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Ethics of inclusion: Cultivate trust in precision medicine:

We must explore how studies enhance diversity, inclusion

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Precision medicine is at a crossroads. Progress toward its central goal, to address persistent health inequities, will depend on enrolling populations in research that have been historically underrepresented, thus eliminating longstanding exclusions from such research (1). Yet the history of ethical violations related to protocols for inclusion in biomedical research, as well as the continued misuse of research results (such as white nationalists looking to genetic ancestry to support claims of racial superiority), continue to engender mistrust among these populations (2). For precision medicine research (PMR) to achieve its goal, all people must believe that there is value in providing information about themselves and their families, and that their participation will translate into equitable distribution of benefits. This requires an ethics of inclusion that considers what constitutes inclusive practices in PMR, what goals and values are being furthered through efforts to enhance diversity, and who participates in adjudicating these questions. The early stages of PMR offer a critical window in which to intervene before research practices and their consequences become locked in (3).

Initiatives such as the All of Us program have set out to collect and analyze health information and biological samples from millions of people (1). At the same time, questions of trust in biomedical research persist. For example, although the recent assertions of white nationalists were eventually denounced by the American Society of Human Genetics (4), the misuse of ancestry testing may have already undermined public trust in genetic research.

There are also infamous failures in research that included historically underrepresented groups, including practices of deceit, as in the Tuskegee Syphilis Study, or the misuse of samples, as with the Havasupai tribe (5). Many people who are being asked to give their data and samples for PMR must not only reconcile such past research abuses, but also weigh future risks of potential misuse of their data.

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Transparency about the conduct and limits of precision medicine research is key to meaningful inclusion.

To help assuage these concerns, ongoing PMR studies should open themselves up to research, conducted by social scientists and ethicists, that examines how their approaches enhance diversity and inclusion. Empirical studies are needed to account for how diversity is conceptualized and how goals of inclusion are operationalized throughout the life course of PMR studies. This is not limited to selection and recruitment of populations but extends to efforts to engage participants and communities, through data collection and measurement, and interpretations and applications of study findings. A commitment to transparency is an important step toward cultivating public trust in PMR's mission and practices.

FROM INCLUSION TO INCLUSIVE

The lack of diverse representation in precision medicine and other biomedical research is a well-known problem. For example, rare genetic variants may be over-looked—or their association with common, complex diseases can be misinterpreted—as a result of sampling bias in genetics research (6). Concentrating research efforts on samples with largely European ancestry has limited the ability of scientists to make generalizable inferences about the relationships among genes, lifestyle, environmental exposures, and disease risks, and thereby threatens the equitable translation of PMR for broad public health benefit (7).

However, recruiting for diverse research participation alone is not enough. As with any push for “diversity,” related questions arise about how to describe, define, measure, compare, and explain inferred similarities and differences among individuals and groups (8). In the face of ambivalence about how to represent population variation, there is ample evidence that researchers resort to using definitions of diversity that are heterogeneous, inconsistent, and sometimes competing (9). Varying approaches are not inherently problematic; depending on the scientific question, some measures may be more theoretically justified than others and, in many cases, a combination of measures can be leveraged to offer greater insight (10). For example, studies have shown that American adults who do not self-identify as white report better mental and physical health if they think others perceive them as white (11, 12).

The benefit of using multiple measures of race and ancestry also extends to genetic studies. In a study of hypertension in Puerto Rico, not only did classifications based on skin color and socioeconomic status better predict blood pressure than genetic ancestry, the inclusion of these sociocultural measures also revealed an association between a genetic polymorphism and hypertension that was otherwise hidden (13). Thus, practices that allow for a diversity of measurement approaches, when accompanied by a commitment to transparency about the rationales for chosen approaches, are likely to benefit PMR research more than striving for a single gold standard that would apply across all studies. These definitional and measurement issues are not merely semantic. They also are socially consequential to broader perceptions of PMR research and the potential to achieve its goals of inclusion.

STUDY PRACTICES, IMPROVE OUTCOMES

Given the uncertainty and complexities of the current, early phase of PMR, the time is ripe for empirical studies that enable assessment and modulation of research practices and

scientific priorities in light of their social and ethical implications. Studying ongoing scientific practices in real time can help to anticipate unintended consequences that would limit researchers' ability to meet diversity recruitment goals, address both social and biological causes of health disparities, and distribute the benefits of PMR equitably. We suggest at least two areas for empirical attention and potential intervention.

First, we need to understand how “upstream” decisions about how to characterize study populations and exposures influence “downstream” research findings of what are deemed causal factors. For example, when precision medicine researchers rely on self-identification with U.S. Census categories to characterize race and ethnicity, this tends to circumscribe their investigation of potential gene-environment interactions that may affect health. The convenience and routine nature of Census categories seemed to lead scientists to infer that the reasons for differences among groups were self-evident and required no additional exploration (9). The ripple effects of initial study design decisions go beyond issues of recruitment to shape other facets of research across the life course of a project, from community engagement and the return of results to the interpretation of study findings for human health.

Second, PMR studies are situated within an ecosystem of funding agencies, regulatory bodies, disciplines, and other scholars. This partly explains the use of varied terminology, different conceptual understandings and interpretations of research questions, and heterogeneous goals for inclusion. It also makes it important to explore how expectations related to funding and regulation influence research definitions of diversity and benchmarks for inclusion.

For example, who defines a diverse study population, and how might those definitions vary across different institutional actors? Who determines the metrics that constitute successful inclusion, and why? Within a research consortium, how are expectations for data sharing and harmonization reconciled with individual studies' goals for recruitment and analysis? In complex research fields that include multiple investigators, organizations, and agendas, how are heterogeneous, perhaps even competing, priorities negotiated? To date, no studies have addressed these questions or investigated how decisions facilitate, or compromise, goals of diversity and inclusion.

The life course of individual studies and the ecosystems in which they reside cannot be easily separated and therefore must be studied in parallel to understand how meanings of diversity are shaped and how goals of inclusion are pursued. Empirically “studying the studies” will also be instrumental in creating mechanisms for transparency about how PMR is conducted and how trade-offs among competing goals are resolved. Establishing open lines of inquiry that study upstream practices may allow researchers to anticipate and address downstream decisions about how results can be interpreted and should be communicated, with a particular eye toward the consequences for communities recruited to augment diversity. Understanding how scientists negotiate the challenges and barriers to achieving diversity that go beyond fulfilling recruitment numbers is a critical step toward promoting meaningful inclusion in PMR.

TRANSPARENT REFLECTION, CULTIVATION OF TRUST

Emerging research on public perceptions of PMR suggests that although there is general support, questions of trust loom large. What we learn from studies that examine on-the-ground approaches aimed at enhancing diversity and inclusion, and how the research community reflects and responds with improvements in practices as needed, will play a key role in building a culture of openness that is critical for cultivating public trust.

Cultivating long-term, trusting relationships with participants underrepresented in biomedical research has been linked to a broad range of research practices. Some of these include the willingness of researchers to (i) address the effect of history and experience on marginalized groups' trust in researchers and clinicians; (ii) engage concerns about potential group harms and risks of stigmatization and discrimination; (iii) develop relationships with participants and communities that are characterized by transparency, clear communication, and mutual commitment; and (iv) integrate participants' values and expectations of responsible oversight beyond initial informed consent (14). These findings underscore the importance of multidisciplinary teams that include social scientists, ethicists, and policy-makers, who can identify and help to implement practices that respect the histories and concerns of diverse publics.

A commitment to an ethics of inclusion begins with a recognition that risks from the misuse of genetic and biomedical research are unevenly distributed. History makes plain that a multitude of research practices ranging from unnecessarily limited study populations and taken-for-granted data collection procedures to analytic and interpretive missteps can unintentionally bolster claims of racial superiority or inferiority and provoke group harm (15). Sustained commitment to transparency about the goals, limits, and potential uses of research is key to further cultivating trust and building long-term research relationships with populations underrepresented in biomedical studies.

As calls for increasing diversity and inclusion in PMR grow, funding and organizational pathways must be developed that integrate empirical studies of scientific practices and their rationales to determine how goals of inclusion and equity are being addressed and to identify where reform is required. In-depth, multidisciplinary empirical investigations of how diversity is defined, operationalized, and implemented can provide important insights and lessons learned for guiding emerging science, and in so doing, meet our ethical obligations to ensure transparency and meaningful inclusion.

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