Achieving Justice in Genomic Translation

Rethinking the Pathway to Benefit

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The Input-Output Problem: Whose DNA Do We Study, and Why Does It Matter?

STEPHANIE MALIA FULLERTON

Discovery research—sometimes referred to as basic science—is an important first step in the development of health care innovations to benefit individuals and populations. In the genome sciences, discovery research typically involves the identification of genes and genetic variants that can be associated with specific health outcomes in reliable and replicable ways. Such known associations include increased susceptibility to certain diseases (e.g., certain familial cancer syndromes), one's likelihood of benefiting from a particular treatment (such as response to treatment for certain types of leukemia), or the risk of having an adverse reaction to medication (e.g., Stevens-Johnson syndrome with exposure to certain anticonvulsants).

Once such an association has been discovered, it might seem a straightforward matter to design a genetic test to identify individuals who may be at increased risk; however, developing such a test is harder than it looks. The simplest case is with certain types of genetic diseases studied at the level of individual families. For example, imagine that a woman with breast cancer decides to have genetic testing to determine whether she carries one of the known cancer-causing mutations in either the *BRCA1* or the *BRCA2* gene. If such a mutation is discovered, then testing for the presence of that specific mutation in other genetically related women in her family would be directly informative with respect to her risk of developing cancer. When discovery is based in population-scale investigation, however, most disease states or adverse drug reactions can be traced to mutations

(either singly or in combination) in multiple genes. In other words, there are usually many different ways to perturb the developmental processes relevant to a given trait. Even for the class of so-called monogenic, or single-gene, disorders there typically are many hundreds, if not thousands, of mutations that can individually interfere with function of a given gene and lead to disease on a population scale. Test sensitivity (the ability to detect a predisposing gene variant when one is actually in play) is necessarily subject to the thoroughness with which these myriad genetic contributions are identified in early-stage discovery research. Thus, systematic biases in genomic discovery can lead to systematic biases in test performance, with important downstream consequences for the effectiveness of health care delivery and individual health.

This chapter focuses on the impact of one particular type of bias in genomic discovery research: bias with regard to population sampling. Varying rates of research participation across racial/ethnic groups, combined with background differences in genetic variation among populations, can negatively affect genomic translation. The ultimate effect of sampling biases may be that certain groups fail to benefit from the public investment in discovery science and interventions that may be based on those findings. In this chapter, three specific classes of discovery bias are examined, and potential policy remedies are discussed.

UNDERREPRESENTATION OF RACIAL/ETHNIC MINORITIES IN GENOMIC RESEARCH

One area for which there is consistent evidence of systematic bias in genomic discovery is the population distribution of study samples. The overwhelming majority of genetic effects have been characterized first, or only, in populations of European race/ethnicity. Although this bias is widely recognized, there have been only a handful of attempts to comprehensively summarize rates of participation of different racial/ethnic groups in genetic epidemiology and genomic research. In one international review of 43 meta-analyses describing 697 independent gene–disease association studies (Ioannidis, Ntzani, and Trikalinos 2004), for example, 76% (n = 224,546) of the individuals studied were classed as being of European descent (i.e., drawn from native populations of Europe or subjects of European descent from Oceania, North America, or South America, including Hispanics), 18% (n = 53,239) were of East Asian descent (i.e., from native populations of China, Japan, Korea, Indochina, and the Philippines), and only 3% (n = 7,961) were of African descent (i.e., African Americans or from populations of sub-Saharan Africa). Moreover, because the review included only meta-analyses that compared results from at least two "racial" groups, these numbers likely *underestimate* the degree to which European-descent samples have been the object of investigation in population-based association studies. The differential participation of non-European groups in genetic research is so taken for granted within the research community that these marked sample-size differences were not even commented on by the authors.

More recently, genome-wide association studies (GWAS) have come to prominence as a key method of genomic discovery. GWAS involve the simultaneous comparison of many thousands of common genetic variants scattered throughout the genome, between cases (individual participants who have the disease or trait of interest) and controls (participants who are matched with cases on many characteristics but do not share the condition of interest). Because the average effects of GWAS-detected genetic variants are quite small, typically many thousands of cases and controls must be compared to reliably identify a disease-associated variant. A recent review of 373 GWAS, as catalogued by the National Human Genome Research Institute, suggests that the underrepresentation of racial/ethnic minorities in such studies has been even more pronounced (Need and Goldstein 2009). As shown in Table 3-1, 96% of participants in single-population GWAS and 92% of participants in mixed (i.e., multipopulation) GWAS were found to be of European race/ethnicity. Not only have GWAS on individuals of European ancestry been performed at a ratio of nearly 10 to 1 versus all other groups combined, but average sample sizes (which affect the statistical power to detect genetic association) have been twice as large for European samples. As a result, racial/ethnic disparities in genomic research participation have become worse, not better, in the period since the completion of the Human Genome Project (Lander et al. 2001).

There are a variety of explanations for the significant underrepresentation of racial/ethnic minorities in genomic discovery science. To a degree, observed inequalities parallel differences that have been observed for other classes of biomedical research, including clinical trial research (Ford et al. 2008), and suggest major barriers to the recruitment and retention of minority research participants (James et al. 2008). Notorious human-subjects violations in the conduct of research with specific minority communities, such as the Tuskegee syphilis experiment (McCallum et al. 2006), are well known and widely discussed in communities, contributing to widespread distrust of biomedical research. Cultural, linguistic, and/or socioeconomic differences between academic researchers and minority communities can also substantially complicate recruitment efforts (Yancey, Ortega, and Kumanyika 2006). In addition, some researchers also acknowledge an analytical preference for populations of European ancestry, due to a perceived "greater ease of discovery" in such populations (Need and Goldstein 2009). Specifically, on average, Europeans have lower levels of within-population genetic variation and a higher degree of chromosomal association, or linkage disequilibrium, than those from non-European backgrounds, making the search for disease-associated variants more straightforward.

The contention that some populations are better suited for genomic discovery research than others reflects a growing recognition within the human genetic research community of the importance of population genetic variation. Despite long-standing consensus that there is "no biological basis to race" (Gould 1996; Graves 2004), numerous empirical investigations have affirmed that small, but statistically significant, differences in genetic variation exist among socially

Table 3-1. Ethnic Origin of Participants in Genome-Wide Association Studies

Race/ethnicity	Number of studies	Total participants		Percentage	Average sample size
European only	320	1,581,776		96%	4,943
Asian only	26	52,841		3%	2,032
Hispanic only	3	1,019		0.06%	340
Native American only	2	1,102		0.07%	551
Jewish only	2	3,479		0.2%	1,740
Gambian only	1	2,340		0.1%	2,340
Micronesian only	1	2,346		0.1%	2,346
TOTAL		1,644,903			
Mixed	11	European	92,437	92%	8,403
		African American	7,500	7.5%	682
		Asian	33	0.03%	3
		Papua-New Guinean	276	0.3%	276
		Other	269	0.3%	24
		TOTAL	100,515		

Adapted from Table 1 in Need AC, Goldstein DB. Next generation disparities in human genomics: concerns and remedies. *Trends Genet.* 2009;25(11):489–494.

constituted groups, particularly when those groups trace their heritage to ancestral populations that lived on different continents (Weiss and Fullerton 2005). Differences exist both in the level of genetic variation found within populations and in variation between groups. These differences are understood to have arisen as a function of regional demographic and selective forces; for example, regional differences in inherited blood disorders are believed to be related to the protective

effects of such changes in regions of the world where malaria is endemic. The extent to which such differences explain disparities in health *outcome* across groups is unclear, and hotly debated (Frank 2007). Nevertheless, the unequivocal demonstration of population genetic differences has made the unequal participation of racial/ethnic minorities in genomic research an epistemic, as well as a political, concern. Recent calls within the genetic community for a more diverse basis for genomic discovery have been based, for example, in a recognition that current samples are not representative of U.S. populations (e.g., Collins and Manolio 2007) as well as a desire to "more comprehensively" identify genetic contributions to disease risk (McCarthy 2008), including ethnic-specific differences in disease risk (Tang 2006). However, the potential implications of sampling biases for later stages of the translational pathway—for example, efforts to design effective screening tests—have been, to date, relatively unexplored.

How worried should we be about systematic sampling biases in genetic and genomic research? There are at least three ways in which biases in genomic discovery can impact downstream genetic testing. First, a gene with an appreciable contribution to disease risk can be overlooked entirely if susceptibility variants in that gene occur at only a low relative frequency in the population chosen for discovery. That is, if a particular variant is uncommon in European-descended populations but relatively common in other groups, a study in which 99% of participants are European will likely fail to identify that variant as important. Second, a disease gene may be convincingly identified, but the full distribution of predisposing mutations within the gene may remain incompletely described. This can lead to the identification of "variants of unknown significance" (VUS), the nature of whose association with disease is uncertain. In this case, even if a validated genetic test is developed, individuals may receive results whose meaning or usefulness is unclear. Finally, a specific susceptibility variant may be replicably associated with disease, but the extent to which the variant increases risk may be inaccurately characterized or may indicate different relative risks in different discovery samples. Here, a test will detect a variant likely to increase disease risk but provide uncertain information regarding the degree of clinical intervention required. Examples of these scenarios are discussed below.

GENETIC DISCOVERY

One way in which over-focus on populations of a single racial/ethnic background can have an impact on discovery is by limiting attention to the genes (and variants within them) that occur at detectable frequency in that population. While this is not a problem if the same susceptibility factors are present to the same general degree in nonsampled groups, many common complex traits and diseases are determined by variants that do *not* occur in all populations to the same degree (McCarthy 2008). So, susceptibility variants common in non-European populations may be missed entirely in a study of European-based samples, and variants

identified as important in samples from European descendants may contribute little to disease susceptibility in populations who trace their heritage to another region of the world.

Example

A 25-year-old man of Japanese descent has a history of diabetes on his mother's side of the family. He has put on 30 pounds since graduating from college. He is aware that obesity is a risk factor for type 2 (i.e., adult-onset) diabetes, and he is worried that the combination of his genetic makeup and weight gain may place him at increased risk. However, his father, who is also overweight, does not have diabetes, and he realizes that it is possible that he did not inherit his mother's (presumed) genetic susceptibility. He decides to have predictive genetic testing for type 2 diabetes risk, which he reasons will give him more specific information about his personal risk of developing the disease and hence help him decide how hard he should try to lose the excess pounds.

After researching potential alternatives, he opts for the Health Edition Test from 23andMe (www.23andme.com), a company that offers genetic testing services directly to consumers, without a physician order. The test, which costs $429, provides information about 156 diseases and conditions and includes a panel of 9 susceptibility variants that have been associated with diabetes susceptibility in European, Asian, and African populations.

When he receives his test results, he learns that while a few of the reported genotypes suggest a mildly elevated risk of developing type 2 diabetes compared with the general population, the composite conclusion from the test panel is that his risk of developing type 2 diabetes is in the "normal" range. He breathes a sigh of relief and decides he does not need to make substantial changes in his diet or join the gym; over time, he also neglects to see his doctor for routine checkups. In his early 40s, he begins to suffer adverse health effects resulting from undiagnosed diabetes:

What Went Wrong?

The test failed to provide accurate information to this individual because the gene(s) contributing to diabetes susceptibility in his family were not included as part of the genetic test panel. This can occur when the genetic variants contributing to disease risk are "private"—that is, unique to a particular family—but that is not what happened here. Instead, his results can be traced to the fact that the genetic test panel was based on data obtained predominantly from populations of European, not Asian, ancestry. There is at least one (Unoki et al. 2008; Yasuda et al. 2008) (and there possibly could be many more) susceptibility variant for risk of type 2 diabetes that is more common in Asian populations but relatively rare in Europeans, and hence not included in many testing panels. Only equivalently comprehensive investigation of genetic contributions to diabetes risk in a

range of Asian racial/ethnic populations would have identified the gene as an important candidate for testing. The individual thus received a false-negative finding, which led to inappropriate reassurance about his potential for developing diabetes.

VARIANT DISCOVERY

Underrepresentation of non-European populations can also lead to an incomplete catalogue of the ways in which specific disruptions in a disease-associated gene contribute to disease risk. If a given gene demonstrates a limited number of possible disease-causing mutations (also called variants), and if the same causal mutations are present in all populations, then the study population used to identify those variants will not make a difference in the analysis. But if many hundreds, or potentially thousands, of different pathogenic mutations are in play, and if some fraction of these are confined to particular groups (McCarthy 2009), then a catalogue of mutations based on analysis of a patients from a single population will leave many causal variants unidentified.

Example

A 30-year-old African American woman whose mother had breast cancer and whose aunt had both breast and ovarian cancer is concerned about her risk of developing cancer. She seeks advice from a genetic counselor about testing for breast cancer susceptibility. After a thorough review of her family history, the counselor suggests that genetic testing could be informative with respect to her personal risk and arranges for genetic testing of the two known susceptibility genes for breast and ovarian cancer, *BRCA1* and *BRCA2*. (Testing in the United States is done at a single laboratory, Myriad Genetics, which holds the patents to the testing process.) If a specific mutation had been previously identified in a family member, or if she had any Ashkenazi Jewish ancestry, she could have a targeted test that would look for the particular variants seen in that group[1]; but as she is the first in her family to be tested and has no known Jewish ancestry, she will need the more comprehensive (and hence considerably more expensive) BRACAnalysis test (www.bracnow.com). This test involves complete sequencing of the *BRCA1* and *BRCA2* genes, rather than targeted genotyping of specific variants. Fortunately, because the woman's family history indicates that she may be at increased risk, her insurance will cover most of the cost.

After several anxious weeks, she receives a call from her counselor and goes in to receive her test results. There she is told that the test has identified a "genetic change of uncertain significance," meaning there is a mutation in one of the tested susceptibility genes that may affect protein function but has not been previously observed and so cannot be definitively said to increase cancer risk. Although the counselor had warned her that such a result was possible, she is upset to learn that her results will likely not be informative until the testing company has identified other women with the same mutation who have gone on to develop breast cancer. She has one sister, who does not want to undergo testing, and her other affected family members are all deceased. The counselor suggests that the best she can do, in the absence of additional information, is to undergo annual mammograms.

1. Three common "founder" mutations (2 in the *BRCA1* gene and 1 in the *BRCA2* gene) are observed among many at-risk women with Ashkenazi Jewish ancestry (Warner et al. 1999). A panel which tests just these mutations is available for such women.

What Went Wrong?

In this case, while the test methodology can detect novel variants in known susceptibility genes (i.e., *BRCA1* and *BRCA2*), the clinical significance of the finding will remain unclear if the specific mutation identified has not been previously associated with presence of disease in other families. Such VUS are quite common in "comprehensive" (i.e., sequence-based) genetic tests. For VUS to be transformed into variants of confirmed clinical relevance, a sufficient number of women diagnosed with cancer must be found to share the same mutation. And while women of any ethnic background can receive inconclusive test results, there is evidence to suggest that minority women are disproportionately affected by such findings (Hall et al. 2009). In this case, if the woman's breast cancer mutation happens to be found more often among women of African ancestry, the fact that fewer such women have been previously tested means that it will be classed as "not seen before" even if, in fact, it is not a private mutation. This woman is disadvantaged because fewer women like her (and their families) have had their susceptibility genes examined for cancer-linked mutations.

EFFECT-SIZE ESTIMATION

Finally, even if a specific gene and its variants are well characterized and significantly associated with disease predisposition, biased sampling can interfere with the comprehensive investigation of the effect size of different variants. Effect size refers to the strength of the association with disease risk. As in the two previous examples, if the extent to which a specific genotype predicts disease outcome is consistent across populations, it makes no difference what population is used to estimate effect size: the results will apply to any individual, irrespective of racial/ethnic affiliation. If, however, background genetic factors or environmental exposures modify the strength of association such that effect size varies with population background (Bamshad 2005; Ioannidis, Ntzani, and Trikalinos 2004), estimates based on data from one or few discovery samples may not be applicable to individuals from other populations. In this case, a test will detect a variant likely to increase disease risk, but it will provide uncertain information regarding the degree of clinical intervention required.

Example

A 45-year-old Puerto Rican man with angina has been sent to a cardiologist for routine clinical follow-up. The cardiologist does a battery of tests but is not sure how aggressive a treatment plan to recommend. He asks whether cardiovascular disease runs in the family, but the patient does not have much information. He remembers that one uncle may have died "young," but he is uncertain of the cause, and he states that he is unable to consult with other family members to learn more. In the face of this uncertainty, the cardiologist recommends that the patient undergo genetic testing for known cardiovascular susceptibility variants.

The cardiologist suggests deCODEme's Cardio Scan test (www.decodeme.com/cardio-scan), which tests for the presence of susceptibility variants in a panel of genes. The test provides information about genetic risk for heart attack, abdominal aortic aneurysm, atrial fibrillation, peripheral arterial disease, intracranial aneurysm, and venous thromboembolism. When the test results are returned, the cardiologist reviews the findings with the patient. Risks for three of the six diseases examined vary by population ancestry and gender, while the other three risk estimates are based on results obtained from samples of European ancestry only; however, risk estimates for individuals of Puerto Rican ancestry are not available. The cardiologist is aware that people of Puerto Rican ethnicity may trace their ancestry to European and African forebears, and so he considers risk estimates relative to each population background. Unexpectedly, the patient's lifetime risk of heart attack is considerably higher if African rather than European ancestry is assumed. Even though the patient does not have any immediate known African heritage, the cardiologist recommends a surgical intervention out of "an abundance of caution."

What Went Wrong?

In this case, at least one of the susceptibility variants contributing to an increased risk of heart attack has been shown to affect risk differently in different populations. This is a well-recognized phenomenon in genetic epidemiological research, and one which is believed to reflect some systematic, but unmeasured, difference in either genetic background or environmental exposure that is correlated with ancestral background of a study sample (Bamshad 2005). Such population differences in estimated "effect size" severely complicate the interpretation of individual genetic risk, particularly when, as was the case for this patient, individuals understand themselves to be of mixed ancestral heritage. While current data suggest that population-level differences in effect size are uncommon (Ioannidis, Ntzani, and Trikalinos 2004), it is also true that, as was the case for the deCODEme panel, risk information is often available only for populations of European origin, which makes it hard to assess how often such differences actually arise. This individual was adversely affected both because his race/ethnicity is atypical of those for whom susceptibility information is usually generated and because he is not readily assignable to a definable ancestral heritage (such as those around which many genetic studies are constructed).

POTENTIAL REMEDIES FOR GENOMIC DISCOVERY BIAS

In each example described above, a failure to adequately investigate genetic contributions to disease risk in a particular population limits the clinical benefit of genetic testing for particular patients. On its face, this is a discouraging phenomenon, but recognizing the practical effect of biases in genomic discovery immediately suggests a potent remedy: eliminate or otherwise address population sampling biases. A fairer distribution of potential health benefit could follow such changes. (This thesis presupposes—somewhat optimistically—that we will be able to simultaneously overcome other barriers to healthcare access and delivery).

There are a few different ways in which systematic sampling biases in genomic research could be remedied as a matter of research policy. First, the *inclusion* of individuals from diverse ethnic groups, in numbers representative of national demographic proportions, could be required as a condition of funding. This sampling preference is, in fact, already a matter of U.S. federal research policy as per the conditions of the NIH Revitalization Act of 1993. Second, the *equitable*, as opposed to representative, ascertainment of individuals from multiple ethnic groups could be required, as recently recommended by Need and Goldstein (2009). Third, population-based ascertainment that takes known effects on statistical power into account (e.g., average levels of genetic variation), such that individuals from certain populations are *oversampled* relative to either representative or equity-based sampling schemes, might instead be encouraged. In the next section, each of these solutions is considered in respect to the effect they might have on the examples discussed above.

Representative Inclusion

As noted above, the inclusion of ethnic minority populations in biomedical research was required by congressional mandate as part of the 1993 NIH Revitalization Act. The NIH Inclusion Guidelines, which went into effect in 1994, require the following:

> [W]omen and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification establishes . . . that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research (NIH 2001).

Investigators are asked to report and justify enrollment plans at the time of grant submission and to confirm participant demographics in study progress reports. Although this policy can be credited with increasing the participation of ethnic minority populations in genetic and other forms of biomedical research (Epstein 2007), it has done little to rectify marked imbalances in population sampling. This is due in part to the fact that the guidelines are enforced

on a study-by-study basis, and population scientists can often justify an exclusive focus on one demographic group. Moreover, because of the way the policy has been implemented, in particular the required use of sociopolitical (i.e., defined by the Office of Management and Budget) categories of race and ethnicity for reporting, the policy has had the additional, unwelcome effect of promoting an analytical emphasis on biological differences among socially constituted groups, a phenomenon sociologist Steven Epstein has coined the "inclusion-and-difference paradigm" (Epstein 2007).

While prominent genetic epidemiologists and policy makers (Collins and Manolio 2007) have advocated that the involvement of research participants in numbers proportional to U.S. population demographics would represent an effective remedy to the sampling biases that threaten genomic translation, this is probably not the case. Because approximately 75% of the U.S. population currently self-identify as having European ancestry (Grieco and Cassidy 2001), a policy of representatively inclusive sampling would continue to support the disproportionate recruitment and analysis of individuals of European origin. In such a sampling regime, genetic discovery would likely continue to be pursued first, and most effectively (from the point of view of having sufficient sample size to achieve the required statistical power), in European-based samples. In the cases discussed above, the test for diabetes susceptibility would remain weighted toward the consideration of variants common in European samples but uncommon in other groups; breast cancer variants of uncertain significance would continue to disproportionately impact minority ethnicity test-takers; and where disease risk (as measured by the effect size of specific variants) is differentially distributed with respect to population background, individuals of European ethnicity would continue to benefit from better-validated and statistically more certain risk information. Hence, if equivalent benefit from genomic discovery is the desired endpoint, representative sampling will simply not suffice.

Equitable Sampling

Another suggestion, advanced in a recent commentary by Duke geneticists Need and Goldstein (2009), is to instead insist on the equitable, as opposed to merely representative, recruitment of minority and nonminority research participants. These authors contend that sampling biases have thus far not affected healthcare because GWAS have largely failed to identify clinically important genetic effects. But they warn that, with an anticipated shift to newly available whole-genome sequencing approaches that will identify many more clinically relevant variants, continuing inequities in genomic discovery could significantly exacerbate health care disparities in the future. To address this concern, they recommend a research policy that would require both the sequencing of equal numbers of samples from European Americans and African Americans (to level discovery efforts) and the collection of equivalently sized control populations (to provide a robust basis for distinguishing causal variants from background "neutral" genetic variation).

Because sequencing studies, at least in the near term, will involve far fewer participants than typical GWAS, Need and Goldstein reason that previously collected research samples would suffice for this purpose.

Leading genome scientists' prominent acknowledgement of population sampling inequities in the genome sciences, combined with concrete recommendations for their address, is laudable. Although prioritized investigation of previously collected samples would do little to remedy unequal rates of *participation* by individuals of minority ethnicity, a concerted push to equalize analyses could go much of the way toward addressing current discovery biases. Regarding the examples discussed above, independent but equivalent investigation of genetic contributions to diabetes risk in an East Asian or Asian American sample would have identified susceptibility genes too uncommon to be detected in Europeans. Similarly, with a larger pool of unaffected African American women to serve as controls, potentially many more pathogenic breast cancer mutations could be distinguished from background genetic variants.

One concern left unaddressed by these recommendations, relevant to the third case example, is the decision regarding which non-European populations to prioritize for analysis. Need and Goldstein (2009) endorse special sampling consideration for African American populations, who are not only underrepresented disproportionately in most biomedical research but are also widely regarded as particularly difficult to study from a genetic standpoint. For evolutionary reasons, individuals of African ancestry exhibit on average greater levels of genetic variation (Weiss and Fullerton 2005), which makes the search for genetic contributions to disease risk more arduous. But given that many other U.S.-based ethnic groups (such as Puerto Rican Americans) are equally poorly represented among current genetic research studies, relying on the analysis of previously collected samples risks neglecting investigation of these groups. At the same time, the equivalent analysis of *all* major ethnic groups may be neither feasible nor, in fact, strictly necessary: if the effect sizes of most genetic variants are not modulated by genetic ancestry or ethnic background, then exhaustive analysis is not required. However, in the absence of systematic consideration of genetic risk across diverse populations, we have no way of distinguishing variants whose effects vary in a population-specific manner from those whose effects do not. Analyzing samples from several (but not all) minority groups would help identify when more intensive investigation of specific genetic effects is needed.

Although equal sampling of individuals from multiple ethnic groups could reduce many of the biases expected to accompany whole-genome sequencing, it is not well suited to addressing all forms of genomic discovery bias. In particular, population-based association approaches, which rely on statistically distinguishing causal susceptibility variants from background genetic noise, can be compromised by high overall levels of variation and differences in variation among ancestral subgroups (Cooper, Tayo, and Xiaofeng 2008; Need and Goldstein 2009). In such cases, equivalent ascertainment may not result in equivalent opportunity for discovery and, by extension, for health outcomes benefit. As noted above, this problem is most pronounced for ethnic minority communities with

large amounts of recent sub-Saharan African ancestry, as such populations generally have higher average levels of genetic variation, inherited in more complex chromosomal arrangements, than populations from other geographic regions (Campbell and Tishkoff 2008).

Oversampling

A policy of directed oversampling might hold the greatest potential for addressing discovery biases in certain cases. For some populations (e.g., those with substantial, recent sub-Saharan African ancestry), oversampling (i.e., studying people in numbers greater than their representative proportions) is needed to achieve comparable statistical power for discovery.

The most important point to emphasize is that sampling decisions can, and really should, be based in a consideration of the ultimate potential health benefit of the data generated, rather than other criteria aimed at ensuring "fair" (representative, equal, etc.) participation. In the case of the examples discussed above, it is likely that an Asian population sample of an equivalent size to the originally ascertained European sample would have been adequate for the identification of genes common to that group. It is also likely that equivalent estimation of effect size among Puerto Rican research participants would have been sufficient to address the concerns of the third example. However, the higher level of background genetic variation in samples of African origin suggests that some degree of oversampling of African American women with a positive family history of breast cancer would be needed to resolve an equivalent proportion of variants of uncertain significance in that ethnic group.

A number of important challenges would be involved in acting on such a policy recommendation. Sustained effort to increase the participation of African and African American communities in genetic and genomic research would be needed, including the use of innovative communication and recruitment strategies aimed at overcoming those communities' well-known and long-standing distrust of research and researchers (James et al. 2008). Such efforts must be accompanied by careful, scientifically informed justification for the required deviation from either representative or equitable sampling, which might otherwise be perceived (incorrectly) as inappropriately "privileging" or, alternatively, "burdening" African American participants. Further, to ensure that the effort involved in attracting greater numbers of participants to research is not wasted by subsequent analytical shortcomings, genome scientists would need to devote greater attention to refining methods for the detection and interpretation of complex genetic variation. Current genotyping tools, such as SNP chips, have been shown to perform less well in populations with greater degrees of African ancestry (Manolio, Brooks, and Collins 2008).

As this brief analysis demonstrates, if the translational *consequences* of specific classes of discovery bias are explicitly considered, it is relatively easy to distinguish and evaluate research policy alternatives. Such consideration not only suggests

that current policy preferences (such as representative sampling) are objectively inadequate, but also helps explain why a one-size-fits-all approach to population sampling will not guarantee equal opportunity of translational benefit. The alternative—a mixed approach of equitable multiethnic analysis, augmented where appropriate by more intensive investigation of cross-population differences and targeted oversampling—holds greater promise and should be promoted by both federal and international research-funding agencies.

CONCLUSION

Although there are few data to bear out the claim, it seems likely that few bench-based genome scientists stop to consider the downstream translational implications of their research. This may be particularly true of scientists who interact rarely (if ever) with research participants. Faced with a defined empirical puzzle (e.g., "What gene or genes contribute to risk for this disease?," "Which variants in this gene explain disease risk?," or "To what degree is disease onset associated with inheritance of this variant?"), researchers may view the ethnic composition of the discovery sample as a simple pragmatic consideration rather than a moral issue. The best sample is the one that can be most easily obtained, on the shortest timetable, and that is that.

Yet, as illustrated here, population differences in genetic susceptibility to specific diseases, when combined with background differences in genetic ancestry among ethnic groups, do render the choice of study sample consequential. These consequences extend beyond purely scientific considerations, such as producing a skewed or incomplete detailing of genetic contributions to disease risk, an effect that has begun to be recognized and commented on by some genome scientists (McCarthy 2008; Tang 2006). Systematic biases in genomic discovery threaten to limit the translational promise of genomic information, denying potential benefits not only to a significant fraction of the U.S. population, but to the majority of individuals of non-European ancestry living around the world. More sustained, and nuanced, attention to the character of population sampling in discovery phase research must begin from the recognition of what is at stake: the just distribution of the benefits that emerge from human genomic research.

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