An Ethical Framework for Research Using Genetic Ancestry

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ABSTRACT A wide range of research uses patterns of genetic variation to infer genetic similarity between individuals, typically referred to as genetic ancestry. This research includes inference of human demographic history, understanding the genetic architecture of traits, and predicting disease risk. Researchers are not just structuring an intellectual inquiry when using genetic ancestry, they are also creating analytical frameworks with broader societal ramifications. This essay presents an ethics framework in the spirit of virtue ethics for these researchers: rather than focus on rule following, the framework is designed to build researchers' capacities to react to the ethical dimensions of their work. The authors identify one overarching principle of intellectual freedom and responsibility, noting that freedom in all its guises comes with responsibility, and they identify and define four principles that collectively uphold researchers' intellectual responsibility: truthfulness, justice and fairness, anti-racism, and public beneficence. Researchers should bring their practices into alignment with these principles, and to aid this, the authors name three common ways research practices infringe these principles, suggest a step-by-step process for aligning research choices with the principles, provide rules of thumb for achieving alignment, and give a worked case. The essay concludes by identifying support needed by researchers to act in accord with the proposed framework.

Genetic research has had a long entanglement with racist belief systems and policy practices. For example, many of the atrocities of the 20th century were carried out in the name of eugenics, the academic discipline that had as its guiding philosophy that Northern Europeans were genetically superior to other groups. The entanglement of racism and genetics continues into the present, with white supremacists and terrorists drawing upon their own interpretations of genetics research to justify their acts of racial hatred (Panofsky 2014; *STAT* 2022). When researchers use genetic ancestry to structure research questions and methodological approaches, they are not just structuring an intellectual inquiry, but also creating analytical frameworks that can have broad societal impacts. Consequently, researchers who conceptualize patterns of genetic variation—whether couched as genetic ancestry, genetic similarity, or something else—must proactively consider the ethical dimensions of their work and take deliberate action to minimize its possible misuse.

This topic is currently under the spotlight for two additional reasons. First, as the use of race across biomedicine is critiqued because of the ways this use can compound racism (Vyas, Eisenstein, and Jones 2020), attention to genetic ancestry is offered as part of the path forward (Borrell et al. 2021; Oni-Orisan et al. 2021). And second, within genetics, the underrepresentation of those other than "European ancestry" individuals in genetic studies is seen both as holding back the achievable scientific insights, and as a pressing ethical concern because it may be one factor in the exacerbation of already existing inequities in the provision of genomic medicine (Martin et al. 2019).

Standard research ethics frameworks are insufficient in the case of research that conceptualizes and uses patterns of human genetic variation for three main reasons. First, much of this research is done on de-identified data—from biobanks,

medical cohorts, or other similar sources that have aggregated large volumes of data on study participants. At least in the US, use of de-identified data does not fall under the definition of human subjects research and hence is not typically subject to further ethical review (HHS 2018). Second, even if the research data is identifiable, standard research ethics frameworks do not address possible harms to those not directly involved in the research, although there is some recent movement to incorporate consideration of "indirect" or societal harms (Lemke et al. 2022; *Nature* 2022). Finally, there are specific challenges that emerge in research domains where genetic and social questions intersect with each other.

Researchers who use genetic ancestry, or otherwise conceptualize patterns of human genetic difference, need a normative framework to guide their decision-making about critical research choices. In this article, we seek to offer such a framework. Our focus is exclusively on research: we do not tackle normative questions pertaining to the use of genetic ancestry in the clinic, by direct-to-consumer companies, or for policy applications. We stress that the choices researchers make do, however, heavily influence the ways in which genetic ideas are taken up in these key downstream areas. These choices also influence the ways these ideas are interpreted and misinterpreted by the public.

Although there have been many prior recommendations on the use of race, ethnicity, and ancestry in genetics research, as reviewed in Mauro et al. (2022), these have generally been quite high level and have not focused on genetic ancestry specifically. To guide researchers who use genetic ancestry, we have developed an ethical framework in the spirit of virtue ethics, a mode of ethical reasoning that encourages people to focus on aligning their choices and actions with a set of ethical values or principles. Rather than focusing on rules or guidelines, it encourages the development of capacities to identify and assess decisions with ethical dimensions.

The overarching principle that should guide researchers and shape research practice is intellectual freedom and responsibility. Research practice is defined by inquiry, and inquiry requires freedom, specifically intellectual freedom. Philosophers have long pointed out that freedom without responsibility is not freedom but license. Someone is free to swing their arms, but not free to do so irresponsibly, such that they risk injuring others. Understanding that the ideal of intellectual freedom necessarily incorporates responsibility is fundamental to getting intellectual freedom right. But what is the nature of the responsibility that defines intellectual freedom? We offer four further principles—truthfulness, justice and fairness, anti-racism, and public beneficence—that define elements of responsibility that support the overarching ideal of intellectual freedom and responsibility. Research teams who use genetic ancestry need to make choices that bring these principles into alignment with each other. Researchers should strive to develop the capacities needed to identify where their choices may contravene the prin-

ciples, and to identify strategies that can help bring their research practices into alignment with the principles.

To aid in cultivating these skills, we provide several tools. First, we identify three common ways that research practices, or the interpretation of research by others, may infringe on these principles. Infringements occur when researchers or others essentialize groups, fail adequately to consider the social determinants of health, or tell oversimplified stories about groups. We provide a rubric for aligning choices with the principles, which first involves mapping out the stages of the research process and calling attention to the ways these choices reinforce each other. Additionally, we provide some rules of thumb that can be helpful in bringing research practice into alignment with the principles, and we apply this rubric to an example case.

We begin with a summary of the types of research that this ethical framework is designed to cover. We then define the normative principles and give their justifications, and continue with a discussion of tools to aid researchers in aligning their choices with the principles. While the ethical framework we present is designed for researchers, we acknowledge that researchers work in an ecosystem, and that the actions of others—including funders, publishers, and educators—heavily impact and constrain their work. We therefore conclude with some suggestions for how these other actors can support research utilizing this ethical framework.

Research Covered by the Framework

In order to understand what types of research use genetic ancestry, and how they evoke the relevant concepts, we carried out a systematic literature analysis and in-depth interviews with researchers (Dauda et al. 2023). This work demonstrated that research in this area is mired by unclear and ambiguous concepts. Researchers who conceptualize patterns of human genetic variation in their work do so with a variety of terms that are often used inconsistently. The most commonly used term is *ancestry*, but this is also often used for nongenetic phenomena. The family of concepts named with the term *ancestry* can be operationalized—made into a measurable property—using genetic data, but other types of data can also be used, such as self-identification or geography. Moreover, *ancestry* is used both in common parlance and by academics across diverse disciplines. Researchers who use the concept often struggle to define it, and what definitions are offered often conflict. While it is mostly a genetic concept for some, for others it is instead about personal or family narrative, or about group cultures. For others, it is a concept that bridges the realms of the biological and social disciplines.

The ambiguity inherent in the concept of ancestry leads to genetic concepts being situated alongside social categories, as when researchers seek to understand race-based health disparities by drawing comparisons between those of different

genetically inferred continental ancestry categories. Conflation of race, ethnicity, and ancestry terminology is frequent. Adding to possible confusion, the term *population* is also used in ambiguous ways, with its meaning varying between the population geneticist's model of a randomly mating pool of individuals, to the statistical notion of a given sample being representative of a population, to simply "a group of large N."

However, as we have recently put forward, the more specific concept of genetic ancestry does lend itself to a simple and coherent definition: an individual's genetic ancestry is the subset of paths through the human family tree by which they have inherited DNA from specific ancestors (Lewis et al. 2022; Mathieson and Scally 2020). This definition equates genetic ancestry to the ancestral recombination graph (ARG), the mathematical object that describes how genetic material has been inherited through the generations. This definition makes clear that the concept does not evoke any groups. Nor does it involve any contextualization of humans with anything other than their genealogical connections. In other words, it does not involve where those humans lived, or what their cultural practices were. Researchers can choose to impose groups using any one of a range of approaches, and they can choose to contextualize those groups in various ways. Such choices should always be clearly articulated and justified, with their limitations acknowledged.

Most of the research that evokes ancestry and that uses genetic data to operationalize the concept, addresses questions that can be grouped into five basic types:

1. Understanding traits with a particular concern for health-related traits. Traits are characteristics about humans that can be described or measured, and the traits studied include health outcomes, life outcomes, environmental exposures, biochemical properties (such as metabolite levels), or model outputs (such as estimates of kidney function). This research can also encompass an understanding of how traits are associated with each other. Multiple types of research are encompassed under this umbrella:

a. *Identifying genetic associations with traits*. Genome-wide association studies (GWAS) all fall under this category, as do admixture mapping and other types of study that, for example, look at the aggregate effects of copy number variants on traits. In these cases, patterns of genetic variation are typically viewed as something to be controlled for to prevent confounding in such models.

b. *Assessing the consistency and stability of the genetic contributions to traits*. For example, can genetic variants identified in one group be validated in another group? To what extent do polygenic risk scores trained in one group generalize to other groups? Typically, the groups or "populations" referred to are defined in terms of "ancestry."

c. *Identifying factors that contribute to a trait*. In studies that seek to identify factors that may shape the understanding of a trait, particularly a life out-

come such as education attained or income, patterns of genetic variation can be seen as a confounder that might be masking the influence of other properties.

2. Understanding whether there are biological underpinnings of between-group health outcome differences. This research may involve comparing the distribution of traits in different ancestrally defined groups or probing the influence of, for example, percentage African ancestry on the distribution of a trait. Some research aims to describe differences in trait-associated genetic architecture between ancestrally defined groups. Some research questions aim to understand what is driving health disparities.

3. Understanding genetic structure, past and present. These research questions encompass the inference of demographic history and how present-day genetic diversity is shaped. They also encompass investigation of evolutionary processes—for example, evidence of factors that may have increased the likelihood of propagation of particular genetic variants.

4. Understanding social identities and lived experiences, past and present. Patterns of genetic variation are used to help understand what shapes social identities. This often involves the comparison of genetic ancestry categories to self-identified categories such as race or ethnicity. It is also used to gain insight into the life histories and lived experiences of those who lived in the past through the genotyping of human ancestors.

5. Investigating how genetic ancestry relates to aspects of clinical care. This covers, for example, questions of whether clinical tools would be improved through incorporation of genetic ancestry, and studying diagnosis rate of genetic testing by ancestry group.

Normative Principles and Their Justification

To guide research scientists who use patterns of human genetic variation—whether couched as genetic ancestry, genetic similarity, or something else—whatever their formal field of affiliation, we offer one overarching principle: intellectual freedom and responsibility.

Human well-being depends on intellectual freedom, both because it is a necessary aspect of the enactment of human autonomy and because free inquiry drives our collective capacity to solve human problems. However, every just concept of freedom carries within it its own limit at the point where harm would be done to others, and thus necessarily incorporates elements of responsibility. In other words, the freedom to pursue inquiry has always been coupled with the requirement to conduct that inquiry responsibly. To conduct inquiry responsibly is to do so ethically, and without harm to others. While two millennia of philosophical analysis has led to this view, one of its best exponents was John Stuart Mill in *On Liberty*. Drawing on Mill, Warburton (2009) writes: "The limit of free speech should be the point at which harm to others is instigated" (p25). That freedom comes with responsibility has also been articulated for the academic sphere (AAU 2013).

The requirement that researchers be truthful and honest is age-old and underscores how fundamental responsibility is to the very definition of intellectual freedom. Other elements of responsibility that support the sound exercise of intellectual freedom include disclosure of conflicts, and standards for responsible treatment of human subjects. We note these elements of responsibility inherent in intellectual freedom only to underscore that responsibility is integral to freedom.

Researchers use a number of conceptual tools related to inquiry and argumentation in order to develop logically sound characterizations and explanations. These tools include reduction, generalization, universalism, and organization. However, the responsible use of those tools is especially challenging in the case of research related to genetic ancestry, because this research fulfills a dual function. Researchers conducting this work simultaneously structure an analytic inquiry—a purely intellectual undertaking—and create analytic frameworks and vocabularies that will be used in clinical practice and public policy-making, and that will impact public understandings of existential questions about our species.

Hence, regardless of whether they desire it or not, researchers who use genetic ancestry—or other ways of conceptualizing patterns of human genetic variation—are laying down the intellectual foundations for translational work, and they are also generating resources that will be absorbed and taken up in social and moral debates. As scholarship across disciplines has shown for many decades now, our concepts are both socially constructed and themselves create social structures (Fricker 2007; Hacking 2000; Latour 2007). The requirements of ethics hence pertain not just to our direct treatment of other human beings, but also to how we contribute to the creation of social infrastructure through our conceptual and analytic work.

Consequently, research scientists must take responsibility for their analytic tools and intellectual frameworks both in relation to the structure of their own inquiry and insofar as their materials are a contribution to the intellectual foundation of translational work and the conceptual framework for contested social and moral debates. This dual function of research that pertains to genetic ancestry expands the nature of the responsibility that is baked into the principle of intellectual freedom and responsibility defining research. We have a responsibility to develop research practices and make research decisions, including about the creation of concepts, in ways that align with four key principles that are crucial elements of responsibility: truthfulness, justice and fairness, anti-racism, and public beneficence. These principles name sought-after outcomes and in turn justify pursuit of those outcomes. Properly operationalized, the principles of justice and fairness, anti-racism, and public beneficence support truthfulness.

Of course, researchers cannot control all of the ways their research will be used over time, but they should take actions to minimize the chances of their results being misconstrued by others, including the media. Minimizing some common ways the principles can be infringed, and avoiding other violations of the princi-

ples, is part of meeting the highest possible standard for intellectual freedom and responsibility.

The challenge researchers face is not to resolve trade-offs among these principles, but rather to seek maximal alignment among them (Allen 2023). In those cases where there are residual and unavoidable trade-offs, researchers often resort to "on par" reasoning, where they recognize that in making their choices, they are defining the values that are most important to them (Chang 2017). This approach to ethical decision making, which belongs to the family of views known as virtue ethics, requires cultivating capacities for judgment and justification, rather than demanding a culture of rigid rule following. For such a capacity of judgment to be cultivated, the most fundamental step is that researchers learn to see where choices with ethical stakes exist.

Before we turn to precisely this work of making the pertinent decision points visible, however, we will complete this section by defining and explaining the four key principles essential to responsibility (see Figure 1).

Truthfulness

Truthfulness encompasses the idea that researchers must commit themselves to working and communicating to maximize their accuracy and never knowingly falsify or misrepresent evidence or findings. This is achieved by adhering to norms for designing research projects, handling evidence, and drawing logical inferences. For instance, results should be based on appropriate methodologies and be replicable, conclusions drawn must follow logically from these results, and tentative conclusions drawn must reflect researcher humility in the face of the complexities of the subject matter. The unambiguous statement of a conclusion involves careful attention to generalizability, or how the results presented are believed to generalize to those not represented in the data used. Ambiguity can be appropriate in stating tentative conclusions, but truthfulness requires adequate contextualization in order to not mislead the reader: the more complex the subject matter, the more contextualization is required. This also involves recognizing that any intellectual discipline depends on tools that only approximate reality and always also obscure some aspects of reality, meaning that any given discipline is inevitably partial and limited in its perspectives.

Justice and Fairness

The principle of justice and fairness relates to the overall goal of supporting human flourishing and well-being. There is broad agreement across a variety of different philosophical approaches to justice and fairness that actions are to be avoided if they benefit those who are well-off within social structures without also benefiting those who are not well off; if they create or support discrimination in relation to relevant dimensions of difference—for example sex, age, race, ethnicity, socioeconomic class, rurality; or if they create or support domination

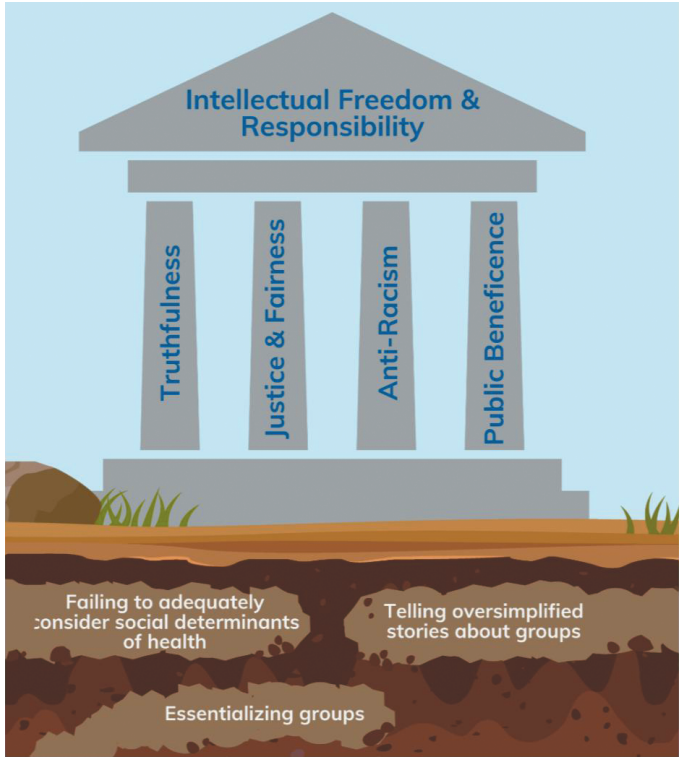

Figure 1

Conceptual architecture of the ethical framework

To uphold their intellectual responsibility, an integral component of intellectual freedom, researchers who use genetic ancestry need to make choices that align with four principles: truthfulness, justice and fairness, anti-racism, and public beneficence. We name three common ways that the principles can be infringed.

through support for the arbitrary power of some over others (Allen 2023; Anderson 1999; Pettit 2014; Rawls 1971). The principle of justice and fairness requires choices that reflect commitments to equity in resource distribution, nondiscrimination, and power-sharing with regard to critical decisions. Geneticists engaged in this work should routinely engage ethicists to evaluate collaboratively where and how their conceptual frameworks may, when used as the foundation for clinical translation or policy development, have implications that touch on dimensions of justice such as this. Those implications may come from the research questions being asked, or from the structure of the research project itself, including its conceptual architecture and its handling of data.

Anti-Racism

The principle of anti-racism communicates a commitment to undo the use of the concepts and practices of systemic racism and colonialism, wherever they

may be in operation. Academics across disciplines have shown how concepts live within and anchor social practices (Sperber 1996). Practices of racial discrimination and domination have long been anchored by recognizable conceptual patterns. For instance, scientific inquiry has contributed to the reproduction of systemic racism and supported white supremacy by treating group categories as natural. The responsible practice of science requires that these pieces of existing conceptual architecture be replaced by ones that support the inquiry at hand *without* reinforcing the undergirding systemic racism. For instance, social identity categorizations linked to ethnicity or phenotype should be disconnected from discriminatory and racist beliefs, practices, and protocols. Importantly, anti-racism is an ethical position that has been expounded by numerous philosophers, scholars, and thinkers over time from Frederick Douglass to W.E.B. DuBois to Ralph Ellison to Toni Morrison to Melvin Rogers. Contrary to much contemporary understanding, the ethical principle is not tied to the work of a single scholar (Givens 2021).

Public Beneficence

Researchers should act to maximize public benefits and minimize public and group harm, by pursuing intellectual inquiry in support of such human goods as knowledge, health, economic well-being, and political freedom (Presidential Commission 2010). Some aspects of existing human subjects research requirements already support public beneficence; for instance, the Nuremberg Code requires that research should "yield fruitful results for the good of society." Beyond this, defining what constitutes public benefit requires engagement between researchers and the public, and with any communities closely connected to the research, via a process of democratic deliberation. This is necessary to bring pursuit of public beneficence into alignment with justice and fairness.

The limited perspective of the research expert can benefit from ongoing contextualization by other perspectives, since definitions of public beneficence require collective intelligence (Farrell and Shalizi 2015; Ober 2010). Consequently, researchers should draw on a process of participatory engagement with stakeholders to bring community perspectives on that question to the surface. Sometimes funding agencies may have already made decisions about what types of research to fund, but even in these cases, community engagement can meaningfully be used to shape aspects of the research—for example, in defining the group labels used to describe research participants. (And if researchers believe that funders priorities do not align well with public beneficence, they should provide this feedback to the funders).

There are many resources already available to guide community engagement tailored to genomics (see, for example, GA4GH 2021; Lemke et al. 2022). Stakeholders likely to be most affected by human genetics research should be prioritized. These include study subjects, people living with the condition(s) under

study, practitioners whose practice will be affected by the work, policymakers with responsibility for science policy, and advocates operating in the relevant space. Additionally, community engagement practices may need to be tailored to specific social and cultural settings, and it may be appropriate to involve a representative group of the public, utilizing survey methodologies to identify candidates. A diversity of opinions should be captured, as public dissent may be a meaningful outcome of community engagement. Currently, funding and infrastructure to enable this kind of work is insufficient, a state of affairs that needs to change.

Infringement of the Principles

Decisions made by researchers may inadvertently infringe the principles enumerated above or even conflict with them. In research that involves genetic ancestry, there are some common ways that this can occur. Researchers should be particularly aware of these risks and be responsive to mitigating them.

Essentializing Groups

Essentialist beliefs are those that assume social categories reflect an underlying "true nature" (Haslam, Rothschild, and Ernst 2000). A large literature links essentialist beliefs to adverse outcomes—for example, making essentialist information salient has been linked to prejudice and ingroup bias (Keller 2005). Extensive use of genetically inferred categories can contribute to essentialist beliefs about them, despite the fact that the human family tree can be carved up in many different ways. This is particularly the case for continental ancestry categories—the most common categories used when ancestry is operationalized (Dauda et al. 2023; Panofsky and Bliss 2017). Because these categories are conflated with racial groups, the use of these categories can reify biological misunderstandings of race and conflict with anti-racism. The categories also serve to focus attention on human bodies rather than policies when it comes to understanding between-group differences (Bliss 2012). Truthfulness can also be infringed, because use of these categories can obscure what we know about human demographic history (Lewis et al. 2022).

Failing to Adequately Consider the Social Determinants of Health

The social determinants of health (SDOH) are defined as the conditions in which people are born, grow, live, work, and age. While they include factors broadly related to the health-care system, such as access to care, they exclude individual medical factors, such as behavior or genetic predisposition. It is now widely acknowledged that the SDOH are responsible for most health inequalities (Daniel, Bornstein, and Kane 2018). Contemporary epidemiology stresses the importance of integrating the SDOH into our understanding of the distribution

of health outcomes (Krieger 2016). Failing to adequately consider the SDOH in studying the distribution of traits or outcomes risks conflicting with public beneficence, because a good understanding of the role of these factors can help motivate efforts to improve outcomes. The failure to adequately consider the SDOH also infringes justice and fairness, because these factors disproportionately affect those least well off.

Telling Oversimplified Stories

Stories about human populations may include describing a country's community as made up of a neat mixture of "migrations"—for example, "the Brazilian genome" might be described as being made up of a mixture of Portuguese, West-African, and Indigenous peoples. Because oversimplified narratives can have negative repercussions, including reinforcing stereotypes, such stories fail to align with public beneficence. Oversimplified stories can also detract from research into more accurate models of the past, thus infringing truthfulness.

Aligning the Research Process with the Principles

In this section we offer a rubric for aligning research choices with the principles identified in the previous section. It is important to recognize that for any given research project, researchers face multiple decisions throughout the research process. Based on experiences of a very large research program, Khan and colleagues (2022) draw attention to the different stages of the research process and how they are related. Here we adapt and extend Khan's framework (see Figure 2). The research question and the concepts and terminology used impact every stage of the research process, including the choice of data, how genetic ancestry is operationalized, the modeling framework, and how results are presented. Choices made in all these areas mutually reinforce each other. Additionally, because the presentation of results includes the hand-off to translational research and the uptake of the ideas by the public, researchers must shape the narrative form and hand off the results appropriately.

In identifying the many ways choices can align or fail to align with the principles, researchers could follow the flow of questions given in Figure 3. Ideally, this should be done at the beginning of the research process, at idea formation and project definition, and revisited at key points in the research process—for example, before analysis starts, and before the results are written up.

Rules of Thumb to Achieve Alignment with the Principles

What follows are some simple rules of thumb that may help researchers achieve alignment with the principles, roughly organized by part of the research process.

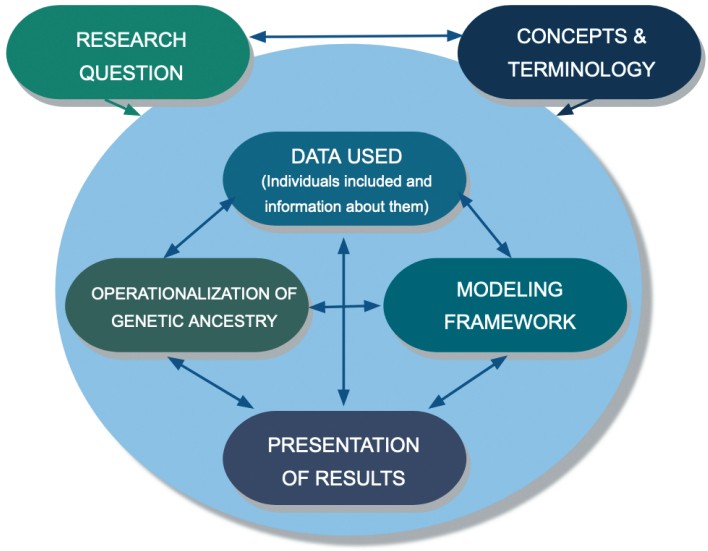

Figure 2

Multiple decision points throughout the research process where the principles can become salient
Decisions made throughout the research process can align with or be out of alignment with the principles. These decisions have mutual influences on each other, as captured by the arrows.

1. What is the current formulation of the research question? What are the key concepts and terminology relied upon in this formulation?

2. How could research answering this question align, or fail to align, with each of the principles?

3. If needed: Is there a formulation of the research question that could better align with the principles? Does it rely on updated concepts or terminology?

4. Can you identify at which points in the research process the principles become salient? What are the options for aligning choices with the principles?

Consider decisions across the Data Used, the Operationalization of genetic ancestry, the Modeling Framework, and the Presentation of Results. For each decision point, identify how the decision could be approached to bring about maximal alignment with the principles.

- *Assess* already identified options for how they could fail to align with any of the principles, making sure that you have considered the three common ways that the principles are infringed.
- If it seems like all options represent some sort of trade off between the principles, attempt to *identify new options* that would align with all the principles

5. Are there any residual sources of non-alignment? How could these be mitigated?

Figure 3

Rubric for applying the ethical framework

These are not an exhaustive set of considerations, and not all are relevant to all the types of research questions identified above.

Concepts and Terminology

Across research endeavors, a lack of clear concepts easily leads to truthfulness being infringed. Specifically in research that uses genetic ancestry, because the concepts deployed often either involve racial categories themselves, or categories that are easily conflated with racial categories, great care is needed to avoid infringing the principle of anti-racism. Rules of thumb to align with these principles include:

- *Avoid referring simply to "ancestry."* This term means many different things to different researchers and also has everyday meanings related to identity for individuals and communities. Instead, this term should always be qualified, as in "genetic ancestry," "genealogical ancestry," or "self-identified ancestry."
- *Consider how a chosen operationalization of patterns of genetic variation relates to genetic ancestry.* An individual's genetic ancestry is the subset of paths through the human family tree by which that person has inherited DNA from specific ancestors (Lewis et al. 2022; Mathieson and Scally 2020). In technical terms, genetic ancestry is the ARG. The idea of "populations" or "ancestral groups" is not inherent in this concept, nor is any contextualization of humans in any way other than via their genealogical relationships. When researchers operationalize patterns of human genetic variation, they need to carefully justify any groups that they choose to impose, and any contextualization (for example, in terms of geographical labels) they choose to give. Researchers should also be aware that all currently available tools give only crude summaries of the ARG, and that these summaries reflect all the biases of the input data used.
- *Take care when using the term "population."* This term can refer to part of an abstract mathematical model (from population genetics), or to the group of individuals a given sample is assumed to generalize to (within statistics), or simply to a large group, defined in any way whatsoever. In many cases where it is possible to refer to "populations," it is instead possible to refer directly to different variables that may be influencing the outcome of interest. In other cases, the term "sample" may be more appropriate (if referring to the sample under study), or simply "group." Referring simply to a "group" of individuals has the benefit that it invites the question (which researchers should answer): why were these particular individuals grouped together?

Research Question

Clearly articulating a research question that is as closely tied to the overall motivation of the work as possible is a key part of delivering public benefit from the research. If the research is explicitly motivated by justice and fairness, perhaps

framed in terms of equity, these considerations are particularly acute. Rules of thumb for supporting these principles in defining research questions include:

- *Engage communities to better understand what would constitute beneficial outcomes of the research.* What constitutes public benefit is ultimately defined by the communities who will be most impacted by the work, and engaging those communities should be an integral part of defining the aims of research. For example, while "preventing diabetes" may be a universally agreed-upon benefit, community engagement could shape *how* this aim is achieved. Seeking community engagement entails humility on the part of the researcher, for example, by being more receptive to the expertise that patients and groups hold about their own bodies and conditions.
- *Align research questions to the overall motivation for the work.* By identifying how research in a given area could eventually have the desired impact, it may be possible to identify adaptations to the research question (and reporting plan) that will more closely help achieve that end. For example, if the ultimate motivation is to improve clinical care through polygenic risk scores, then the research questions could encompass production of the metrics most appropriate to assess potential clinical validity and utility.
- *State research questions in as much detail as possible.* For example, "Running a GWAS" is not a research question: rather, it names a methodology that can be deployed for different research questions and can be used differently depending on these questions. A GWAS for locus discovery to aid in understanding molecular mechanisms is importantly different from a GWAS whose output could be used in a polygenic risk score designed to be integrated into a clinical risk model.

Data Used

Research using genetic ancestry can be incredibly sensitive to the data used. This is true along two axes: *who* is in the data, and *what* is known about them (genetic data, but what else?). Specifically for this type of research, who is in the data can affect the results directly (and not just how they generalize, which is true of all research), in a way that risks all three of the common ways by which research practices can infringe on the principles: essentializing groups, failing to adequately consider the SDOH, and telling oversimplified stories. Rules of thumb to avoid these risks include:

- *Identify the nongenetic variables relevant to answering the research questions.* These can be identified based on the (usually extensive) literature outside of genetics, or in collaboration with researchers in different disciplines. Researchers should use data that includes good diversity across all these variables when possible. If these data are not available, researchers should communicate the limits of the data they do have access to, and make a call for the type of data they believe would be necessary.

- *Characterize data sets using multiple dimensions of difference.* When researchers report on the characteristics of their data set, they should present what is known about how the data reflects as many of the dimensions of diversity identified as important to the trait or outcome of interest as possible, and reflect on how this may limit the generalizability of findings. This will include the common dimensions of race, ethnicity, sex, gender, and age, but depending on the trait or outcome, it may also include socioeconomic status, environmental exposures, or other factors. It will rarely be appropriate to just show the breakdown by continental ancestry categories or by racial categories.
- *Identify how the particular individuals analyzed could impact findings.* This is particularly important for the reference data used, but should be considered for all data drawn upon. Researchers should know which sampling schemes were used to collect the data they use, and how the sampling scheme might affect their results and conclusions. For example, the sampling schemes of the most commonly used reference data were designed to capture between-group differences, rather than the continuity of human diversity.

Operationalization of Genetic Ancestry

One of the consequences of bringing clarity to the concepts related to patterns of human genetic variation is that it makes clear the vast set of choices that researchers have available to them in operationalizing patterns of genetic variation. These can be thoughtfully deployed to avoid the risk of essentializing groups. Rules of thumb include:

- *Avoid categories where possible.* There are no genetically defined categories of humans in nature. We can deploy models that use categories, but because using them risks essentializing groups, if categories can be avoided, they should be.
- *If use of categories is unavoidable, use multiple ways of defining them.* There are an almost infinite number of ways of summarizing the structure contained within the ARG, including different ways to summarize the similarity between any two individuals, and different criteria by which they are grouped. Some sets of genetically defined categories may be helpful in shedding light on the research question, but which sets often will not be obvious ahead of time. If researchers do need to use categories to answer their research questions, they should probe different sets of categories.
- *Understand and communicate the limitations of tools used.* This can help support truthfulness, because it helps underscore the ways that results depend on the assumptions made by the tools employed, and the data that are used.

Modeling Framework

To date, most research involving patterns of human genetic variation has deployed fairly simple modeling frameworks. These simple approaches can contrib-

ute to all three of the common ways that research practice infringes the principles. Rules of thumb to promote the adoption of modeling frameworks that avoid these risks include:

- *Use DAGs to capture the different factors that may be influencing key variables of interest.* Directed acyclic graphs (DAGs) are visual representations of causal assumptions that are routinely used across much of epidemiology. At a minimum, the use of DAGs can serve as a communication and brainstorming tool. But it can also suggest the most appropriate modeling framework to employ, for example, in identifying potential confounders.
- *Think through the historical processes that have led to current observations.* Historical processes might include, for example, the social and political influences of who had children together. Thinking through these processes can help bring conceptual clarity to what the confounders are for a particular analysis, and the extent to which different approaches (such as Principal Components) accurately capture them.

Presentation of Results

As with all research, how the results are reported contributes to the overall impact of the work. This applies not just to how results are communicated in words, but also to the graphical presentation of results (Carlson et al. 2022). One of the ways that research practices fail to align with all the principles is through over-interpretation of the results. Two rules of thumb to help mitigate this are:

- *Make quantitative findings prominent.* Do not simply state whether a statistically significant effect was found. For example, researchers should state how much of the overall variance within or between groups is captured by the finding.
- *Contextualize the effect sizes of genetic findings against nongenetic factors.* Context is important for understanding the significance of results. For example, it may be helpful to compare the proportion of variance explained by a polygenic risk score to the proportion of variance explained by socioeconomic status, or to compare the likely influence of genetic determinants of a drug response to social determinants such as access to appropriate drugs.

A major motivation for presenting this ethical framework is to avoid the misinterpretation or deliberate misuse of research that uses ideas of between group genetic differences to justify racism. A suggestion that may help in mitigating this risk is to be creative in imagining how results could be misused and take precautions. For example, at the start of a research project, a research team could conduct a "pre-mortem" exercise, whereby they imagine what could go wrong (in contrast to a post-mortem, which is when something has already gone wrong), with the purpose of avoiding negative outcomes. With potential misuses identified, precautions can then be taken. All of the simple rules of thumb listed so

far could potentially help, and researchers should consider and then implement additional mitigation strategies.

Using the Framework: An Example

Below we present an example of how the ethical framework could be applied to one particular case, using the rubric outlined in Figure 3. Readers are invited to think about how they would respond to this case.

The Case

Shani recently completed her doctoral work in genetic epidemiology. She is now writing a career development grant that would help her gain new skills and launch herself as an independent investigator. She wants to focus on prostate cancer, a disease that killed her grandfather and that her uncle was recently diagnosed with. Specifically, she is interested in understanding why Black men in the US have higher prostate cancer mortality and morbidity than White men. She thinks a better understanding could help improve the health of everybody, and also help address the observed disparities.

Recent work has claimed that a "substantial fraction" of the observed disparity in incidence could be due to differences in allele frequencies between men of European ancestry and African ancestry at a few hundred variants associated with prostate cancer (Conti et al. 2021). There's also evidence that, if social determinants of health are taken into account, the observed differences in mortality for men diagnosed with prostate cancer disappear (Dess et al. 2019).

Shani doesn't see much prior research that attempts to integrate genetic perspectives with the myriad social determinants of health. New data is coming online that she hopes might enable a better integration of this—for example, data from the All of Us or Connect for Cancer Prevention Cohort studies, which contain genome-wide genetic information, electronic health record data, and questionnaire and linked geographic information system data on social determinants of health.

Shani is worried that the program of looking for genetic explanations for the observed disparities will be lapped up by white supremacists as evidence of the biological inferiority of Black individuals. She was horrified by how genetics research was cited in the "manifesto" of the White gunman who killed 10 Black people in a racist mass shooting. And she also fears that the identification of such differences could be used by the medical establishment to justify ongoing health disparities and prevent the action needed to close them.

Shani is wondering how to plan research in this area in an ethically responsible way. She does not need to solve all the issues herself; her grant proposal should integrate multiple other researchers and can include seeking additional training.

Applying the Framework

1. What is the current statement of the research question? What are the key concepts and terminology relied upon in this formulation?

Shani realizes that she doesn't actually have a sharply defined research question yet. Instead, she has an area of interest, which is about developing an understanding of any genetic and other contributors to the observed morbidity and mortality differences between Black men and White men, and developing such an understanding in a way that will actually help improve the disparity. The key concepts and terminology include: race, genetic ancestry, mortality from prostate cancer, genetic determinants, social determinants, primary and secondary cancer prevention, and improving outcomes.

2. How could research answering this question align, or fail to align, with each of the principles?

Truthfulness. In order to align with this principle, the research must rely on models that are not overly simplistic. In her initial research, Shani has realized that epidemiologists have developed sophisticated conceptual models for how health disparities arise, including how structural racism can influence both the distribution of social determinants of health and the distribution of genetic factors across racial groups, for example, via de jure and de facto segregation (Howe et al. 2022). She realizes that she is going to have to work out how to capture correlations, confounders, and interactions between the genetic and social determinants. She also realizes that it is not just the genetic variants identified that matter, but their effect sizes, and her work must adequately capture the limitations of existing approaches to estimate these. A priority for her will be to identify a mentorship team that includes this relevant expertise. To align with truthfulness, her work must also explicate the way that the approach taken is limited, and in particular, the ways that the results could fail to generalize. As she seeks to integrate an understanding of environmental effects and social determinants of health, she is also going to have to consider how well the available data captures these factors.

Justice and fairness. This research could align with justice and fairness if it helps identify clinical or policy interventions that would improve the prostate cancer outcomes for Black men. For this to happen, factors that disproportionately influence Black men would have to be understood well enough such that interventions could be designed (or existing interventions further supported). It could fail to align with justice and fairness if it hinders the development of clinical or policy interventions that would promote the health of Black men, or that would produce interventions that would only benefit other men. It could also fail to align if it creates discrimination by race. This could happen if the research draws attention away from the social determinants of health, or if it promotes fatalism ("Black men are at higher risk of prostate cancer due to genetics; nothing can be done about that"), or if it leads to genetically targeted therapeutics or genetic screening that are better accessed by those who already experience better health

outcomes. Shani can investigate if there is a way to integrate an understanding of how different interventions could help alleviate the disparity—perhaps she can set herself up for a following grant to focus on this.

Anti-racism. This research could help undo use of the concepts and practices of systemic racism and colonialism by focusing on the health of Black men in the US. But it could fail to align with anti-racism if it treats racial categories as biological, rather than recognizing that they are socio-political constructs. This could happen if race and genetic ancestry are conflated—for example, by using continental ancestry categories, which are an oversimplification of human demographic history (Lewis et al. 2022). In investigating the relevance of the distributions of the variants that increase risk for prostate cancer, Shani can look beyond continental categories: she can gather more information about these variants' global distribution via investigating finer-grained categories, and potentially even track their demographic history using diverse ancient DNA samples. She can also ensure the framework she chooses can allow for an investigation of how social determinants end up affecting biology—for example, through looking at processes such as the role of inflammation (Nelson et al. 2022). Again, she will need to seek out those with the relevant expertise to help her.

Public beneficence. This research can be conducted in a way that aligns with public beneficence if the benefits sought align with what the relevant stakeholders in question themselves would view as a benefit—in this case, the relevant stakeholders are Black men in the US, and particularly those who have already been diagnosed with prostate cancer. Shani could integrate a community advisory board into her grant proposal, to help delineate what successful outcomes could look like, including how the outputs of the work should be disseminated.

3. Is there a formulation of the research question that could better align with the principles? Does it rely on updated concepts or terminology?

This exercise reveals that simply attributing most or even some portion of the disparities in prostate cancer incidence, morbidity, or mortality to genetics fails to align with key ethical principles. Rather, the focus should be: how do genetic and social determinants of health contribute to the development and progression of prostate cancer, how do these factors interact to cause poorer outcomes in Black men compared to White men in the US, and what can be done to eliminate this gap? This exercise highlights the importance of appreciating that continental ancestry categories are a gross oversimplification of genetic ancestry, the importance of potential confounding of genetic associations due to systemic racism, and the importance of broad and detailed measurements of social determinants of health. In addition to the concepts already considered, the concepts of causality and actionability will be very important.

4. Can you identify at which points in the research process the principles become salient? What are the options for aligning choices with the principles?

Data used. To capture as many of the relevant social determinants of health as possible, Shani will need to integrate electronic health record data, neighborhood level data and individual-level questionnaire data (for example, on witnessing or being the target of racist discrimination). To do this, she will need to devote time to gaining expertise herself, and she will need to work alongside experts who can mentor her.

Operationalization of genetic ancestry. Care will be needed in adjusting for potential confounders. Whether it is sufficient to operationalize genetic ancestry with principal components to adjust for confounding should be assessed by drawing out the underlying causal DAGs. It may be necessary to include direct measures of any exposures—such as a social determinant of health—as confounders.

Modeling framework. Shani is going to learn from experts at modeling health disparities about their preferred approaches, and she will combine this with some of the more sophisticated ways of thinking about gene-environment interactions. It is likely that the framework she settles on will be a causal modeling approach.

Presentation of results. Shani will ensure she contextualizes the effect sizes of any and all contributions to the disparities her work identifies, alongside all other known effects. When she writes up her results, she will stress the implications for intervention strategies. The work she proposes with a community advisory board will further help to define an approach here.

5. Are there any residual sources of nonalignment? How could these be mitigated?

This research agenda may still detract from the social determinants of health. Shani could find ways to amplify the voices of those who focus on the SDOH, and particularly those who are working on solutions. Additionally, there is still a risk that this work could reify biological misunderstandings of race. Shani could ensure that if she ends up defining genetically defined groups, she finds ways to introduce narratives that distinguish these from racial groups.

Conclusion

The framework we present here is designed specifically as a tool for those who conduct research that uses patterns of human genetic variation—related to genetic ancestry or genetic similarity. Others—including funders, publishers, and educators—could support the responsible development of research in these fields through taking actions that would align with these principles. First and foremost, this would involve supporting researchers who prioritize aspects of their work that engage with the concerns that motivate this framework. In this final section we draw attention to additional actions that could better support researchers in

making use of this ethical framework: the development of new tools, support for community engagement, and additional professional development.

Particularly as new whole-genome data comes online, there is an opportunity to create and normalize the use of tools that expand the ways that patterns of human genetic variation are conceptualized and operationalized. Funders should support these efforts, placing emphasis on making tools accessible by other researchers. Accessibility includes ease of use and resources to understand the limitations of the tools. This should include tools that incorporate ancient DNA, that explicitly model the ARG, that enable probing multiple scales of patterns of genetic variation, and that emphasize relations rather than categories.

The importance of community engagement is now broadly agreed upon, but funding and other sources of support for doing community engagement well are not yet in place. This should be an urgent priority for funders.

There are several areas where strengthened opportunities for professional development would be helpful. First, while population geneticists are generally sensitive to the ways in which their models are simplistic and very limited ways of understanding human diversity, and to the many caveats that should attend use of their tools, appreciation of these limitations is not part of the training of those who then use them. Second, current training of geneticists does not prepare them to model how best to integrate nongenetic factors into their analysis, including how to work jointly with social scientists. This pattern is decades old and needs to change. Genetics researchers need to see incorporating the social determinants as their turf, even if they do this via productive collaborations with others. Inculcating this attitude needs to be part of the professional development of geneticists. And finally, researchers who use patterns of genetic variation need support to design, conduct, and report on their research in a manner consistent with their intellectual responsibility. It is to this end that we have written this article. We have also produced some resources designed to enable the integration of consideration of this ethical framework into the professional development of those who do this type of research.

Researchers who use genetic ancestry are motivated to do good science that has a positive impact on the world. This framework is designed to help enable those researchers to achieve the type of impact they are hoping for, via strengthening their abilities to identify and react to the ethical dimensions of their work.

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