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Towards equitable brain genomics research, for us by us

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The increased inclusion of samples from individuals from minoritized communities in biomedical research will help to mitigate health disparities that stem from a medical enterprise founded in racism and exclusion. In this issue of *Nature Neuroscience*, Benjamin et al. investigate how genetic ancestry influences the expression of genes in the brain, an effort supported by community leaders who raised funding, partnered in shaping research questions and had a central role in the interpretation and communication of the study's findings. Here, we outline the public and social context that motivated these efforts towards ensuring equitable access to the benefits of science for all.

Science is a human enterprise. It matters who asks the questions. It matters who interprets the results. It matters who tells the stories.

Since the formation of the USA, societal structures have prevented persons of African descent (that is, Black people) from fully participating in the scientific enterprise. These structures include laws that were used to prevent enslaved Africans and their descendants from reading, the Black codes that emerged following the Civil War, the systematic deprivation of early education resources imposed through racial segregation policies, and the designed exclusion of Black people from some of our nation's most prominent higher educational institutions. This systematic and comprehensive exclusion in the USA became the foundation of an enterprise for which research institutions, hospitals and society further weaponized science against those excluded.

Perhaps the most well-known example of this weaponization is the Untreated Syphilis Study at Tuskegee launched in the 1930s. In this experiment, led by the US Public Health Service, poor Black American men who naturally contracted syphilis were monitored to determine the long-term effects of the disease. The study participants were not given informed consent nor were they provided with standard-of-care treatment for syphilis, despite the development of a therapeutic (penicillin) during the study. Yet another example of weaponized science is the eugenics movement. This movement, which was anchored in the notion that human society should be advanced through selective breeding, ultimately led to the forced sterilization of Black women up until the 1970s. Although both the US Public Health Service's Untreated Syphilis Study and the eugenics movement serve as prominent examples of science weaponized against those excluded, the biases that grew alongside the USA's exclusionary scientific practice were equally insidious. This system was conjoined with pseudoscience (such as phrenology) to promote the false belief that Black Americans were somehow less intelligent than other racialized groups, and that the Black brain was inferior.

The remnants of this structural exclusion and weaponized science persist. Although Black people make up 14% of the US population, fewer than 5% of science and engineering faculty members at higher educational institutions in the USA are Black[1]. Only 2–3% of the research project grants from the National Institutes of Health (NIH) are awarded to Black scientists[2]. Notably, a landmark study in 2011 demonstrated that Black scientists were less likely to be awarded these NIH grants even when their academic attainment was the same as scientists in other racial groups[3].

Science is a human enterprise. It matters who asks the questions. Tragically, structures within the US scientific system continue to institute barriers to the full participation of Black Americans as drivers of scientific inquiry.

Nearly two thirds of the residents of Baltimore, MD, are Black. Given the known toxicity of lead, the city banned the use of lead in new homes in 1951. Despite a nation-wide ban that followed in 1978, nearly all of the low-income housing in multiple, predominantly Black neighborhoods in Baltimore remained contaminated a decade later. Half of the children in these neighborhoods had elevated levels of lead in their blood[4]. To evaluate the effectiveness of less expensive strategies for lead abatement in these housing facilities, researchers at the Kennedy Krieger Institute (located in Baltimore) launched the federally funded Lead-Based Paint Abatement and Repair and Maintenance Study (hereafter, the Baltimore Lead Paint Study) in 1992. In this study, which was performed in conjunction with the Maryland Department of Housing and Community Development and the US Environmental Protection Agency, families who were living in homes in Baltimore with different approaches to lead abatement were tracked, and the level of lead in the home and in their children's blood was measured across several years[5].

Many of the Black American children in the study would go on to develop persistent neurological deficits due to toxic lead exposure. Litigation between the community and the medical establishment followed the conclusion of the study[6]. Indeed, such a study raised important ethical questions for the scientific community. Was it was ethical to quantify the health of children exposed to low-cost lead abatement approaches when optimal strategies for lead abatement (albeit more expensive) were already known? Some concerned members of the local Baltimore community also asked whether these children been intentionally exposed to lead. In 2001, the Maryland Court of Appeals framed the Baltimore Lead Paint Study as a modern-day Untreated Syphilis Study[7]. Others within the medical legal system argued that

the study participants were exposed to lead as a downstream effect of racist structures built into the framework of all society. In contrast to the Untreated Syphilis Study, the researchers sought to determine the best methods for mitigating the effect of these structural inequities on the health of children within their city. Yet, on the backdrop of Black exclusion from the scientific workforce and a longstanding history of mistrust in the Baltimore Black community of the scientific establishment, one must now wonder whether there was a more optimal and ethical way to pursue such a study. What if a lead scientist on the study had grown up in these low-income neighborhoods? What if two-thirds of the scientists at the institute looked and sounded like the community that they earnestly set out to serve? What if it was an advocate from within the community leadership that had led such an inquiry, driving science forward in open collaboration with the research team at the institute?

Science is a human enterprise. It matters who asks the questions. When even the most well-intentioned scientists or research institutions fall short of instantiating this principle at the heart of their work, increased mistrust from the communities they strive to serve may flower from the seeds of a society that is designed with structural racism and systematic exclusion.

In April 2003, the scientific community ushered in the completion of the first draft of the human genome. This monumental discovery carried with it the potential to unravel the mysteries of what makes us human, and to determine the biological rules that dictate the ways in which we are different from one another. Nowhere did this promise present greater hope than in the context of our individual health, and scientists launched an earnest effort to map genes to health and diseases via genotyping and phenotyping large populations. These efforts have become the basis of precision or personalized medicine, the biomedical enterprise's quest to identify the best treatments for everyone's health challenges on the basis of their individual biology. Yet, it soon became clear that exclusionary practices endemic to US scientific practice had taken root in shaping the establishment of a 21st-century precision-health-care delivery system. Although the descendants of Europeans represent only 16% of world populations, genomic databases rapidly became overrepresented with samples from individuals of European ancestry (to this day exceeding 80%)[8]. The health implications of this overrepresentation eventually started to manifest. Although genomic profiles successfully predicted disease risk for people with predominantly European ancestry, these patterns failed to effectively classify risk in individuals from an African ancestral background[9].

The manifestations of the aforementioned historical practices within the brain health domain were even more concerning. In large genome-wide association studies and meta-analyses for schizophrenia[10], autism, Alzheimer's disease, Parkinson's disease[11] and depression that involved over 4 million people, not a single Black person was included. Although Black Americans are more likely to experience severe mental illness than white Americans, Black people had been excluded from studies of these disorders. Our community felt forgotten, as American science marched forward championing precision medicine and the ideal of benefit for all.

Ultimately, the sequencing technologies that ushered in the genomic revolution were advanced to sequence the makeup of individual cells within organ systems. The insights from these studies raised hopes for a new generation of targeted treatments for heart, liver and kidney diseases. Riding on this wave of hope, the NIH launched a bold plan through its BRAIN 2.0 Initiative to apply these technologies to map the composition of the most complex organ of all. The initiative sought to create an atlas of all the cell types that compose the human brain. This atlas promised to unlock the biological rules that the brain uses to guide its path from health to disease. Yet, it was unclear to us at the time whether and how this bold plan would be implemented to ensure that the discoveries that emerged advanced health for all people.

Well aware of the exclusionary framework at the foundation of the genomics revolution, the lack of generalization of the large genomics studies to Black people[9] and the relentless pace that science continues to march forward, we, the authors, resolved that we could not let our community be left behind again.

Science is a human enterprise. We were now in the position to ask our own questions, and we wanted to know whether there were variations in the cellular composition of brains from Black Americans that may be meaningful for health and disease. Our goal was to ensure that this human brain cell atlas included brains from Black people, and that the full benefits for this transformative project were ultimately realized by all.

To achieve our goal, we had to overcome two major challenges. First, we needed Black Americans to donate the brains of their loved ones to scientific research after they passed away. We recognized that such an endeavor would require overcoming a long history of concern within the Black community of the medical establishment taking their organs without consent, or weaponizing brain science against them to argue for their inferiority. Indeed, such mistrust was warranted given the historical veracity of such practices[12].

Second, such science comes along with great risk, when viewed under a broad historical microscope. Specifically, studies that seek to determine innate biological difference which are organized based on genomic ancestry run the risk of being confounded by biological differences that emerge because of the environmental impacts of racism.

Race is a social construct. In the USA, race dictates one's experience with racism, and thus the persistent structural inequities under which our society was constructed. These inequities can determine one's access to clean drinking water, nutrition and early life education, all factors that have well-established effects on human biology and health. As such, scientific studies that strive to discover biologically anchored contributors to health and disease across race have the potential to interpret the biological effects of racism as indelible rather than imposed.

Returning to the Baltimore Lead Paint Study as an example, lead poisoning can cause brain damage in youth, and ultimately result in neurological and cognitive disabilities in adulthood. Thus, if children from one racial background have a greater exposure to lead paint based on structural inequities rooted in racism, one would anticipate increased signs of brain damage in one racial group compared to another. Such findings could have two interpretations. A group of scientists with no knowledge or understanding of the history of structural inequities imposed on one group could falsely conclude that brain biology is inherently different between the so-called races in a manner that shapes intelligence. On the other hand, an appropriately informed group of scientists would rightfully conclude that racism harms brain development and function, and that this effect can be mediated through early life exposure to toxins. The potential for misinterpretation of such studies by those who do not fully consider social context in their work raises great potential for continued harm to the communities that most require redress.

How then to address the critical question as to whether health-related differences exist in the cellular composition of the brain across racialized groups without getting hampered by confounding variables mediated by the chronic impact of racism?

Our answer was simple. We, the community, must contribute to asking the questions, and we, the community, must contribute to interpreting the results.

We first chose to focus our inquiry on ancestry rather than race. We recognize that both concepts are complex. Genetic ancestry, although not directly observable, signifies the origins of one's genetic code, and its migration patterns across history. Although race in the USA has historically been defined, in part, on the basis of presumed genetic ancestry, ancestry and race are not equivalent. Genetic ancestry is rooted in biology. Race in humans is not. Thus, we set out to determine whether there were variations in the cellular composition of brains from Americans of African ancestry that may be meaningful for health and disease.

Second, we sought to knit our community into the laboratory and the clinical translational enterprise, with the community at the helm. We reasoned that if we could demonstrate the success of this model in Baltimore (a city with a largely Black population and a long history of racial trauma and mistrust of medical institutions), we could institute a model that is suitable to be applied throughout neglected communities across the nation.

Thus, the African Ancestry Neuroscience Research Initiative (AANRI) was born, a 'from the ground up' model with four key components — community leadership and engagement; African ancestry brain science; science communication; and scientific training. AANRI was built as a collaboration between community leaders, Morgan State University (Maryland's largest and second-oldest historically Black university) and the Lieber Institute for Brain Development located on the John Hopkins Medical Campus[13]. Together, we, the community leaders, raised over 3 million dollars from the state of Maryland and philanthropic sources, including Brown Capital Management, The Abell Foundation, the Chan-Zuckerberg Initiative and the Lieber Institute for Brain Development, to support our first study of how genetic ancestry influences the expression of genes in the brain, published in this issue of *Nature Neuroscience*[14]. We worked directly with scientists at the Lieber Institute to pursue the scientific questions, and with BlackInNeuro to evaluate the study's rigor.

It is with a deep sense of humility, appreciation and pride that we share our first set of scientific findings with our community, and the scientific community at large. We believe that our efforts serve as a down payment on bringing redress to the harms caused by the exclusionary practices that have been foundational to US science. More importantly, we contend that our efforts advance a new framework for discovery science for which the community is at the heart of coordinating the laboratory and the clinic, ultimately ensuring that all citizens of our great nation have equal access to its benefits.

Science continues to move forward. But this time, we will not be left behind. These are our questions. This is our story.

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Competing interests

The authors declare no competing interests.