetic variants linked to ancestry. An overhaul of how researchers use terms such as race and ancestry is necessary, according to clinical geneticist Alice Popejoy at Stanford University in California.

Descriptors such as Black or Hispanic that are used to assign a person's race, ethnicity or genetic ancestry are often used interchangeably and incorrectly, she says. These categories have no clear basis in human genetics. The groupings were developed for legislative reasons and deployed in science to ensure that everyone is equally represented in, and benefits from, taxpayer-funded research. Over time, researchers began to analyse data based on these categories, leading to a vast body of evidence that Black or Hispanic populations with various cancers have worse outcomes than white people.

"When you group your patients as Black and white and find higher rates of disease in Black people, the assumption is that there's something genetic underlying the difference," Popejoy says. But although the differences might be the result of a genetic variant that occurs more frequently in people of African ancestry — who might also identify as Black — it's also likely that "in a society that treats people differently based on race, you might be observing the effects of racism", she explains.

Those effects are created and made worse by widespread differences in living conditions, environmental exposure to chemicals and access to preventive care — all of which can increase a person's risk of getting cancer and dying from it. Access to genomics-based tests and drugs might be further limited owing to factors such as their high cost.

For precision oncology to explain and overcome disparities, researchers will need to venture beyond the genome to chart the socioeconomic landscape that governs an individual's health. "Precision medicine needs to integrate and recognize social and economic influences," says biomedical ethicist Lester Darryl Geneviève of the University of Basel in Switzerland. "People think about genetic data as a way to reduce health-care disparities, but non-genetic factors play a bigger role."

Before genomics

Outside genomic-based medicine, ancestry, race and socioeconomic factors have already spurred disparities in health care (see 'An uneven backdrop'). One 2010 study, for example, reported that among people with early-stage lung cancer — which is treated by surgery — only 55% of Black people had operations compared with 66% of white people.

Clinicians' unconscious stereotyping of people of colour, a phenomenon known as implicit bias, was one reason for the difference, says oncologist and author of the study Samuel Cykert at the University of North Carolina at Chapel Hill. White clinicians were less likely to prescribe aggressive treatments (such as lung resection) to a Black person than to a similarly ill white person because they perceived the Black person to be more unwell or less likely to benefit from the surgery[1]. In interviews with people who had recovered from breast cancer, Cykert and his colleagues found that physicians more commonly disregarded complaints about common chemotherapy side effects, such as pain or nausea, from Black people than they did from white people[2]. Their data also revealed that clinicians were aware of health disparities, but not of their possible causes. "I don't think the medical community buys into the fact that there are systemic structures — including implicit bias — that push patients of colour away," Cykert says.

Health insurance and location matter, too. Newer treatments become available in hospitals in low-income neighbourhoods later than they do at hospitals and academic health-care centres in more affluent areas. And, in a 2019 study, oncologist Hala Borno at the University of California, San Francisco, and her team found that among people with metastatic prostate cancer, those with government or military insurance provided by the US Department of Veterans Affairs were more likely to receive hormonal therapy than were people with private medical insurance, who were instead more likely to receive the cheaper but more debilitating option of surgical castration. People from minority racial and ethnic groups and those from lower socioeconomic backgrounds, were also more likely to undergo surgical treatment[3].

Similar disparities have begun to emerge with genomic approaches. People diagnosed with metastatic lung cancer are typically tested for tumour mutations in the *KRAS* gene. If these mutations are present, the first line of treatment is a drug that targets these specific mutations. But studies have found that Black and Hispanic people are less likely to be tested than white people[4]. And even when Black people are tested for mutations, those who are found to harbour the breast-cancer marker HER2 receive the targeted drug trastuzumab (Herceptin) — which reduces mortality by around 40% in people with high levels of this protein — considerably less often than white people[5]. "Neighbourhood, access to insurance, food and other social determinants of health have vast implications," Borno says. "And they certainly have implications for an individual's access to the technologies required to deliver precision medicine."

Deepening disparities

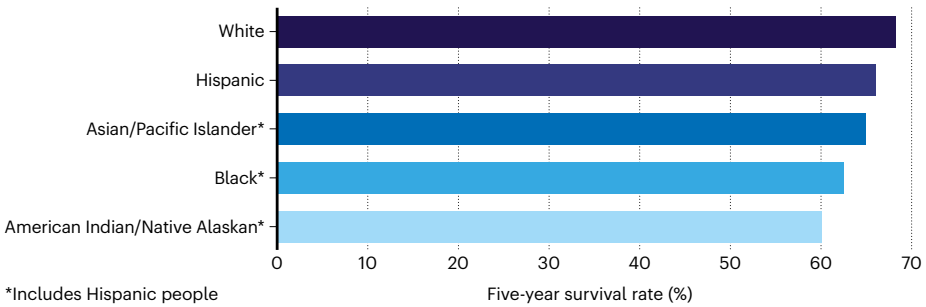
Those technologies largely rely on databases such as The Cancer Genome Atlas (TCGA), which catalogues mutations found in around 20,000 tumours across 33 types of cancer. Since 2010, these data have been openly available for researchers to use to calculate whether certain variants are more common in people with more aggressive cancers, or among those who fail to respond to treatments. Once the associations are made, those variants are then used to help identify people at risk of severe disease, or who might or might not respond to particular drugs.

In 2016, Spratt and his colleagues tested whether the database could reveal genetic variants that would explain inequality in, for example, incidence, severity and treatment outcomes between different communities. But they soon found that the database would be unable to provide the answer[6].

Of the tumour samples collected in TCGA, 77% were from white people, 12% were from Black people, 3% were from Hispanic people, and less than 0.5% were from people of Native Hawaiian, Pacific Islander, native Alaskan or American Indian descent. Superficially, this might seem reasonably diverse. Around 13% of the US population is Black, and 12% of the

AN UNEVEN BACKDROP

In the United States, between 2010 and 2016, white people who had cancer were more likely to survive for five years after their diagnosis than were people of any other race.



SOURCE SEER

TCGA samples were from Black people. But that proportion means that there are only about 50 samples from Black people per tumour type in the database — a sample that is too small to reveal statistically significant mutations. Even if 10% of Black men had an ancestral mutation that put them at higher risk of prostate cancer, it would go undetected in this data set.

"When you're trying to understand the frequency of mutations in one population versus another, it's not just about their relative representation," Spratt explains. "The absolute numbers start to matter."

In 2019, researchers reported that if scores based on these data were put to clinical use, they would systematically benefit only people of European ancestry[7]. The paucity of data from people of colour meant that tests lacked the statistical power to support anything more than a random guess — effectively widening the gap between those who already benefit from cancer treatments and those who do not.

Already, these risk-associated biomarkers are being used to select people for clinical trials, to the detriment of the involvement of people from minority ethnic groups. "If you only include people in clinical trials based on their genetic profiles, minorities are once again excluded because we don't have their information in the first place," Genevieve says. And according to Borno, such biases could have downstream implications for drug development. "Precision medicine, especially the genomic piece of it, is leaning on biased data sources," she says. "Differential access to these technologies is widening the treatment gap, so we might see the haves getting all the benefits, and the have-nots missing out."

Ineffective inclusion

The NIH and other funding agencies have long recognized these concerns, beginning with the 1993 NIH Revitalization Act, which created guidelines for the inclusion of people from minority ethnic groups in research. More recently, the All of Us initiative launched in 2015 with the aim of gathering genetic data from one million volunteers, with a particular focus on recruiting people from minority racial and ethnic groups. But these measures have not yet proven effective in reducing disparities, Borno says.

Some people who engage in clinical research have dealt with egregious exploitation and misuse of their data for decades. Henrietta Lacks' cells, for instance, were gathered and used for research without her consent. Native American communities have long mistrusted the research community because their data have been improperly used in the past. These injustices have led some, such as the Navajo Nation, to place a moratorium on any genetic studies that involve their people. As of 2019, more than half of the All of Us database was populated with data from Black, Hispanic and other minority groups, but recruiting Native American volunteers remains a struggle. "There's a perception that minority communities don't want to be included because of past abuses," says bioethics researcher Shawneequa Callier of George Washington University in Washington DC. "But we need to do more to understand the perspectives of vulnerable populations rather than just make assumptions."

Even if recruitment efforts work, Spratt points out that representation in databases alone will not be enough. Including diverse populations in genomic studies will only capture the genetic variations associated with cancer risk. It is unlikely to reveal how environmental and social factors associated with race contribute to disparities.

"Neighbourhood, access to insurance, food and other social determinants of health have vast implications."

For instance, established risk factors for cancer — such as a lack of preventive care, environmental exposure to chemicals and untreated chronic diseases such as diabetes — are more prevalent among some minority groups, including Black and Hispanic populations and those from lower socioeconomic backgrounds. Simply determining a person's ancestry says little about their odds of experiencing these risks. Adequate sampling of diverse populations is therefore only a first step. "Studies have to go beyond that and ask questions that don't have to do with race," Callier says. "For example, what effect does a high-school education or post-high-school education have on hypertension?"

Genomic research rarely, if ever, accounts for socioeconomic or educational differences. "We don't collect any of that information — the best you're going to get is whether a person is Black or white," Spratt says. "We're not approaching disparities in health care in the way that they really exist in the United States."

Inching toward equality

Researchers working towards solutions are becoming more conscious of how they measure and address different sources of disparity. For example, people of African descent often have a low count of the white blood cells known as neutrophils and it is not related to cancer[8]. But in many clinical trials, the frequency of neutrophils in a blood sample is used to determine who can participate — and could mean some Black participants are excluded. "Every line item in a trial protocol that defines what kind of patient can enrol needs to be thought out in a very intensive fashion to ensure inclusion," Borno says.

Another route to making access to trials fairer is financial. In unpublished data, Borno and her colleagues found that when financial reimbursement programmes are available to help with costs such as travel, people of colour engage in clinical research more frequently.

Community engagement is "absolutely critical" to the long-term success of precision medicine, Callier emphasizes, particularly because precision approaches need data on genetics, lifestyle and health care gathered over years, a process that requires consistent engagement and trust. "We have to go beyond just recruitment and create good models for partnerships," she says.

Those models are beginning to appear, at least at the local level. In North Carolina, Cykert and his team at the Greensboro Health Disparities Collaborative are developing systems that identify and address health-care gaps in real time, particularly those caused by biases or a lack of access. At two cancer centres, the team placed milestones in an individual's health-care record to mark when a person should have received treatment. If, on average, a person with breast cancer received a biopsy or surgery within six months of diagnosis, researchers would receive an alert if that milestone was missed — an issue that occurs more frequently for Black people than it does for white people[9].

The team found that this and other real-time actions narrowed race-based disparities in the treatment of people with lung and breast cancers. "Genetic tests and biologic treatments tend to be more complicated, expensive and require more communication, and we're already seeing disparities in their use," Cykert says. "We need to build [the right] systems if we're not to create a whole new world of disparities with precision oncology."

Jyoti Madhusoodanan is a science writer in Portland, Oregon.

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