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Precisely Where Are We Going? Charting the New Terrain of Precision Prevention

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Abstract

In addition to genetic data, precision medicine research gathers information about three factors that modulate gene expression: lifestyles ,environments, andcommunities.Therelevantresearchtools —epidemiology,environmental assessment, and socioeconomic analysis—are those of public health sciences rather than molecular biology. Because these methods are designed to support inferences and intervention sad dressing population health ,the aspirations of this research are expanding from individualized treatment toward precision prevention in public health .The purpose of this review is to explore the emerging goals and challenges of such a shift to help ensure that the genomics community and public policy makers understand the ethical issues at stake in embracing and pursuing precision prevention .Two emerging goals bear special attention in this regard: (*a*) public health risk reduction strategies, such as screening, and (*b*) the application of genomic variation studies to understand and reduce health disparities among population groups.

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INTRODUCTION

Since the publication of the 2011 National Research Council report *Toward Precision Medicine* (82), the aspirational goals of translational genomic research have been under renovation. Personalized genomic medicine was initially presented in terms of its promise to replace traditional clinical approaches to diagnosis and treatment with genomic profiling and individually tailored prescriptions. This framing is being both qualified and expanded in reference to population health. Both trends reflect acknowledgment that patients' genes provide only one of the multitude of intersecting environmental, social, and behavioral factors that clinicians have traditionally taken into consideration in addressing patients' complaints. Although this causal heterogeneity has always been appreciated in the abstract, the amount and variety of biomedical data becoming available through contemporary bioinformatic technologies are making the coordinated analysis of both "below the skin" genomic, epigenetic, and metabolic factors and "above the skin" behavioral and environmental determinants of health increasingly attractive as points of intervention for improving public health (36). Against this background, translational genomic research is merely the backbone of a broader pursuit in which genomic findings are interwoven with other sources of patient data to provide clinicians with a more complete understanding of the health problems they treat.

To signal their conversion to this new vision, genomic researchers, clinical programs, and professional journals that heralded the arrival of personalized genomic medicine at the turn of the twenty-first century now widely adopt the language of precision medicine to frame their translational goals (48). With the launch of the US Precision Medicine Initiative in 2015 (recently rebranded as the *All of Us* Research Program), the days of a narrowly construed genomic medicine, with its attendant risks of deterministic and essentialist patient profiling, seemed all but over.

However, as much as some emphasize the multifactorial nature of precision medicine, genomics has not surrendered its pride of place in this vision. Within the flux of circumstantially imposed health risk factors that can influence precision medicine's calculations, it is genomic variation that gives precision medicine its power to rebuild clinical nosologies and predict individual health outcomes. *Toward Precision Medicine* (82) positions molecular biology at the heart of the ambition to develop a new taxonomy of disease. As a result, although large-scale precision medicine research projects like the Precision Medicine Initiative *All of Us* Research Program include efforts to collect many kinds of data about research participants, their centerpieces are still translational genomic research efforts aimed at understanding and harnessing human genetic variation to help improve human health.

To link these genomic data with information about people's lifestyles, environments, and communities, research on precision medicine must shift its gaze from individual patients to the populations of which they are part. As leaders in public health genomics point out,

> As paradoxical as it may seem, while precision medicine focuses on individualized care for each patient, its success truly requires a population-based perspective. First, . . . [t]o be informative, data on an individual need to be compared with data from large numbers of people to recognize important individual characteristics and to identify relevant population subgroups that are likely to respond differently to drugs and other interventions. Second, collecting information from large numbers of people is far more informative when these people are representative of the underlying population from which individuals are drawn. (54)

Of course, the health sciences that elucidate above-the-skin health risks—such as epidemiology, environmental health science, and health behavior—have traditionally been concerned with the protection and promotion of the public's collective health rather than with individual medical treatment. These goals animate precision research methods, frame research priorities, and shape subsequent interventions. As much as precision medicine professes to be aimed at individual health care, the assimilation of these population sciences also imports their ideals and imperatives, moving the ambitions of the enterprise from the clinical setting into larger public health and social policy goals. The Precision Medicine Initiative *All of Us* Research Program is thus depicted not only in terms of individual health, but also in terms of community:

> *All of Us* represents the hope for all of us to come together to change the future of health care. The more people across America that participate, the more data they contribute to this research platform, and the more researchers who tap into the data, the greater our chances of unlocking medical breakthroughs. We are calling every person in every community in America to give, for ourselves, for our communities and for our future. (80)

For scholars and researchers who study the ethical, legal, and social implications of human genome research, the idea of genomically inflected precision medicine at the population level raises significant questions. For example, how should precision prevention in the service of public health be operationalized (4)? What challenges might its different applications face (103)? In this review, we examine two proposed applications of translational genomic research that raise these questions: the integration of genomic tools into risk stratification for screening, and the use of genomic variation to reduce health disparities among population groups. Both of these applications are already endorsed as goals in the emerging literature of precision medicine research. If accepted uncritically, however, each risks unintentionally exacerbating the social problems it is supposed to help address.

FROM PRECISION MEDICINE TO PRECISION PREVENTION

One of the reasons why the goals of precision medicine research are easily expanded to address public health is that its promise to predict and prevent future disease resonates well with the traditional public health mission to prevent the emergence and spread of health

problems within the population. By incorporating population sciences into its efforts to improve clinical medicine, precision medicine research sets the stage for shifting its aspirational goals from personalized prevention in health care to precision prevention at the population level. As the head of the Public Health Genomics Program at the US Centers for Disease Control and Prevention writes,

> [W]hile precision medicine is currently focused on treatment, a compelling case can be made for giving even more attention to early detection and disease prevention. Although personalized treatments can help save the lives of people who are already sick, disease prevention applies to all of us. “Precision prevention” then may be useful in using both science and limited resources for targeting prevention strategies to subsets of the population. (54)

As this explanation of precision prevention suggests, public health risk stratification involves building predictive models that differentiate population subgroups according to greater probabilities for specified health outcomes (34). Precision prevention risk reduction strategies, by extension, take genomic markers as their index risk factors and then try to modulate the predictive models they suggest in order to account for other above-the-skin influences, such as exposure to environmental contaminants or occupational risk factors, health behaviors related to activity or diet, or interactions between these factors (12). In this way, precision prevention combines key genetic insights with other forms of data to offer new opportunities to reduce morbidity and mortality (114).

The overall goal of these models is to target risk reduction interventions to those at greater risk for a particular condition, without requiring universal measures that might achieve the same benefit but at a greater cost and with the potential for overtreatment (34). This idea can be operationalized in two ways: (*a*) by screening everyone for known genetic markers of health risk to let the subpopulations of interventional interest emerge from the bottom up, or (*b*) by identifying subpopulations that seem to bear disproportionate health burdens from the top down and seeking the genomic variations that distinguish them from other groups as clues to the disparity. Each approach addresses different goals, but together they provide the scissoring movement that gives precision prevention its power. However, in this metaphor, both the top and bottom blades of precision prevention carry their own ethical and social hazards that need to be anticipated and addressed if this tool is to be used safely for public welfare.

SCREENING POPULATIONS TO PREVENT GENOMIC HEALTH RISKS

The paradigm for the bottom-up blade of precision prevention is traditional newborn genetic screening. Newborn genetic screening programs focus on mitigating the harms of serious genetic conditions by detecting their causal genotypes at birth and enabling interventions that prevent or mitigate the effects of disease (63, 97). Some see similar potential in expanding the range of newborn genetic screening through whole-exome sequencing (2, 97, 107). Others propose the application of genomic sequencing technologies to efficiently screen healthy adults for unrecognized genetic health risks, which are promoted as a way to detect subsets of the general population that might benefit from increased medical surveillance or intervention (24). For example, researchers have recommended that some

methods of identifying deleterious variants be used for opportunistic screening during clinical sequencing (51), studied as a clinical service (1, 22), or implemented within major health systems (11, 21). Projects like these have been included on the promissory agendas of public health genomics and precision public health (55, 56).

Of course, newborn screening programs have rarely featured the evidentiary robustness to which precision prevention aspires because a key criterion has been to screen only for genotypes that are highly predictive of clinical consequences. The need for strong predictive power for a mutation to be included in newborn genetic screening is rooted in traditional principles for public health screening that emphasize the predictive reliability of screening tests (113). To a large extent, today's adult genomic screening efforts concur that the safest kinds of genomic health risk markers to seek for intervention are those with the highest levels of penetrance and predictability (3, 9, 65, 81). As a result, the public health utility of these programs is limited to a small set of relatively rare genetic diseases that have a modest collective impact on population mortality and morbidity, even though they can be devastating for the individual patients and families they affect.

For newborn genetic screening, the resulting tension between population and personal benefits has sustained a long-running debate over whether this screening is better understood and operationalized as a public health tool or a form of preventive clinical care (46). As Roberts et al. note, the result is that newborn screening programs operate at the intersection of public health, clinical care, and public policy. Historically, public health agencies have justified sponsoring newborn genetic screening programs by amending their normal population-based reasoning with appeals to the rule of rescue (78, 98, 108). And when several rare yet devastating variants are bundled together in a screening platform, incidence and subsequent benefits in reduced morbidity and mortality begin to aggregate (24). Even when a health problem is rare, these agencies argue, a society that has the means to effectively intervene to rescue defenseless and dependent individuals, such as newborns, from oncoming harm should do so (110). The same argument is essentially being made today in clinical settings to justify "looking for trouble" in adults through preventive genomic sequencing as a matter of professional medical ethics (24, 39, 65).

Both public interest and professional integrity rationales for screening appear to allow practitioners to curtail the level of control that those screened have over the process. As a result, precision prevention programs of this sort face several important ethical challenges out of the gate. Three challenges create a potentially problematic cascade for precision prevention policy making: the erosion of individual control over genomic information, the inflation of individual interventional responsibility, and the logical drive toward human reproduction as precision prevention's ultimate target for intervention.

Control

The first challenge for precision prevention policy is the growing backlash against contemporary notions of patient autonomy and informational control. Within medicine, the limits of paternalism, beneficence, and patient autonomy have been long contested, with a focus on disputing clinicians' exclusive role in medical decision making (115). In clinical genetics, some have noted that the complexity of genetic findings highlights how "medicine

is, to at least some extent, an inherently paternalistic endeavor simply because of an inevitable asymmetry in knowledge and because those who practice medicine are pledged to avoid causing harm" (23, p. 2377). In 2013, for example, even without the additional authority that a public health frame can provide, the primary American medical genetics and genomics professional society declared that a list of 56 (and later 59) medically actionable mutations should be opportunistically examined whenever genomic sequencing is performed for clinical reasons, regardless of the patient's wishes (39, 51). Their goal was to put clinicians in a position to warn patients of risks related to highly penetrant genetic disorders, even if these were not risks for which clinicians ordered genomic sequencing. This was recommended in the name of clinical professional duties to prevent harm and to apply the rule of rescue.

Because public health agencies embrace the same rescue rationale and already make the same arguments in favor of curbing parental autonomy in newborn screening decisions, it is plausible that future population-based genomic screening programs might recommend return of genetic information on the basis of public health feasibility and other screening criteria (3, 113), in lieu of a high degree of responsiveness to individual preferences. Although clinicians cite fiduciary duties in navigating when and what genetic variants to disclose (77), public health practitioners and policy makers will need to consider when the public good justifies a new set of responsibilities as the gatekeepers of genetic information (48).

Moreover, the incorporation of public health guidance into clinical contexts is complex, demanding coordination of public health policy, clinical guidance, and individual patient needs. For example, as in precision medicine, cancer genetics is currently leading the way toward precision prevention through condition- or disease-specific screening (76). If a genomic cancer risk model were sufficiently predictive, a physician could take into account a patient's risk score in recommending when a patient should begin mammography (12, 86). Precision prevention extends the drive to refine cancer screening recommendations or other public health interventions on the basis of risk profiles. Some researchers have investigated how public health guidelines for breast cancer screening could be specified on the basis of such scores, rather than on the basis of age alone (10, 86).

Some screening proposals in breast cancer aim for selective prevention within a population, such as women (38). For instance, King et al. (60) proposed universal screening solely for *BRCA1* and *BRCA2* variants. Extrapolating from a population study of Ashkenazi Jewish women (33), the proposed screening program highlights the benefits to women who lack a family history of breast cancer (60). In reviewing the merits of this proposal, the authors acknowledged the possibilities of finding variants of unknown significance but made a moral appeal that the perfect should not be the enemy of the good, as current tests can provide the present population with excellent resources (60). This proposal has been critiqued on the basis of cost-effectiveness (69); however, King et al. anticipated the addition of other variants, such as *PALB2*, to the screening in the future as the evidence base expands. Such proposals do not yet make use of next-generation sequencing technologies, as the screening program is based on bundling together several more targeted types of genetic sequencing, but they do illustrate the growing public health implications of advances in genetics.

Other screening proposals concern indicated preventive programs, or additional preventive measures within a population already diagnosed with a condition (38). For example, researchers have highlighted a case of risk stratification in bladder cancer patients (12, 35). When risk modeling took into account the contribution of 12 genetic variants and smoking behaviors, researchers found that successful smoking cessation programs would prevent more instances of bladder cancer if they were targeted toward those with the greatest genetic risk (35). Such findings alone do not provide sufficient ethical or public policy rationale for the targeting of smoking cessation programs; smoking carries many health risks, and it is not clear that bladder cancer outcomes should be considered in isolation (35). However, clinical geneticists have long been cautious about the extent to which knowledge of genetic risk alone can change health behaviors, as most evidence points toward a mix of behavioral outcomes (24, 44).

Responsibility

The second challenge for precision prevention policy making is the potential to misuse these explanatory frameworks to reassert the idea that the moral and material responsibility for attending to one's health risks lies with the affected individuals themselves. Traditional public health measures and prevention strategies operate largely to alter above-the-skin variables to reduce a population's overall risk. These strategies have included measures such as lead exposure reduction and a statewide tax to reduce tobacco use and secondhand exposure to smoke. However, with precision public health as the frame, there is a risk that as certain populations are deemed more susceptible than others, risk reduction strategies will also shift to burden those identified with higher-risk genotypes with the responsibility for reducing their own risks through regular medical surveillance and behavior modification strategies, as has been suggested by physicians as one of the primary purposes of giving patients genomic susceptibility information (75). Advances in genomic risk stratification might hold public health promise, but they are likely to be adopted within the contemporary US medical context, where neoliberal thought is influential. In such a setting, patients are considered consumers, and the long-standing tendency to construe patients as consumers and their health problems as individual issues of self-care, rather than as social risks, could hamper the implementation of genetically informed public health interventions (67).

Sociologists point out that the biomedical exhortations to be "proactive" and "take charge" of one's health are ultimately part of a consumerist discourse that blends the goal of becoming an actualized and autonomous person with the goal of becoming a socially and personally responsible citizen (14, 29, 99). Compared with prevention strategies that attempt to alter above-the-skin systemic sources of environmental toxins, poor diets, and social stressors, shifting responsibility for genetic risk factors to the individuals who carry them may seem socially more efficient and effective, even if it is more burdensome for those subgroups (47). Thus, although neoliberal political thought celebrates individual choice and responsibility, there is also the potential for individual choice to slide into obligation, simultaneously relieving the broader society of the responsibility to care for and protect its citizenry (67).

Direction

A third challenge for precision prevention policy making is a need to acknowledge the normative implications of different forms of prevention that concern genetic traits. Historically, prevention in public health has been explained in terms of primary, secondary, and tertiary levels of prophylaxis (46, 52). Primary forms of prevention attempt to forestall health problems before they occur by changing the conditions that cause them. Sanitation and immunization are classic examples of primary prevention because they anticipate and forestall the spread of infection. In genetics, primary prevention can include phenotypic forms of prevention, such as reducing exposure to toxic agents during pregnancy or increasing the influence of protective factors, such as glycemic control in mothers with diabetes (109). In medical genetic contexts, genotypic prevention usually refers to interventions that prevent the transmission of deleterious genotypes from one generation to the next. Examples would include contraception, sterilization, and genetic carrier screening and subsequent management of reproductive genetic risk factors through assisted reproductive technologies and prenatal screening. Genotypic prevention of this form is, of course, focused on preventing people with specified genotypes from being born. This is the most ethically contentious form of prevention because it implicates core personal values and responsibilities and has a long history of abuse in the eugenics and racial hygiene movements of the twentieth century (46, 85, 94).

Classically, secondary and tertiary levels of prevention involve interventions designed to forestall the harmful sequelae of some initial infection or insult through early detection and preemptive treatment. In medical genetic contexts, examples include screening newborns for deleterious alleles so that their developmental effects can be avoided and intervening in the expression of a genetic disease to mute its symptoms. Although public health programs aimed at phenotypic prevention, such as newborn screening, face important challenges of their own, they are in concept consistent with the norms and traditions of health care.

The expanded newborn screening and adult genomic screening proposals of the precision prevention movement are phenotypic forms of prevention—they attempt to interrupt the manifestation of particular genetic diseases within patients rather than to prevent the existence of the patients themselves. But as acknowledged by Gordon, faulty logic could view primary, secondary, and tertiary forms of prevention as a lexical ordering, shifting attention earlier and earlier in disease progression to maximize dividends of reduced morbidity and mortality (38). In the precision prevention context, this logic could drive public health researchers and policy makers to look to the genotypic prevention of inherited health problems as preferable, running the risk of resurrecting all the past concerns that accompanied attempts to pursue prevention through reproductive decisions (43, 46). Although screening for somatic genetic changes—such as in cancer—would not run this risk (53), such logic brings the risk that precision prevention will slide into authoritarian practices and punitive attitudes that curb personal reproductive freedoms on behalf of public health goals—a kind of new precision eugenics.

Eugenic tendencies might initially appear overblown in today’s day and age, especially when more recent prevention typologies are beginning to hold sway (38, 83). However, as genomic tools are integrated into clinical practice, they are already being accompanied by

decreased individual control over genomic decision making and fueled by increased perceptions of individual responsibility. Public health gains through genotypic prevention are more likely to result from decreased individual control over genomic decision making. Studies have shown that access to even clinical prenatal testing does not necessarily increase patient autonomy (92), and prenatal screening in the public health context has an even bleaker history of routinization and structural coercion (8). For instance, reproductive decisions may be further constrained and challenged by the routinization of expanded carrier screening in prenatal care because the reproductive pathways that are available to those receiving positive screening and diagnostic results in the context of pregnancy are all reactive rather than proactive (74, 106). Paradoxically, practices that constrain reproductive genetic choice are likely to thwart the public health gains that would result from fostering contexts in which women specifically, and prospective parents generally, can exercise greater control over reproductive decision making more broadly. Hence, the timing and implementation of public health genomic screening can affect the range of reproductive choices that may follow.

Like newborn genetic screening, the value of bottom-up use of genomic screening is to identify individuals with mutations that convey high risks, setting the stage for greater utility of clinical or public health interventions. On one hand, the focus on strongly penetrant markers means that the health problems these programs can address are often not ones that are causally influenced by the above-the-skin social and environmental factors that are supposed to give precision prevention its versatility and reach as a public health strategy. On the other hand, epigenetic health risks constitute changes in gene expression that, it is claimed, make them perfect candidates for precision prevention approaches. Epigenetic risks entangle genetic, environmental, and social causation, opening them to above-the-skin preventive approaches beyond behavioral change. For example, studies that link pesticide exposure to epigenetically mediated developmental delays in the children of migrant farm workers could be used to galvanize environmental controls and occupational policy reforms at the community level (68, 72). Such outcomes would help counter a tendency toward victim blaming in these settings.

Critics of genetic determinism often hope that a wider lens on the causal flux shaping health would be an antidote to a myopic focus on genetic drivers. Ironically, the correlation of pathological gene expression with above-the-skin behavioral and environmental factors seems to only be exacerbating the problem. One example is the way that new animal research findings in epigenetics—a domain that exemplifies the multifactorial synergies sought by precision medicine research—are being extrapolated into heavy-handed messages to prospective and new parents about health risks in their offspring, and their responsibilities for behavioral and environmental factors that might exacerbate those risks (47). As the direction of genetic attention shifts toward earlier prevention, efforts at epigenetic risk stratification will increasingly confront a historical and social context long marked by a tendency to blame mothers for the illnesses of their children (96).

By contrast, genetic findings can also facilitate corrections in health and social dynamics. For instance, in conjunction with rising feminist social critique, genetic findings have been able to counter misdirected parental blame, as in the case of the schizophrenogenic mother

whose parenting was mistakenly thought to cause schizophrenia (40). It will be important going forward to keep preventive options open, to employ the combined strength of emerging genetic evidence and critical analysis to guard against the resurgence of punitive approaches.

PRECISION PREVENTION AND POPULATION HEALTH DISPARITIES

Precision risk stratification and its translation into population health screening programs raise several ethical concerns relating to social justice, including the possibility that the cost of advances will result in highly disparate access that reflects and could exacerbate existing inequalities in access to care (42, 74, 76). Risk stratification that aligns groups along ethnic, racial, or socioeconomic lines also raises the possibility of worsening social problems that already concern these groups (49, 100, 105). At the far end of the aspirational spectrum, moreover, are claims that a precision agenda might even help eliminate disparities in health and health care outcomes among different social groups (79). The detrimental social justice implications of risk reduction are important to consider in part because these directly undermine the social justice rationale offered in favor of precision prevention, which could exacerbate the very injustices that precision prevention hopes to address.

Among the most prominent population health problems in the United States are the disparities in health and health care outcomes. Although socioeconomic factors have long been associated with health (13), the narrower focus in genomics is frequently on health disparities among racial and ethnic groups. A dominant theme of the new precision prevention discourse has been the use of population genomic information to address this problem. Public health advocates worry, however, that genomic technologies will be disproportionately applied in elite medical environments, potentially further deepening health disparities along socioeconomic lines (64).

To operationalize the idea that precision prevention might help address health disparities, advocates must make an important conceptual move that is not strictly necessary within a narrower vision of precision medicine. That is, they have to equate the genetic health risk groups into which individual patients might be stratified with the kinds of human groups of concern to public health officials and policy makers: visible groups with names, locations, and legitimate claims on public resources. This is extraordinarily difficult, if not impossible, for two reasons.

First, the genetic marker groups relevant to stratifying patient risk are usually relatively invisible subpopulations before their members' risks are even realized, making it difficult to know how to precisely target any preventive interventions in advance. For example, patient advocacy and support groups can come to center their efforts around genetic status, like the *BRCA* variant carriers who have dubbed themselves "previvors" (28). However, to pursue precision prevention, public health professionals need to be able to associate the genetic health risks it targets with more visible phenotypic group characteristics, often before such communities coalesce. Such campaigns seek greater resonance with specific communities, like family, community, or racial identifiers, especially when the success of subsequent interventions hinges on public outreach and uptake. Educational interventions to reduce

behavioral health risks are often tailored to people in markedly different social circumstances (84). Similarly, individuals who are genetically at risk are likely to be identified for public health messaging through social groups that have previously proved useful in health communication strategies. Novel genomic research with public health implications confronts the challenge of needing to generate participant interest among groups that are not yet—and might never be—socially cohesive.

Second, and even more important, the genetic risk marker subgroups that emerge from bottom-up genomic screening programs are not the kinds of human groups that public health is designed to serve. For reasons of justice, effectiveness, practicality, and political necessity, public health must define the collective targets of its preventive services along socially discernible lines, as constituencies rather than statistical constructs. Among the most relevant of those discernible characteristics for genetic risk prevention are the social categories that we might expect to overlap with patterns of genetic inheritance in the population, such as family, ancestry, community identity, ethnicity, race, and where people live. As a result, the kinds of public health problems that offer the best opportunities for population health assessments aimed at precision prevention are those that segregate along those socio-geographic lines (101).

Decades of research has shown that differences in health outcomes among ethnic and racial groups in the US health system are overwhelmingly determined by social forces like poverty, environmental exposures, and access to health care (6). The frequency of some genetic risk factors, of course, varies across identified social groups, like the melanocortin variants associated with melanoma risks (31), and some genetic diseases seem to be loosely correlated with people's geographical origins, like sickle cell disease (88). The bulk of health disparities among groups, however, are caused by institutional and systemic factors that flow from and perpetuate the history of injustice experienced by these communities in the United States (87).

If it even made scientific sense to isolate ethnic and racial groups as discrete genetic subpopulations of Americans, the medically relevant genomic differences that might be attributed to such groups are completely eclipsed by the well-documented social, political, and cultural factors that lead to worse outcomes. Although this research may well succeed in elucidating genetic factors that contribute to diseases associated with health disparities, the reporting of these studies too often downplays the fact that nongenetic factors are substantial contributors or that the onset or severity of a disease results from a complex interaction of genetic and environmental factors (102).

Moreover, framing attempts to address above-the-skin factors in terms of genetic variation carry material risks. Genetic diversity is too easily conflated with racial diversity, especially in the context of seeking biospecimens that are in some way reflective of the wider population. With equal facility, genetic ancestry is confused with self-identified race and personal family history (116). To imply that a self-identified community of people who face shared social challenges and feel the tug of collective bonds can be reduced to a genetic subpopulation only reinforces old-fashioned racist tendencies to label entire communities as

biologically different from other parts of our society. On the whole, genomic thought leaders have a strong record of cautious, sophisticated, and nuanced reflection on this score (16, 17).

However, acknowledging the social and historical construction of race is easier than operationalizing this acknowledgment in public health genomic research and practice. Rather than precision prevention at the group level, the hope has been that, once the entire spectrum of human genomic variation has been mined for its health implications, the racial and ethnic categories that framed its collection and analysis could fall away, and the DNA markers could be used directly for individualized risk assessment in a race-neutral fashion (30). But as precision medicine's population-based foundations are extrapolated into public health initiatives, the mounting weight of clinical and epidemiological research framed against societal minority group membership and self-identified race seems to be creating a politically irresistible temptation to follow suit in genomics.

Despite valiant efforts to clarify the concepts of race and ethnicity for genomic research (18, 32, 66), these notions and their links to health disparities remain badly tangled with the logic of genomic risk stratification in precision medicine's promotional discourse and public health initiatives. This entanglement opens three ethical traps that are important for precision public health efforts to avoid: the stigmatization of ethnic and racial communities through medicalization, the disempowerment of political minorities through distraction, and the invidious perpetuation of ancestrally ascribed identities as loci of moral obligations and loyalties.

Stigmatization and Group Harms

The precision agenda demonstrates the expansion of medical jurisdiction, authority, and practices marked by technologically enmeshed processes (14), and the medicalization of social problems like health inequities comes with its own risks. The risks of associating health disparities with genetic variation among subpopulations involve more than the perpetuation of socially dangerous perceptions that race and ethnicity define essential differences among people. Such associations can also exacerbate racism and interethnic prejudices in social and political contexts that have nothing to do with population gene frequencies (111). When the genetic markers that are used to distinguish different social groups are also markers of poorer health care outcomes, adverse reactions to treatments, increased susceptibilities to disease, or differential vulnerabilities to environmental exposure, they also become vehicles for opportunistic group stigmatization and discrimination (19). Ironically, stigmatizing attitudes are one of the primary social determinants of health outcome disparities (41), undercutting the ability of genomic research to help address disparities even further. In this light, it is not surprising that members of minority groups express concerns about participating in genomic research (37).

Moreover, stigmatization is not the only form of group harm that genomic research can generate. In their study of genomic variation studies in Africa, de Vries et al. (19) documented three other forms of group harm that "are disadvantageous for ethnic groups but that do not constitute 'stigma' in the way that it is currently understood in literature" (p. 1406): (*a*) reputational harms from comparisons across ethnic groups when investigating diseases with normative implications (e.g., misattributed paternity frequencies that can carry

implications of promiscuity); (*b*) find-ings that constitute evidence of immoral behavior, such as consanguinity or nonpaternity; and (*c*) projects looking for evidence of group origin or composition, where these are in conflict with social and traditional narratives. In the United States, the risks of commercial exploitation (50), insurance underwriting (91), and ethnic profiling for security purposes (61) might also be added to that list.

Distraction and Disempowerment

As Sankar et al. (102) have pointed out, genomic explanations for health disparities can distract and even exculpate society from taking responsibility for the structural determinants of those inequities, undermining the political momentum of those seeking justice:

> First, overfocusing on genetics might divert attention from what evidence already suggests are the central causes of health disparities and might lead scientists to overlook possible actual environmental contributors. Second, overemphasizing the potential of genetic research to alleviate health disparities fosters the misconception that disparities in health status will be easy to solve. Standardizing access to health care and reforming attitudes towards minority patients poses a far greater challenge than introducing new treatments facilitated by genetic research. (p. 2988)

Precision medicine and precision prevention approaches seek to combine and synthesize a wide variety of causal factors. However, this objective is in tension with the drive to focus on downstream molecular nosology, including genetic traits, especially because those with a strong causal role are most likely to connect with interventions that have clinical utility. Particularly with respect to health disparities, the very features that are likely to render a genetic intervention successful are exactly those that will draw attention away from the upstream social determinants of health (112). Effective mitigation of population risk ought to be lauded for improving health outcomes, but this improvement alone does not redress any initial injustice that led to greater susceptibility in the first place. If social policies or institutions distribute health risks in ways that unfairly render some populations more vulnerable, the just solution is social reform, not merely remediation of downstream consequences. As precision public health research advances, it will be increasingly important to resist the eclipse of these broader social dynamics.

Precision prevention supporters should also attend to the complex relationships among inclusive genetic research, social determinants of health, and the rhetoric of empowerment. Much ado has been made of the potential for the translation of genomics to create new health disparities because of the lack of diversity in most genetic research (71, 89). A highly visible case has been the possibility of misdiagnosing individuals of African descent with deleterious variants that are likely to lead to hypertrophic cardiomyopathy. According to Manrai et al. (71), seven patients have been initially informed that they had pathogenic or presumed pathogenic variants that were subsequently reclassified as benign. A common response to such evidence has been to seek increased racial diversity and inclusion in genetics research; in turn, increased research participation is couched in terms of participant empowerment (90).

However, it is important to put these hypertrophic cardiomyopathy false positives in context, given the other important drivers of health disparities and their relationship to empowerment.

Although more inclusive research will provide a firm evidentiary foundation for all future patients, it is less obvious that research participation will engender the kind of social empowerment that will best reduce health disparities. There is generally a dearth of evidence regarding social determinants of disparities in hypertrophic cardiomyopathy, but Ingles et al. (45) reported underrepresentation of the socioeconomically disadvantaged in a specialized Australian clinic. Importantly, in the United Kingdom, where individuals of African descent have equal access to health care, researchers recently evaluated black and white cohorts with hypertrophic cardiomyopathy and attributed increased adverse health outcomes to hypertension, not ethnicity (104).

By contrast, in the United States, Fang et al. (25) reported that approximately 20% of hypertensive patients identified obstacles to accessing appropriate care, with insurance (or lack thereof) being the most important predictor of whether an individual has a personal doctor, a health provider, or the ability to afford a doctor's visit. Although it is likely that both sound predictive genetics and hypertension risk management are needed to achieve the best health outcomes among such patients, it is equalizing access to these elements of health care that will be crucial to redressing racial disparities caused by systemic injustice. This evidence suggests that the current portrayal of health disparities, genetics, and empowerment warrants much further examination. Ethics, social, and public health policy research, in particular, might seek out understandings of empowerment from various stakeholders (for example, see 7) to better capture policy levers beyond the possibilities of greater inclusivity in genomic research.

Reinforcing Genetic Loyalties

One consequence of translational genomics' new interest in preventing and redressing health outcome disparities has been a steadily increasing effort to recruit people from "disparity populations" into genomic research. As Cohn et al. (15) describe the situation,

> Precision-medicine studies are designed to identify genetic variants that contribute to disease risk or affect treatments, the frequencies of which differ substantially within and across populations of varying ancestries. However, improvements in diagnosis and treatment may be distributed unevenly . . . if studies are based on data . . . from persons of European ancestry. . . . The implications of [African] variants for dosing strategies may not be understood until a sufficient number of people with African ancestry are included in relevant study samples to account for within-group and between-group variabilities. (p. 157)

To the extent that people's ancestral identities are played upon in efforts to recruit research participants, however, such appeals risk reinforcing convictions that biological connections support moral allegiances independent of other relationships. For example, Rhodes (95, p. 38) says, "To the extent that any group abstains from participation, their members will be less able to share in the rewards precisely because their genetic and microbiomic samples are absent from the pool. When you and yours are not studied, the information to help you will not be available." When race, participation in large genetic cohorts, and rhetoric regarding individual responsibility for health outcomes combine, the stage has been set to blame some minorities for the perpetuation of their own poor health outcomes.

Translational genetics will continue to confront the complexities of ethnicity, group identity, migratory and colonial history, and genetic ancestry. In 2010, Arizona State University settled a lawsuit with the Havasupai Indian tribe; the focus of original recruitment had been on diabetes, but researchers also used samples to study other topics that the tribe found objectionable (73). This case demonstrated the importance of being aware of how community values can be considered distinctly from personal attitudes toward research. The meaning ascribed to blood, tissues, and genetic material can lead to different perceptions of the risks and benefits of participation in genetic research. However, it is also important not to treat communities as monolithic, thus underestimating intragroup disagreement.

It is difficult for agencies like the National Institutes of Health to avoid the political realities of group identity when dealing with public health problems like outcome disparities. But that is because health disparities are fundamentally social and political problems. It seems like a conceptual non sequitur to look for genomic differences among constituencies in order to explain the effects of their unjust social situations. At the very least, it drags the efforts at precision prevention into the heart of the debate over how best to correlate human genetic variation with human social identities and the wisdom of reifying categories like race in genomic terms (18, 62, 93).

CONCLUSION

Achieving population-wide benefits from translational genomics research, through either public genomic screening programs or the genomic stratification of health disparity risks, is an even more ambitious goal than overhauling the theoretical foundations of medical science, but it is certainly more likely to appeal to the general public. This suggests another driver for the rise of public health policy goals for precision medicine, in addition to the ideological reorientation provided by assimilation of the population sciences. Precision medicine research is expensive because it requires amassing and correlating biological and environmental data from large numbers of people.

If public investment is needed, precision medicine research will require a more appealing public case for the investment. To date, the bulk of that case has been centered on the promise that it will go beyond expanding the tools of concierge medicine (27, 48, 64) to result in “tangible health benefits for all” (59, p. 643). Public investment in genomic translation has also been pitched as a remedy for current clinical care inadequacies, seeking greater shared or more equally dispersed benefits, especially “at a time of increasing fiscal restraint and widespread recognition that the US health care system underperforms in terms of health outcomes” (57, p. 2117). Thus, at a recent Precision Public Health Summit, one commentator voiced the common view that precision medicine and precision prevention are complementary: “[I]n fact, only through being able to telescope down to the genome and the microbiome and then back out to the family and the community will the power of precision medicine come into focus” (5).

However, there is deep tension in the precision agenda’s commitment to public health. The Precision Medicine Initiative, after all, was funded through the 21st Century Cures Act only by cutting $3.5 billion from the Prevention and Public Health Fund, which directed

resources toward dementia, hospital-acquired infections, chronic illnesses, and other public health goals (70).

These tensions raise the possibility that the precision medicine and precision prevention components of translational genetic research might not constitute as united a vision as initially presented. Well before the inception of the Precision Medicine Initiative, work on bringing both medical and public health perspectives to bear on genomic sciences explored these long-standing tensions in efforts to reconcile them (26, 58). Thus, at the same Precision Public Health Summit, another commentator framed precision prevention in a corrective vein: "[W]e face a threat that precision medicine will further increase inequities in health at home and abroad. . . . [D]espite this threat, we have an opportunity to use big data and other precision medicine technologies for everyone's benefit" (20).

In sum, the commitment of precision prevention to incorporate more environmental and social data into genomic medical decision making gives its promoters and architects an important opportunity to move social determinants of health into the foreground of public health genomics research and practice. To the extent that structural determinants of health are rooted in unfair social practices like racism, economic exploitation, opportunity bias, cultural blindness, or political marginalization, precision prevention will begin to open doors to other forms of public health intervention. Doing so, however, could drive a wedge between the project's public health methods and its emphasis on the genome sciences. Alternatively, a precision prevention agenda that seeks to bridge genetic advances with other public health approaches could leverage a greater array of research methods, multidisciplinary expertise, and translational interventions. As is so often the case with large research endeavors, bridging professional silos and disciplinary divides might require explicit effort; analysis of the ethical, legal, and social implications of precision medicine could help articulate the professional norms that govern these differing viewpoints on the future of genetic research. As the Precision Medicine Initiative *All of Us* Research Program continues to take shape, reflection on how to achieve its promised preventive goals could reshape new research collaborations and foster key health policy developments.

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