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Utility and Diversity: Challenges for Genomic Medicine

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Abstract

Genomic information is poised to play an increasing role in clinical care, extending beyond highly penetrant genetic conditions to less penetrant genotypes and common disorders. But with this shift, the question of clinical utility becomes a major challenge. A collaborative effort is necessary to determine the information needed to evaluate different uses of genomic information and then acquire that information. Another challenge must also be addressed if that process is to provide equitable benefits: the lack of diversity of genomic data. Current genomic knowledge comes primarily from populations of European descent, which poses the risk that most of the human population will be shortchanged when health benefits of genomics emerge. These two challenges have defined my career as a geneticist and have taught me that solutions must start with dialogue across disciplinary and social divides.

INTRODUCTION

There is tremendous optimism about the potential for genetic information to improve disease prevention. Over the past decade, genomic technology has expanded its reach with tests that guide medication use, aid in cancer prevention and treatment, and identify a range of health risks (95, 138). These developments offer proof of principle for what is anticipated to be a broad expansion of genomic information in clinical care, extending beyond single-gene diseases to the evaluation of predispositions to common disorders. But as attention moves from highly penetrant genetic conditions to less penetrant genotypes and genetic risk profiles, the question of clinical utility becomes a major challenge. Exactly what sort of genetic information can help a particular patient—and how do we know? What harms does genetics pose? The determination is particularly difficult when applying genetics to the care of "average" patients—that is, individuals without strong indicators of genetic risk.

When a test is found to have clinical utility, the American healthcare system poses another challenge: How do we assure that the intervention is available to all who can benefit from it? Persistent inequities in healthcare delivery are an important barrier to improving care. But concerns about equity lead to a more fundamental problem for genomics: the lack of diversity. Most genomic data derive from populations of European descent. Populations of African and Asian descent have limited representation, and Indigenous populations are notably absent (115). These deficits limit the insights and development opportunities that can be derived from genomic research and risk shortchanging most of the world's population as benefits emerge. This problem is already apparent in US healthcare, where the likelihood of a noninformative test result is greater for Americans who are not of European descent (36, 92). Similarly, limited research in non-European populations reduces the efficacy of pharmacogenomic tests to guide drug use in these populations (125). Unless the diversity gap can be closed, the shortfalls will increase.

I had little awareness of these issues when I began my career as a geneticist, but my path has placed them front and center—and has taught me that the solution must start with dialogue across disciplinary perspectives and between researchers and the communities they seek to engage in research.

BEGINNINGS

I had completed three semesters of college in 1966, changing my major as many times (classics, Romance languages, and history), when I took a break for the birth of my first child. I had not resolved the direction I wanted to take when I returned to school. But walking the college halls one day, I saw a poster advertising PhD programs in the biomedical sciences. I was struck with the thought that these programs offered the kind of career a grown-up would pursue.

I was ready: I switched my major to biology and registered for my first science class. The following year, I had room for an elective course and chose genetics. In that class I had a defining experience that I expect is familiar to many geneticists: a combination of awe, delight and intellectual satisfaction on first encountering the central dogma—DNA, the genetic code, transcription and translation. I was soon working in my instructor's laboratory and thinking about graduate school.

At about the time I began my graduate studies at the University of Washington, Gunther Stent, a pioneering molecular biologist, wrote a book that seemed to claim that all the exciting work had been done; what remained was merely working out the details (129). To a beginning graduate student, this was nonsense. A new foundation for biology had been created, but the science was just beginning. The "details" of foreseeable questions—about DNA replication, cell division, the translational process, and so on—were complex enough to engage a generation of scientists, and

inevitably, this research would lead to unforeseen questions and observations, not least concerning the complexity of the central dogma.

The University of Washington's Department of Genetics, chaired by Herschel Roman, was a place where scientific excellence went hand in hand with generosity and open communication. Talk about science was continual, ranging from informal to loosely organized to highly structured, and immersed us in the scientific questions of the day. In the laboratory where I did my thesis research (24), we worked with *Saccharomyces cerevisiae*—that is, yeast, the one-celled eukaryote that has proved indispensable to molecular genetics—and a weekly Yeast Club brought together all the laboratories working with the organism. The club included luminaries, but, by the nature of the academic environment, graduate students made up the majority. And while we listened with respect to our seniors, everyone was encouraged to speak up. This was a freewheeling, democratic scientific environment. I thought I had found my intellectual home and assumed I would pursue a career as an experimental scientist. However, I had also begun to attend the weekly Medical Genetics Clinic, and this experience introduced me to an entirely different and even more compelling aspect of genetics.

IN THE CLINIC

Although the concept of genetic disease is well understood by geneticists, a scientist with PhD training may have no exposure to affected individuals. So it was intriguing to learn about the physiological manifestations associated with particular genetic diseases, to observe the heterogeneity in phenotype among individuals with the same disease, and to witness the Mendelian laws of inheritance playing out in different families. But I was also struck by the social and emotional needs of patients and the ways in which medical genetics can address those needs or fail to do so. Genetic counseling offers patients and families important validation, support for the burdens they carry, and, sometimes, new opportunities for treatment and health. It may also reveal uncertainties that cannot be resolved and broader social implications of a genetic diagnosis.

One family stands out in my memory.[1] A middle-aged man sought evaluation to determine whether he had hemochromatosis. He was in good health and had already been evaluated by his family doctor, who found no evidence of liver disease, the characteristic complication of the disorder. However, the patient sought an expert opinion to address the concerns of an insurance company. The patient's father had died, rapidly and unexpectedly, from end-stage liver disease at the age of 55. There had been no history of alcohol misuse, hepatitis, or exposure to liver toxins. The physician caring for the patient's father speculated that the cause might be hemochromatosis, and this diagnosis appeared on the death certificate. This family history was flagged by the insurance company, which refused him life insurance coverage. In an attempt to overturn the decision, or at least to resolve whether he faced the same liver disease his father had experienced, the patient sought help from the university's Division of Medical Genetics.

The patient had normal serum iron measures, ruling out iron overload and making the diagnosis of hemochromatosis unlikely (the gene had not been discovered, so genetic testing was not an option). Furthermore, the patient's a priori risk was not high, given the autosomal recessive inheritance of hemochromatosis and the low likelihood that his mother was a carrier. However, to provide as thorough an evaluation as possible, the Medical Genetics Clinic obtained copies of the father's medical records. These were scanty but included one normal serum iron measure and a liver biopsy report that included no mention of iron deposits, arguing against a diagnosis

[1]Details of this and other clinical stories have been modified or omitted to protect confidentiality.

of hemochromatosis. Based on this information, the patient received the clean bill of health he sought.

This story speaks to some of the challenges in present-day genomic medicine. The speculation about hemochromatosis as the father's cause of death was admirable, because the diagnosis is often missed (101); however, the putative diagnosis was not adequately assessed, and the family was not informed about the potential implications for family members. As a result, an important prevention opportunity could have been lost. There is also an irony in the patient's dilemma about life insurance. His normal serum iron measures at midlife would have been exceedingly reassuring if he had indeed carried a genotype for hemochromatosis; at most, the insurance company could have issued a policy conditional on regular medical evaluation and treatment if iron overload occurred. These themes of limited clinical knowledge about genetics, missed opportunities for prevention, and potential social costs of a genetic diagnosis remain important considerations as genomics advances into clinical care.

The clinical exposure motivated me to pursue medical training, with the intent of becoming a medical geneticist. I did not expect to leave the laboratory behind, but looked forward to adding a clinical component to my work. In the course of medical training, however, I found a much broader set of clinical challenges than I had glimpsed in the Division of Medical Genetics.

A friend of mine once described himself as a "cough and sore throat kind of doctor"—in contrast to the doctors one sees on TV, saving lives in the midst of high drama in the operating room or emergency department. Because medical training generally starts in hospital wards, where patients are acutely ill, even medical students can get a distorted picture of healthcare that emphasizes the dramatic end of the spectrum. Eventually, however, students arrive at the clinic and discover a different kind of medicine.

At the heart of outpatient medicine is primary care, in which a physician assumes responsibility for the medical needs of a group of patients. This kind of medicine involves the development of long-term relationships with patients, the assessment and implementation of opportunities for prevention, and the formation of therapeutic alliances with patients to address the challenges of chronic illness. Primary care is usually undramatic but also crucial; in its requirements for broad knowledge, a sense of the big picture, and coordination of services, it has been compared with conducting an orchestra (99). Although my ties to genetics remained strong, I wanted to solidify my knowledge of this kind of clinical practice. So, after completing my clinical training, I worked as a primary care doctor in a community hospital for six years before returning to academics.

My main focus as a primary care provider was on ordinary medical problems—those coughs and sore throats, and also, in an adult clinic population, cancer and chronic diseases like diabetes and heart disease. This type of medical practice throws into sharp relief the importance of social and behavioral health risks. Smoking, unhealthy diets, lack of physical activity, and the associated rises in blood pressure and blood glucose account for much of the disease burden in the United States (42, 54). Medical treatment plays a role in addressing these risks, but counseling patients about a healthy lifestyle is also part of the job. And it quickly becomes evident that most patients have difficulty making changes.

A cursory glance at our social environment is enough to explain the problem. We are surrounded by advertisements that encourage the consumption of sweet and fatty foods. The foods are designed to taste good and are an inexpensive option for families on tight budgets (109). Regular exercise is difficult with long workdays and lengthy commutes. Many patients may not have safe places to walk or access to gyms, or may be working two jobs or dealing with pressing family responsibilities that leave them with limited time for taking care of their health.

These realities speak to the importance of social determinants of health (54). Stepwise socioeconomic gradients in health have been consistently observed in the United States and other

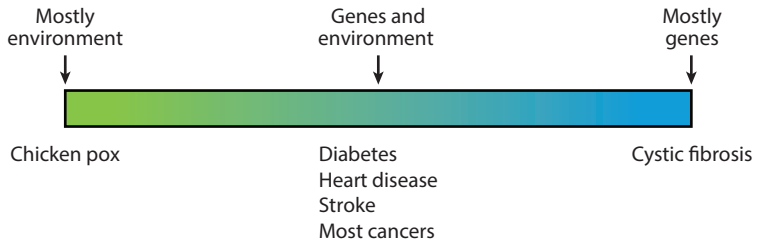

Figure 1

The contributions of genes and social environment to health outcome. Genetic contributions to health occur along a continuum. Outcome in rare genetic diseases is determined primarily by genes; outcome in other diseases, like chicken pox, is determined primarily by the social environment. In the middle are diseases with a varying mix of genetic and environmental contributors, such as diabetes, heart disease, stroke, and most cancers; these conditions represent the major disease burdens in the United States.

developed countries (16). A wide range of evidence indicates the importance of differences in access to knowledge, money, power, prestige, and beneficial social connections as contributors to individual health (113); those who are most disadvantaged are "at risk of risks," because their life circumstances leave them without knowledge or opportunities to protect their health (54, 113). Racism also contributes, through limited educational and employment opportunities and through contributions to chronic stress (16). In clinical practice, it was easy to discern the role of the social environment and life experience in patients' health prospects: the public housing that exacerbated a patient's asthma, the military experiences that precipitated a patient's panic attacks, the childhood abuse that limited a patient's life opportunities.

So, where was genetics? I could see it in the occasional patient whose life had been dramatically affected by familial or inherited disease. One of my patients had had her childhood disrupted by her father's untreated bipolar disease; as a result, she was able to diagnose her own symptoms as a young adult and bypass that trauma. Another patient had few personal health concerns but was preoccupied with the medical problems of her grandsons with hemophilia. But I knew these unusual stories were only a small sampling of the ways in which genetics can impact health. Many of my patients had family histories pointing to risks for common diseases like diabetes, coronary heart disease, and cancer (60), and early genetic findings, like the discovery of the role of low-density lipoprotein (LDL) receptor variants in hypercholesterolemia (61), pointed to the potential impact of greater genetic knowledge. Like other geneticists, I began to wonder how family history could be better used for prevention, what scope other genetic information could play in achieving this goal—and how opportunities for genetics should take into account the importance of social environment.

In this context, the contribution of genetics to health outcome is best conceptualized as a continuum (**Figure 1**). Genetic diseases are caused primarily by pathogenic genetic changes, but even these diseases may be influenced by the environment; as an example, life expectancy in cystic fibrosis is influenced by access to health insurance (41). At the other end of the spectrum, diseases like chicken pox are determined by environmental exposure, but here too the effect is not absolute; it seems likely that genetic variation in the HLA region reduces the risk of shingles, a late complication of chicken pox (40), and might conceivably also reduce the likelihood of being infected in the first place. In the middle of the continuum are the common complex diseases that are the main cause of population disease burden; in most people, they are the result of a varying mix of genetic and environmental contributors (136, 137), particularly the behaviors shaped by the social environment. From this perspective, genomic medicine has two challenges: to identify

outliers—people with rare disorders found on the genetic end of the spectrum—and to determine whether genetic information can be leveraged to improve outcomes for the common disorders in the middle.

About the time I was starting to consider these opportunities, the phrase "evidence-based medicine" entered clinical care (64). It offered a framework for thinking systematically about the benefits and harms of medical interventions and was driven by certain harsh realities of clinical practice: Innovative treatments are not always better than those they replace, many treatments work for some patients but not others, and patients are sometimes seriously harmed—even killed—by medical intervention (93, 122). At the heart of the evidence movement is the concept that different types of evidence provide different levels of certainty about the value of a particular intervention. A randomized clinical trial indicating benefit, for example, provides a higher level of certainty than observational data, such as a case–control or cohort study, or clinical logic (64, 74). In this hierarchy, evidence based on expert opinion is considered the least reliable, because any individual's experience is limited and because decision-making based on personal experience is open to a range of biases (83). Yet there is a tension here. The practical wisdom derived from clinical experience is essential in applying the available evidence to a particular patient (132). It is not an either-or proposition (131); good quality care is always individualized (31), and familiarity with the full range of evidence provides the best basis for clinical judgment.

Randomized clinical trials, the most rigorous test of an intervention, are not always feasible or ethically permissible; for example, an intervention like prophylactic mastectomy could not be evaluated in this way. However, some of these trials have been key to improving preventive care. As an example, the Women's Health Initiative provided critical information about the scope of benefits and harms from postmenopausal hormone therapy. This therapy was widely used, based on epidemiological data suggesting that it reduced risk of cardiac disease. The trial demonstrated not only that cardiac protection was lower but also that breast cancer risk associated with postmenopausal hormone therapy was higher than anticipated (96); in other words, healthy women had been harmed by such therapy. These results led to a radical drop in estrogen prescriptions and a correlated drop in the incidence of estrogen-receptor-positive breast cancer (90). As this trial suggests, the need for adequate evidence is inherent to medical practice (47) and has a particular importance for interventions in healthy people: We should have reasonable certainty about benefits and harms before subjecting a healthy person to testing and preventive treatment.

It follows that screening programs—that is, efforts to test healthy people (by genetics or other means) to identify an unsuspected health risk amenable to treatment (32)—require careful scrutiny. The benefit can be tremendous—newborn screening for phenylketonuria is a case in point—but the harms of screening can be significant as well. A screening program to detect heart murmurs in young children, for example, led to significant morbidity without discernible benefit (9), and newborn screening for neuroblastoma exposed infants to iatrogenic harm without improving population outcomes (141). Even well-established screening programs, such as mammography, may have limited benefit and involve the harms of false positive and false negative results and overdiagnosis—that is, the identification of people who meet diagnostic criteria for a disease but are unlikely to receive benefit, and could be harmed, by treatment (142). These observations raise cautions about genetically driven prevention.

JOINING THE ELSI COMMUNITY

I returned to an academic position at the University of Washington in 1988, as associate director of the Internal Medicine Residency Program. My position also included clinical work (in both

primary care and medical genetics) and the opportunity to develop a research program. Early on, I worked on a project led by Al Jonsen, who was then chair of the Department of Medical History and Ethics. The project sought to explore the ethical implications of the data emerging from genome sequencing. As one component of the project, we considered the rise of the "unpatient," a healthy individual found by genetic testing to face a significant health risk (81). We speculated that this opportunity could accelerate a shift in medicine from symptomatic treatment to identification of future risk, with the potential to empower prevention but also to increase the "worried well" and expose individuals with health risks to stigma and discrimination. In short, health information from genome sequencing raised the evidence question: What did we need to know to be sure that identifying "unpatients" was a good idea?

The project was supported by the Ethical, Legal, and Social Implications (ELSI) Research Program (107), a new grant-funding unit created within the National Center for Human Genome Research (now called the National Human Genome Research Institute). This program is unique among National Institutes of Health (NIH) research programs for its support of a broad range of projects and research methods. Although the social sciences have predominated, ELSI researchers are also trained in the humanities, law, health services, anthropology, and other disciplines. Many are dually trained in genomics and other relevant disciplines, including bioethics and medicine. The ELSI community is geographically dispersed but nevertheless a real community, supporting a vigorous exchange of views and a commitment to defining and evaluating important questions related to genomics. For me, the ELSI program offered an extraordinary opportunity to participate in multidisciplinary research and to learn from many wonderful colleagues in this community.

Implications of Breast Cancer Gene Discovery

In 1994, the ELSI program formed the Cancer Genetics Studies Consortium (CGSC), bringing together a group of projects investigating the clinical, social, and ethical implications of cancer genetics. Some CGSC studies investigated genetic testing in high-risk families following the discovery of the *BRCA1* and *BRCA2* genes as well as genes associated with Lynch syndrome. But there were potential implications for lower-risk women. An early direct-to-consumer advertisement for commercial *BRCA1/2* testing used the slogan "She was told not to worry about her risk of breast cancer; unfortunately she'll be diagnosed next year" (12, p. 681).

As part of the CGSC, I worked with colleagues in medical anthropology and behavioral medicine to explore the impact of information about breast cancer genetics on women whose family history of breast cancer was modest and who were thus unlikely to carry cancer-predisposing gene variants, but who might be offered testing. A family history of breast cancer is relatively common: 5–10% of women have a mother or sister with breast cancer, but only about 1 in 400 women have a *BRCA1/2* mutation (105).

Our studies included the development of counseling and educational strategies for women whose family history indicated moderate risk, assessment of women's interest in genetic testing, and evaluation of clinicians' skills in taking a family history (13, 14, 21, 22, 46, 116, 117). We found that women at both average and moderately increased risk had a high interest in testing for inherited risk of breast and ovarian cancer (14, 46, 117). The majority considered themselves candidates for testing and favored ready access (46). After counseling, interest in genetic testing was reduced but remained high (22). However, an interview study revealed that women's interest was based on two misconceptions: an exaggerated estimate of their own breast cancer risk and unrealistic expectations about the information a genetic test could provide (117). Women sought a test with high positive and negative predictive value, leading to effective, noninvasive prevention;

for the women we studied, *BRCA1/2* testing could not deliver this kind of certainty. Women also appeared to seek graded information about their risk, enabling them to calibrate their prevention efforts, as opposed to a test that would assess a very small possibility of high risk but otherwise give them no useful risk information. As *BRCA1/2* testing became clinically available, the frequency of variants of uncertain clinical significance also became apparent, offering another reason to be cautious about testing in women with a low likelihood of a positive result (127).

In addition, although women were interested in the potential to tailor breast cancer screening to their risk, most (>80%) rejected prophylactic mastectomy as a prevention measure (46); as one participant said, "That's like chopping off a finger because you're afraid it might get broken" (116). These studies, early in the development of genomic medicine, presaged three issues that remain today: optimistic assumptions about the predictive value of genetic tests, particularly among individuals without indicators of strong genetic risk; health messaging that emphasizes risk in seemingly healthy people (3); and the reality that some preventive measures (like mastectomy) will have limited acceptability.

The question of whether women at average or moderately increased risk should be offered *BRCA1/2* genetic testing—that is, whether genomic testing should be undertaken to screen for this condition—remains open. Mary-Claire King and colleagues have proposed population screening, but with the proviso that variants of uncertain significance not be reported; this approach would enable the identification of women at high risk who are currently missed, either because their family history is limited or because it was not adequately evaluated, while avoiding confusion for those found to have a variant of uncertain significance (88). This approach, however, would arguably carry the obligation to ensure variant follow-up, so that the small percentage of these variants reclassified as pathogenic or likely pathogenic (102, 127) could be identified and patients notified of the positive result (2).

The Challenge of Ascertaining Family History

One could also ask what measures might be taken to improve family history assessment in routine clinical care. In the early 2000s, using unannounced standardized patients, we found that primary providers could readily identify a strong maternal family history of breast cancer but missed a paternal history of breast and ovarian cancer about half the time (21). In addition, only half took sufficient information to fully evaluate risk in a patient with a limited family history, and few made referrals to genetic counseling (21). Realistic appraisals of the primary care setting suggest that lack of knowledge, limited time, and billing constraints all limit the quality of family history taken in primary care (118, 144). Our findings were in keeping with other studies documenting limitations in assessing family history (60), underscoring the need for innovative approaches.

Tools that enable direct collection of family history from patients (118) and provide guidance on interpretation are needed, and such approaches are now being developed. As a promising example, the MyTree tool, developed by investigators at Duke University, combines collection of family history information from patients with decision models based on practice guidelines, to generate recommendations for primary care providers regarding prevention, testing, or other follow-up (143). Preliminary assessment of this approach suggests that as many as 44% of primary care patients may be candidates for nonroutine preventive care or genetic counseling referral (110). Questions remain about the clinical validity and utility of family history; risk predictions are variable, and systematic evaluation of outcomes is limited (60). If collection and use of family history information can be systematized, however, it may take its place as the key genomic tool for primary care. And, as experience with coronary heart disease demonstrates, risk assessment can be improved by combining family history with behavioral and clinical risk factors (94); this strategy

will likely be equally valuable with polygenic risk scores (86) if they prove to be sufficiently predictive for clinical use.

Implications of Hemochromatosis Gene Discovery

In 1996, at around the time *BRCA1/2* testing became clinically available, the *HFE* gene was discovered, and two *HFE* alleles were found to account for most cases of hemochromatosis (49). This offered a different kind of genetic screening prospect. Identification of hemochromatosis at a presymptomatic stage could prevent life-threatening complications, such as cirrhosis, hepatic carcinoma, and heart failure, through timely use of phlebotomy. As part of a group of ELSI investigators, I had the opportunity to work with colleagues at the Centers for Disease Control and Prevention in evaluating this opportunity.

At the time of gene discovery, the evidence available to evaluate a screening approach was minimal (33). The biggest question concerned risk associated with different *HFE* genotypes. A pooled analysis of case–control data confirmed that the risk was predominantly for individuals with the C282Y/C282Y genotype (25), but the penetrance of the genotype was uncertain, with anecdotal observations suggesting that people with the C282Y/C282Y genotype sometimes remained asymptomatic (33). A screening study was undertaken that evaluated 101,168 individuals with both serum iron measures and *HFE* testing (1). The study documented a benign natural history for the majority of people with the C282Y/C282Y genotype and concluded that population screening was not appropriate. Instead, a case-finding approach was recommended, with evaluation of close relatives after a diagnosis of hemochromatosis, and testing for hemochromatosis as part of the workup of nonspecific findings commonly seen early in the disease, such as fatigue, joint pain, and abnormal liver function tests (1).

However, some argue that in addition to case finding, a targeted screening approach should be considered, focusing on adult men of European descent (112); this approach takes into account higher morbidity in men and the higher prevalence of hemochromatosis genotypes in European versus other populations (56, 114). For example, a longitudinal population-based study in Australia found that 28% of men and 1% of women with the C282Y/C282Y genotype had evidence of iron-overload-related disease (56). Additionally, a French study demonstrated a progressive reduction in the severity of hemochromatosis over a 30-year period, possibly reflecting decreased alcohol intake (43). However, UK Biobank data also showed that men with the C282Y/C282Y genotype had a higher likelihood of death from hepatic carcinoma, a potentially preventable complication (6). Thus, most people with the genetic predisposition do well without treatment, but a minority have preventable complications, some of which are life-threatening. One suggestion is to reserve the diagnosis of hemochromatosis for those with clinical evidence of iron overload and to consider the genotype as merely conferring an "iron-avid" predisposition (70); controversies remain about whether and whom to screen.

Some experts anticipate a future in which universal genome sequencing will be the norm (87). If so, interrogation of the *HFE* gene for hemochromatosis-associated alleles would offer obvious benefit to some patients, although most of those identified would remain healthy without treatment (representing overdiagnosis). In this scenario, the key question for many healthcare systems is likely to be whether effective case finding, using serum iron measures, could deliver the same benefit as genomic screening at lower cost. Arguably, the most important lesson of the hemochromatosis story is that any assessment of genomic screening should compare it with viable alternatives, like the case-finding approach, and take into account the complexity of the genotype–phenotype relationship. In either approach, harms would need to be considered as well as benefits (32); for genomic screening, these harms might derive from data breaches (10) as well as from overdiagnosis.

Deliberating About the Value of Genetic Information

As the breast cancer and hemochromatosis examples suggest, initial evidence about the use of a genetic test is usually very limited, knowledge accumulates slowly, and the optimal use of genetic information is not always obvious. In developing guidance for clinicians, deliberation involving people with a full range of relevant expertise is needed, supported by systematic review of the available evidence, with plans for updating over time (123).

My first introduction to this challenge was as a member of a CGSC committee that developed consensus statements on the care of individuals found to have hereditary breast and ovarian cancer or Lynch syndrome (23, 29). As with hemochromatosis, a key finding was that evidence to guide test use was extremely limited, particularly for hereditary breast and ovarian cancer. As a result, recommendations related to *BRCA1/2* testing were based solely on expert opinion, with appropriate caveats (23).

The process also provided a revealing cross-cultural comparison. A French group had undertaken a similar consensus development process for *BRCA1/2* testing. Their conclusions about appropriate care generally paralleled the CGSC statement, but the two groups came to different conclusions about breast self-exam: The CGSC was in favor of breast self-exam for women with pathogenic *BRCA1/2* gene variants, while the French statement was against it (48). Both groups agreed on the evidence—namely, that a randomized trial had found that breast self-exam did not reduce cancer mortality in average-risk women—but made different assumptions about potential benefits and harms for high-risk women. The CGSC group reasoned that breast self-exam might have benefit in high-risk women even if it did not benefit average-risk women; the French group, on the other hand, was concerned about the potential harms of false positive findings (48). A likely contributing factor was that breast self-exam was established as a preventive measure in the United States but not in France. This contrast points to the role of clinical judgment in generating practice recommendations, particularly when the evidence base is limited, and to the importance of clarifying the reasoning that informs a guideline group's thinking.

I have since had a number of opportunities to participate in deliberations about genetic test evaluation and use, information needs of policy makers, guidelines for test use, and other implications of genomics (e.g., 18, 19, 104, 145). Three aspects of these processes have been particularly striking. The first is that most participants bring prior assumptions and intellectual commitments to the process. These can lead to interesting disagreements about the issue under consideration. If there is time for open discussion, and all views are aired and respected, a reasonable consensus is likely to emerge. If these conditions are not met, the process may generate lingering debate and mistrust.

The second aspect is that determining the stakeholders who need to be included and the perspectives that are essential to the discussion has an important effect on the consensus achieved. In health-related policy-making, there is a tendency to define expertise according to credentials—for example, healthcare decision-making typically falls to individuals with clinical training or relevant scientific expertise. But the individuals who will be affected by the decision have an equal stake in the discussion and a comparable, if different, expertise. Inclusion of patients or research participants in deliberations about healthcare and research policies is important to the relevance and legitimacy of the resulting recommendations, but also challenging. Assuring representative input is not easy, and unbiased background information is needed to allow all participants to engage equally in the conversation.

The third aspect of deliberations about healthcare and research policy is that they are never fully completed. Any particular deliberation is an installment in an ongoing process, primarily because the evidence keeps being updated. In addition, the promulgation of a particular consensus

statement may evoke reactions that lead to further discussion and refinement. This was the case when the American College of Medical Genetics and Genomics issued its initial guideline recommending that 57 genes be evaluated when clinical exome or genome sequencing is done, in addition to any analysis undertaken to address the clinical question in hand (62). The guideline offered a careful rationale for the approach, based on the potential to identify actionable gene variants for serious disorders, but some aspects of the recommendation were hotly contested. As an example, I joined with several colleagues in disputing three aspects of the guideline: that patients not be given an opportunity to opt out of the additional analysis, that the recommendation included assessment of adult-onset risks in pediatric testing, and that the evidence base for some of the genes offered insufficient support for an opportunistic screening program (28). Others spoke up as well, and a lively debate ensued; modifications in the guideline were made, but undoubtedly some differences of opinion remain and will continue to be discussed. This kind of debate is, I think, an inevitable and appropriate component of responsible decision-making (5, 27).

Limited evidence is likely to be a continuing issue for genomic medicine (87, 89, 111). Innovative approaches, including cross-center collaboration to increase sample size for rare disorders, the use of implementation science approaches, and effective use of electronic medical records to measure clinical outcomes, all hold promise (87, 89, 111). However, clinicians will need guidance before definitive evidence is available. This reality suggests the need for an evolutionary approach to guideline development. I joined other ELSI colleagues in proposing that guidance should start with a provisional document—a clinical practice advisory document—that lays out justifications for potential uses of genomic testing, including alternative approaches; identifies uncertainties concerning benefits and harms; and clarifies the research that would be most useful in developing more definitive recommendations (20). Input would be sought from all stakeholders, including patients. The goal would be to promote transparency, help clinicians evaluate trade-offs when considering testing for particular patients, and advocate for needed research. As new evidence emerged, the document would be upgraded to a more definitive practice recommendation.

This process might also help to refine hypotheses for benefits from genomic medicine and clarify elements of study design. As an example, some have speculated that polygenic risk prediction could improve diabetes prevention; however, three clinical trials have shown little impact of genetic risk information on preventive behaviors for diabetes (34). This result is consistent with other data suggesting that genetic risk information does not motivate behavioral change (68) and is not surprising, given the powerful effect of the social environment on behavior (54). Furthermore, an elevated risk for diabetes is common, affecting a third of Americans and half of individuals over age 65 (34); it seems reasonable to hypothesize that community-based approaches to address this problem, rather than interventions based on stratified risk, will be the most effective (34, 54). Conversely, polygenic risk assessment may identify a small proportion of individuals whose risk is markedly elevated and who might therefore benefit from personalized case management (86), although testing this strategy against a community-based approach would be reasonable. Deliberation on issues of this kind has the potential to focus and improve genomic medicine approaches.

Deliberating across disciplines is also likely to improve physician education. An early faculty development initiative offers some insights into the value of this approach (17). The initiative brought together representatives from 37 participating organizations, representing primary care disciplines, medical education, consumers, and medical genetics. The group identified several areas of consensus that led to new ideas for genetics education. They emphasized the value of demystifying genetics by connecting it to existing primary care practice—for example, using cases in which family history is already a part of clinical decision-making, such as decisions about the initiation of lipid-lowering therapy, as a starting point for broader discussion of the use of family history to identify health risks. In addition, they identified value in combining the family history taken

in genetics with the information provided by a genogram, an approach in which social relationships and communication patterns are also noted (17). However, the group also identified differing perspectives on the intrinsic value of genetic risk information that would benefit from ongoing deliberation. Primary care providers emphasized actionability and sought to avoid the collection of information that would not inform clinical management, whereas genetics participants tended to support the view that information about risk was inherently valuable (17).

These perspectives speak to differences in the clinical experience of geneticists and primary care providers and also to ethically salient differences in genetic information (30). Thus, when a test diagnoses a highly penetrant condition and effective treatment is available, there is arguably a health system obligation to ensure that all who can benefit from testing have access to it—this is the category in which screening should be considered, and is the justification for newborn screening. For tests with limited predictive value, like those for hemochromatosis, the availability of safe, effective, and acceptable therapy (or the lack of such therapy) is a key factor in deciding whether testing is clinically useful. These categories of tests fit naturally into the framework of primary care practice, and professional societies representing primary care specialties undertake sophisticated guideline development efforts to evaluate tests with these kinds of properties. Conversely, when no effective treatment is available, testing is likely to be of value only when the information is highly predictive, as in prenatal diagnosis of genetic disorders. Such tests are a familiar part of medical genetics practice (26), leading perhaps to a higher value being placed on risk information (and on a patient's option to pursue such information) than in primary care; in the faculty development initiative, the difference in perspective appeared most pronounced when testing identified a moderately increased risk for which no treatment is available, such as *APOE* testing to identify an increased risk of Alzheimer disease (17).

EQUITY

As clinical applications for genomics meet evidence standards for use (35), the issue of equitable access arises (55, 73). Even after implementation of the Affordable Care Act, 29 million Americans remain without health insurance (55), and many more face limitations in insurance coverage, substantial copay requirements, or a lack of availability of medical services near where they live. Racial minority populations in the United States are disproportionately affected by these healthcare disparities (73). Consistent with these findings, multiple studies have documented disparities in access to genetic services for low-income and minority patients (36, 53, 63, 65, 69, 119, 126). Barriers include limitations in physicians' genetics knowledge, use of genetic testing, and referral to genetic services; availability and cost of services; lack of translation services; and failure of appropriate follow-up after testing or referral occurs. Although clinic-based interventions can improve genetic assessment and referral rates (63, 69), many of the barriers reflect underlying social determinants that constrain patient options (53).

In addition to access barriers, however, minority patients also face the prospect of reduced benefit from genetic testing. Asian and African American patients have a higher likelihood of a noninformative genetic test (36, 92, 119) and are likely to have less benefit from pharmacogenomics testing (125). These problems reflect the failure of genomic research to adequately capture human genetic diversity.

Current genomic data point to as many as 21 ancestral groups within human populations and a high rate of diversity within each group, with 97.3% of individuals showing some degree of mixed ancestry (8). The genetic variation seen across racially defined groups is thus only a rough measure of the variation present in the human population, but it points to the problems generated by a lack of full representation in human genomic data (91). Without correction, increasing use of

genomics in healthcare—for example, expanded use of pharmacogenomic testing or introduction of polygenic risk scores—will exacerbate the problem of reduced benefit (98). This problem is widely recognized, and a variety of initiatives are underway to increase minority participation in genomic research (67, 82, 98, 115). However, achieving this goal requires both a strong commitment and a willingness to build bridges between genomic researchers and underserved communities.

A CENTER OF EXCELLENCE IN ELSI RESEARCH

In 2000, I became chair of the Department of Medical History and Ethics (now the Department of Bioethics and Humanities) at the University of Washington. The department was a partner in an innovative cross-disciplinary training program, the Institute for Public Health Genetics. Faculty from the Schools of Public Health, Medicine, Nursing, and Law participated, and the program attracted highly competitive master's and doctoral students who were interested in combining science and ethics in their graduate training.

In 2003, when the ELSI program invited applications for Centers of Excellence in ELSI Research, I collaborated with colleagues from the Institute for Public Health Genetics on a proposal that focused on questions related to clinical utility and health equity. This proposal led to the formation of the University of Washington Center for Genomics and Healthcare Equality (2004–2017), for which I served as principal investigator. The center was fundamentally concerned with justice: Given the large public investment in genomic research, there was an obligation to ensure that the health benefits could reach all Americans. We sought to understand how the utility of genetic tests might be perceived by different stakeholders (121, 135) and to make connections to health systems in traditionally underserved areas to identify barriers to the use of genetics in healthcare. Although I anticipated that our work would have a clinical focus, in fact our questions led increasingly to research ethics and, in particular, to the ethical obligations inherent in assuring diversity in genomic data.

Because of our location in the Pacific Northwest, we reached out to Tribal healthcare systems in the region to seek their perspectives about the potential for genetic information to offer healthcare benefits to American Indian and Alaska Native (AIAN) people. We met with considerable skepticism. Genetics, we were told, represents high-end, expensive healthcare, not likely to be appropriate for systems trying to deliver basic needs with limited resources. The funding for the Indian Health Service is much lower than the funding for other healthcare in the United States. The per capita expenditure for Indian Health Service patient health services was $2,834 in 2015, as compared with average US expenditures of $9,990 (106). Any intervention that is costly—for example, *BRCA1/2* testing—is likely to be less available with this level of funding. AIAN communities also experience geographic and cultural barriers to healthcare. In a study by a Center for Genomics and Healthcare Equality postdoctoral fellow, for example, transportation loomed large as a barrier to mammography services, in addition to competing family responsibilities and discomfort with testing procedures (77). Healthcare systems and providers may also generate mistrust or dissatisfaction as a result of their lack of knowledge of AIAN patients' cultural heritage (128).

The Indian Self-Determination and Education Assistance Act of 1992 allowed Tribes to assume responsibility for healthcare previously provided by the federal government (72). Our conversations ultimately brought us to Tribal organizations managing their healthcare in this way. Although they were skeptical about the role of genetics in healthcare, they also recognized the importance of genetic research as a source of healthcare innovation, potentially leading to breakthroughs that AIAN communities would want to benefit from, as much as any other communities.

Thus, there was interest in continuing discussions to determine whether a collaborative research opportunity could be identified.

In these conversations, we met with a more stringent standard of clinical utility than in other conversations about genomic innovation. Healthcare leaders in AIAN-serving facilities looked carefully at cost-effectiveness and opportunity costs. They considered the resources that would be required in adopting a new test, the scope of benefit, and the number of patients who would benefit. In US clinical practice guidelines, cost is rarely explicitly considered, but the AIAN-serving healthcare organizations we spoke with saw prudent management of resources as essential to delivering high-quality care. Over several years of conversation, however, we identified a mutual interest in evaluating the potential benefit of pharmacogenomics.

A substantial body of data points to the contribution of genetic variation to individual differences in drug disposition (absorption, distribution, and elimination) and supports the concept of pharmacogenetic testing to guide drug dose or selection (120). An early example was testing for *TPMT* gene variation, to avoid severe leukopenia associated with 6-mercaptopurine therapy in *TPMT* poor metabolizers (45). Other important developments included the discovery of *HLA-A* and *HLA-B* variants that increased the risk of serious adverse reactions to abacavir and carbamazepine, and variants in the *CYP2C9* and *VKORC1* genes that were associated with warfarin dosing requirements (120, 125). As these data emerged, they revealed significant population variation in the relevant alleles. These data meshed with the sense among many of the people we spoke to that medications and dosing regimens developed in the US healthcare system are not always optimal for AIAN people. But very little was known about pharmacogenomic variants in the Indigenous populations in North America, in large part because no research had occurred (76).

A NEW VENTURE: A REGIONAL PHARMACOGENOMICS RESEARCH NETWORK

Our conversations led to the formation of the Northwest-Alaska Pharmacogenomic Research Network (2009–present), a collaboration involving three Tribal health organizations and four universities in the Pacific Northwest (15, 103, 140), directed by Ken Thummel, chair of the Department of Pharmaceutics in the School of Pharmacy—who had been a key science advisor to the Center for Genomics and Healthcare Equality—and myself. The proposal called for the study of the pharmacogenomics of drugs used in cardiovascular disease and cancer treatment, reflecting the priorities of our Tribal partners.

After receiving our initial funding, we met with partners at each of the participating universities and healthcare systems. At one of these meetings, after we had agreed about some initial grant activities, we asked whether we could also plan a meeting to discuss NIH data-sharing policies. We had been required to submit a data-sharing plan as part of the grant application. In that plan, we had explained that our partnership agreement specified that our Tribal partners had decision-making authority over any sharing of data, but we also committed to discussing NIH data-sharing policies with our partners.

In reply to the question, one of the Tribal officials slapped his hand angrily on the table and said, "There's always something else under the hood you didn't tell us about!" He assumed he was about to hear about a data-sharing requirement we had failed to disclose at the time of the grant submission. We reiterated our commitment to Tribal control over the data to be collected. We explained that the purpose of the meeting would be to provide the NIH with appropriate explanations for how we handled data from the project—in particular, to explain why we might choose not to place data in federal repositories. The anger subsided, and we went on to other matters.

However, the memory of that moment lingered. It spoke powerfully to realities I had had little reason to consider when I was growing up in a white, middle-class suburb. Native Americans have a place in any American child's imagination—in cowboy movies and stories about Thanksgiving—but the actual histories of AIAN people are largely invisible. In part, this absence reflects a general tendency in American public life to ignore poverty and its pervasive effects on health and opportunity. In part, as Bryan Stevenson notes in reference to the US history of slavery, "we don't do mistakes very well. We don't apologize very well" (71, p. 87). Mistrust of research is one small reflection of a shameful history of displacement, neglect, and bad faith (139). In light of this history, the Tribal official's suspicions were not unreasonable.

Unfortunately, biomedical scientists are often ill prepared to understand the mistrust of research that exists in marginalized US communities. Few come from such communities, and preparing for a career in science is a competitive and consuming process. An undergraduate science major is demanding, leaving little time for engagement with other topics and disciplines. One's intellectual life focuses even further in graduate school and during the launching of a professional career. Exploring the humanities may seem like a luxury.

Beyond that, today's research universities—although not free of bias—have fortunately become places where students are welcomed irrespective of race, gender, or religion. As a result, scientists often lack exposure to explicit racism and are uninformed about seminal events in the history of US Tribes—such as Native American removals from the eastern United States and forced settlement on reservations; assimilation measures that included abusive boarding school experiences for Native American children, outlawing of religious practices, and federal decertification of some Tribes; and repeated failures to uphold treaties when they conflicted with the interests of white settlers (139)—and the many ways in which this history is reflected in the lives and opportunities of AIAN people today. I came to understand that the preparation I would need in order to participate as a research partner with Tribal communities included learning about this history and reflecting on its implications for the responsible conduct of research.

Our work in the Northwest-Alaska Pharmacogenomic Research Network has confirmed the relevance of pharmacogenomic research for AIAN people. We have identified novel gene variants and haplotypes relevant to commonly used therapeutics, as well as differences in the prevalence of common variants compared with Asian and European populations (50, 51, 66, 85, 100). Our work has also investigated potential interactions between diet and genetics in platelet hemostasis, with implications for anticoagulant therapy (7), and both dietary and genetic contributors to vitamin D levels (4, 52). Importantly, we see genetic differences among the different AIAN populations we work with (51, 66, 85), consistent with the complex genetic diversity of human populations.

A Native American Research Center for Health led by one of our partners has extended the pharmacogenetic research focus to tobacco cessation treatment, with potential implications for improved clinical management (38, 130). We have also explored interest in pharmacogenetics in the communities where we work (44, 124). In focus groups at one of our partner health organizations, we heard views that echoed those we had heard earlier from organizational leaders: There was strong support for community oversight of any use of genetic testing and concern about opportunity costs related to medical innovation, but with these caveats, there was support for pharmacogenetic testing if it could be shown to improve healthcare (124).

We ultimately held a meeting to talk about sharing genetic data. The meeting included our Tribal partners, other Tribal scholars and officials, researchers, and representatives from the NIH. The primary outcome of the meeting was a paper articulating Tribal views about data sharing (79). Tribal participants noted the importance of recognizing Tribal authority—that is, the power conferred by Tribal sovereignty to regulate research occurring on Tribal lands. Any NIH policies related to this authority, including the application of data-sharing policies, would require

government-to-government negotiation. Tribal participants also noted that in the use of their oversight power, Tribal leaders have a fiduciary responsibility to address two concerns vital to their communities.

The first is to ensure that research is done in ways that do not harm their communities—a highly salient concern given the history of research abuses in the United States. An instance that remains prominent in AIAN memory, for example, is research assessing the safety of radiation exposure, in which Alaska Native women, some of them pregnant or nursing infants, were exposed to radiation without their knowledge (108). Although institutional review boards now ensure voluntary consent to research and protect against unacceptable physical risk to participants, AIAN communities have also been harmed by research in other ways. A northern Alaska town suffered a drop in its bond rating, unrelated to financial performance, after researchers publicized findings about alcohol misuse present in the community (97). Another prominent case involved the Havasupai Tribe in Arizona; in this instance, samples collected with the Tribe's permission for studies of diabetes were deidentified and shared with other researchers, to investigate other questions (11). The research occurred without Tribal knowledge or permission and included study questions the Tribe deemed unacceptable. It resulted in a lawsuit on the part of the Havasupai against Arizona State University, claiming fraud, negligence, and other violations. People have disputed whether the Tribe's claims were legitimate; a Tribal attorney recalls being told during mediation meetings, "There's no broken bones—you haven't been harmed" (11). From the Tribe's perspective, however, the unauthorized research represented a breach of trust. As one Tribal member said, "They lied to me. . .I trusted them, and that was broken" (11). Another emphasized that his purpose in participating in the research was to help his community by providing samples that might shed light on the community's high rate of diabetes, and he felt violated when he found out that researchers were "using [his] blood for their own goals" (11). The unauthorized research, which included investigation of consanguinity, schizophrenia, and human migration, was viewed as potentially stigmatizing and spiritually harmful. Western researchers may characterize these views as hostile to science, but voluntary participation is a bedrock of research ethics, based on the principle of respect for persons. The trust inherent in that principle was clearly missing; as a researcher unrelated to the Havasupai case noted, "you should not end up in court with your research subjects" (58, p. 60).

The formulation of accountability we heard at our meeting included a second element, unrelated to harm, that speaks to the fundamental purposes of research. Tribal communities have objected to what is sometimes described as helicopter research, in which researchers come into a community, collect samples, and are never heard from again. Failure to return research findings to the community makes it impossible for the community to derive benefit from what was learned. But the accountability described at our meeting goes beyond assuring that communities will be informed; it includes an imperative to ensure that research addresses questions that matter to the community, as opposed to "curiosity-driven" research; in the words of one Tribal leader, "We are not interested in pursuing research to build your CV."

Conceptual approaches articulated by AIAN researchers to address this issue (e.g., 37, 57, 59, 97) align with the framework of community-based participatory research (75). In this approach, research partnerships are formed around the investigation of problems relevant to the community, and research proceeds with community oversight and collaboration. Community-based participatory research is thus based on normative concerns to assure that research is focused on community benefit and involves sharing of power. There are pragmatic benefits as well: Community input can improve study design by assuring that research questions and methods are informed by community knowledge and geared toward sustainable improvements. In the Tribal context, these values

emphasize understanding and respect for Tribal authority, development of cultural understanding, and reciprocity (59, 97).

Capacity development is also important; academic institutions make a key contribution by training scientists from underrepresented minorities, who can provide leadership going forward. The training pathway is sometimes "leaky," when AIAN and other minority students return to their communities, leaving academic opportunities behind. But these students may become future community-based partners, particularly if their exposure to research has been positive, including, for example, exposure to community–university partnerships that incorporate the values of community-based participatory research (78). Equally important, university-based researchers need to develop their own capacity to work in partnership with community partners; in addition to acquiring cultural knowledge, they need to be able to engage in dialogue and frame their research in terms of community priorities (97).

Tribes may set a priority on research that addresses questions of obvious immediacy (97), creating a potential dilemma for genomics. Thus, efforts to define the full scope of human genetic variation constitute a necessary foundation for the development of clinically useful genetic tests, but may not strike Tribal communities as having priority. Often, communities must deal with limited resources across a broad range of social needs, and participation in the research process itself includes resource demands. This point speaks to the kind of dialogue that must occur in building research partnerships involving Tribal organizations (15, 97, 103, 140) and the values questions that should be asked (84). Researchers must be able to situate research proposals on a path to potential benefit, without overselling what can be achieved or underestimating the time frame required. Even for basic research, it is reasonable to ask what kind of research trajectory toward benefit is possible, over what kind of timeline (84). The uncertainties involved in research must also be acknowledged: There is always the possibility that the research will fail to establish an anticipated benefit. Tribal communities must be able to evaluate research proposals and seek modification when they see the need, place a proposal in the context of their overall priorities, and exert their prerogative to decline a research opportunity if they deem it appropriate to do so (97). On both researcher and community sides, there is a need to learn from each other. The process of developing true dialogue may be slow. The benefits of the process are many, however: long-term partnerships, increased mutual understanding, and the opportunity to pursue valuable research in Tribal communities. Partnerships of this kind are essential if genomics is to deliver its full promise.

One might ask whether these issues and concerns are applicable to other communities. Because federally recognized AIAN Tribes have sovereignty, they are able to establish control over research procedures occurring on Tribal lands. Democratically elected governments in each Tribal jurisdiction determine the procedures for research oversight. It is worth noting, however, that other disadvantaged communities, including urban AIAN communities (80), have similar preferences, even though they lack the sovereignty to impose them. The concept of community-based participatory research, although embraced by AIAN communities, arose in other settings to address concerns similar to those of AIAN communities. For example, we undertook a project in three African American communities to explore views concerning the discovery of gene variants in the *APOL1* gene that increase the risk of kidney disease and are found predominantly in people of West African descent (145). Community advisory board oversight in the three study locations was essential to the project, community members strongly endorsed research to elicit community views on policy issues related to gene discovery, and the importance of informing the community about research findings was emphasized. Communities that have suffered discrimination may be more attuned to these issues than others, but it is not a stretch to imagine that many research participants from nonminority communities have similar concerns. In focus groups among white

research participants in an urban HMO, for example, we found that participants value opportunities for dialogue with researchers, want to hear back about research findings (particularly any that provide important personal information), and want to have confidence that the research to which they contribute is meaningful (133, 134). These views were similar to those we heard from Alaska Native research participants (134).

CONCLUSION

Science is never disconnected from the larger world. In speaking of the Human Genome Project, Francis Collins proposed that "scientists wanted to map the human genetic terrain, knowing it would lead them to previously unimagined insights, and from there to the common good" (39, p. 28). The jump from good science to the common good is perhaps more of an ideal than a tangible goal for most scientists. But in incremental ways, work that seeks to improve the utility of genomic information and the diversity of genomic data has the potential to contribute to this goal.

My experience suggests that an important starting point is a willingness to participate in dialogue across disciplinary and social divides. Dialogue among geneticists, other clinical specialists, policy makers, and consumers is likely to enhance mutual understanding of the outcomes that matter in defining clinical utility, and can lead to study designs that will enable better evidence. Dialogue holds the same value when researchers seek to involve community members in research aimed at expanding knowledge of human genetic variation, and is essential if meaningful partnerships are to occur. Dialogue takes time, and researchers initially may find themselves poorly prepared to engage in such discussions. Awkward moments and disagreements may occur. But the trust and mutual understanding promoted by respectful dialogue provide the necessary path forward.

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Errata

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