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Will tomorrow's medicines work for everyone?

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Throughout much of the world, 'race' and 'ethnicity' are key determinants of health. For example, African Americans have, by some estimates, a twofold higher incidence of fatal heart attacks and a 10% higher incidence of cancer[1,2] than European Americans, and South Asian– or Caribbean-born British are ~3.5 times as likely to die as a direct result of diabetes than are British of European ancestry[3]. The health care that people receive also depends on 'race' and 'ethnicity'. African Americans are less likely to receive cancer-screening services and more likely to have late-stage cancer when diagnosed[2] than European Americans. Health disparities such as these are one of the greatest social injustices in the developed world and one of the most important scientific and political challenges.

Most current health disparities have little or perhaps nothing to do with genetics, depending instead on socioeconomic and other environmental factors[4], including inequalities in the delivery of health care. But this fact should not make us reject the possibility that biological differences associated with 'race' or 'ethnicity' will contribute to disparities in the future. Substantial changes are occurring in how medicines are developed and how they are used, and some of these changes present risks that medicines will become less inclusive. Some of the variation in how medicines work may correlate with racial or ethnic groups, exacerbating health disparities. Here we review ways in which genetics could contribute to future health disparities and outline some general research approaches that could counter this.

Why might medicines become less inclusive?

Advances in genetic technologies should improve our understanding of disease etiology and of the factors influencing response to treatment[5]. Although there has been relatively little progress to date in using genetics to improve the treatment of common diseases, there are some encouraging signs of progress in basic research[6–8]. If genetics does eventually prove relevant to the treatment of common diseases, then to the extent that genetic advances are uneven among racial and ethnic groups, disparities may result. Perhaps the most immediate concerns about the clinical use of genetics involve pharmacogenetics, which seeks to identify the genetic factors that influence responses to medicines. Studying drug response might be more clinically useful

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than studying disease predispostion[6,9], at least in the near term. Pharmacogenetics also seems poised to become a common component of the drug-development pipeline[10], with proof-of-concept studies having demonstrated its potential[11]. For these reasons, we focus this perspective on pharmacogenetics.

For convenience of presentation, we shall not attempt to define 'race' or 'ethnicity' here. Our primary aim is to discuss the evidence for differences among groups, and so we consider mainly how people are distinguished in the current medical literature, for example, in clinical trials; therefore, we refer to different groups as 'racial' or 'ethnic' groups. We do, however, briefly review debates about the extent to which human genetic structure correlates with racial or ethnic groupings.

The influence of race or ethnicity on the efficacy and safety of existing medicines may guide our expectations for the future. Therefore, we begin with a review of evidence concerning whether specific drugs work differently in different racial or ethnic groups. The concerns about how genetics might influence the inclusiveness of medicines can be broadly divided into three partially overlapping categories: (i) pharmacogenetic diagnostics, in which individual genotype is used to guide the selection of medicines; (ii) molecular subclassification of disease, in which genetic features of a disease are used to guide the choice of therapy; and (iii) pipeline pharmacogenetics, in which genetics is used during the evaluation of new chemical entities.

Inclusiveness of current medicines

At least 29 medicines (or combinations of medicines) have been claimed, in peer-reviewed scientific or medical journals, to have differences in either safety or, more commonly, efficacy among racial or ethnic groups (**Table 1**). But these claims are universally controversial[12–14], and there is no consensus on how important race or ethnicity is in determining drug response.

Nevertheless, from 1995 to 1998, the labels of 8% of new drug products (15 of 185) contained a statement about racial or ethnic differences in effectiveness[15]. For an overview of the relationship between racial or ethnic group and drug response, we compiled a list of drugs claimed to have different effects in different racial or ethnic groups on the basis of reviews[16] and PubMed literature searches using combinations of the following key words and phrases: ethnic*, race, racial, drug response, pharmacokinetic*, cytochrome P450. We also determined whether there is any evidence for a genetic or a physiological contribution to the reported racial or ethnic differences in drug response, or any other evidence that the differences are real. In cases where the differences in response are associated with underlying physiological differences (as in the case of angiotensin I–converting enzyme (ACE)

inhibitors), these physiological differences may be influenced by environment, genetics or both. Genetic epidemiology methods, including migrant studies, studies of admixed populations and comparisons of populations in different geographical locations (*e.g.*, West Africans and African Americans), can be used to assess the basis of racial or ethnic differences in response to drugs[17]. The most direct way to assess differences in drug response among racial or ethnic groups is to find the causes of the variable drug response and investigate how these causes differ among the groups. In most cases, however, the genetic bases of variable drug responses are too poorly known to allow a direct assessment. The one exception is beta-blockers: a polymorphism in the drug target may contribute to the differences in responses.

Many studies of drug response are small, and study designs vary. There is also a bias towards studies comparing European Americans and African Americans, reflecting a focus on the American racial or ethnic context. Certain therapeutic areas are particularly prominent among the list of medicines, most notably those related to cardiovascular disease. For example, there is arguably a consensus in the literature that African Americans respond less well than European Americans to beta-blockers, ACE inhibitors and angiotensin-receptor blockers, some of the main agents now used to treat heart-related conditions. Conversely, African Americans may respond as well as or better than European Americans to diuretics and calcium-channel blockers.

Some have argued that these differences result from underlying differences in the causes of hypertension in individuals of (west) African ancestry and of European ancestry[18]. For example, European American and African American hypertensive individuals typically differ in characteristics such as salt sensitivity, plasma volume and renin levels[19]; there could be differences in the pathogenesis of hypertension. Decreased sensitivity to beta-blockers might be associated with the higher proportion of low-renin hypertension found in African Americans, and nonadrenergic mechanisms might contribute more to blood pressure maintenance in African Americans than in European Americans[20].

Differences in response to ACE inhibitors may be related to lower bioactivity of endogenous nitric oxide in African Americans than in European Americans[21]. The increased benefit of treatment with nitrates and hydralazine in African Americans is consistent with this hypothesis. For example, BiDil, a drug that combines isosorbide dinitrate (a nitric oxide donor) and hydralazine (a vasodilator agent), was not sufficiently effective in treating congestive heart failure in two large, ethnically mixed clinical trials[22,23] to win regulatory approval. A retrospective analysis of the original trials, however, indicated that the drug was more effective in treating the African American than the European American participants in the trial[24]. On that basis the US Food and Drug Administration approved a trial of BiDil in African Americans[25]. The trial recently terminated early because interim analyses showed the drug to be highly effective, and the makers of BiDil will now seek approval for its use in the African American population. But any genetic basis to the difference in nitric oxide bioactivity between African Americans and European Americans remains to be elucidated. Furthermore, there have been no comparative studies investigating differences in nitric oxide bioactivity between Africans and African Americans, and any relationship between endothelial nitric oxide synthase variants and plasma nitric oxide levels or other intermediate or clinical phenotypes is not fully understood[26].

Genetics probably contributes to some of these reported differences between different racial or ethnic groups. On the other hand, at least some of the differences can be attributed to confounded environmental factors.

A recent study investigated blood pressure response to quinapril, an ACE inhibitor, in 533 African Americans and 2,046 European Americans with hypertension. African Americans had a lower average response to quinapril than European Americans, but age, gender, body size and pretreatment blood pressure significantly predicted blood pressure response[27]. These factors correlate with race or ethnicity, and when they are accounted for, the effect attributable to race or ethnicity is reduced.

Some claims for differences among racial or ethnic groups in drug response will be false positives, and these may be more likely to be reported than a negative finding[28]. The blood pressure response analysis makes the point that, even for real differences, it is not clear which differences (if any) are due to genetic factors and which are due to environmental correlates with race or ethnicity. The analysis also shows that there is substantial variation within racial or ethnic groups in environmental correlates of response, as will also be the case for genetic factors.

Genetic contributions to differences in drug response

In discussing possible genetic factors, it is useful to distinguish genetic factors that are specific to the drug used from those that influence the nature of the condition itself. Drug-specific effects include both pharmacokinetics (*e.g.*, drug-metabolizing enzymes (DMEs) and transporters) and pharmacodynamics (*e.g.*, drug targets and target-related proteins, which are often not involved in disease etiology) of the drug.

For both the disease-associated and the drug-specific effects, there is scope for intergroup differences; many pharmacogenetic variants known to influence drug response show frequency differences among racial or ethnic groups[6]. For example, the beta-1 adrenoceptor Arg389 variant, associated with increased response to beta-blockers[29,30], is less common in African Americans than in European Americans (frequencies of 0.575 and 0.723, respectively). Many DME variants also vary in frequency among populations[31], and for some DMEs (*e.g.*, CYP2D6, CYP2C19, CYP2C9 and NAT2) the proportion of individuals with little or no functional enzyme varies substantially among populations. As a relatively benign example, because they carry null alleles of *CYP2D6*, up to 10% of individuals of north European ancestry experience no analgesic effect from the prodrug codeine[32], whereas 98% of the inhabitants of the Arabian peninsula are able to transform codeine into the active form morphine[33].

These examples show that gene variants that causally influence how individuals respond to treatment often have important differences in frequency among racial or ethnic groups. This suggests that genetic differences among racial or ethnic groups will often lead to differences in drug response. The examples we selected are consistent with the general pattern for variants known to influence drug response. Of 42 genetic variants that have been associated with drug response in two or more studies, more than two-thirds have significant differences in frequency between people of European ancestry and people of African ancestry. The average frequency difference for all 42 variants is 0.15, and nearly one-third of the variants have frequency differences greater than 0.2 (ref. 6). Many of the differences in drug response among racial or ethnic groups reported in **Table 1** are therefore expected to be influenced to some degree by genetics. These differences will often be modest and may not be clinically significant, but we must expect that such differences will exist and will be partially genetic.

Overall, analyses of responses to existing medicines and new chemical entities are far from conclusive about the scope for genetic differences among groups to contribute to variable drug response. In most cases it is difficult to separate genetic from environmental factors. For example,

Table 1 Examples of drugs reported to have different response in different racial or ethnic groups

Drug class	Examples	Difference in response	Sample size	Is the difference real?	Evidence
ACE inhibitors	Enalapril	Less response in AAs than in EUs with left ventricular dysfunction[62].	1,196 EUs, 800 AAs	B	Probably related to lower bioactivity of endogenous nitric oxide in AAs than in EUs[21].
	Lisinopril	Response (lowering of blood pressure) in EUs but not in AAs[63].	124		
	Trandolapril	AAs with hypertension required 2–4 times greater dose to obtain similar lowering of blood pressure to EUs[64].	207 EUs, 91 AAs		
Combination of two vasodilators	BiDil	Greater efficacy in AAs than in EUs with congestive heart failure[65].	Trial 1: 180 AAs, 450 EUs. Trial 2: 215 AAs, 574 EUs	B	
Vasodilator antihypertensive	Sodium nitroprusside	Attenuated vasodilation response to methacholine and sodium nitroprusside in normotensive AAs compared with EUs[66,67].	11 AAs, 9 EUs; and 21 AAs, 19 EUs	C	Attenuated responses to multiple vasodilators commonly observed in AAs[66]. Mechanisms not fully understood.
Beta-adrenoceptor blocker (nonselective)	Propranolol	More effective in EUs than AAs for initial treatment of hypertension[68].	NA	A	Hypertensives and healthy volunteers carrying two copies of the allele encoding the Arg variant of the R389G polymorphism in β1-adrenergic receptor have greater response to metoprolol and to metoprolol and atenolol, respectively[69–71]. The Arg variant is more frequent in EUs than in AAs (0.723 versus 0.575; ref. 72). There is a higher proportion of low-renin hypertension in AAs, and nonadrenergic mechanisms contribute more to blood pressure maintenance in AAs than in EUs[20].
	Nadolol	More effective in EUs than in AAs for systemic hypertension[73].	365		
	Oxprenolol	Mean blood pressure reduction less for AAs than for EUs[74].	NA		
	Bucindolol	Survival benefit only in non-AAs[75].	2,708		
Beta-adrenoceptor blocker (β1-selective)	Atenolol	More effective in EUs than AAs for hypertension[74].	1,105	D	Basis of ADR not known and study not replicated.
Vasopeptidase inhibitor	Omapatrilat	Risk of angioedemas greater in AAs than in EUs for hypertension[77].	NA		
Anticoagulant	Danaparoid	Significantly more EUs than AAs had favorable outcome at 3 months (for ischemic stroke)[76].	292 AAs, 801 EUs	D	No significant difference in other response measures. Other measures (e.g., age) better predictors of outcome[78]. Danaparoid is not hepatically metabolized. Results not replicated.
	Warfarin	Average warfarin dose required to maintain the INR between 2.0 and 3.0 is greater in ACs than in EUs and greater in EUs than in ASs[79]. ACs and Indo-ASs require more warfarin to hold their INR between 3 and 4.5 than do EUs[80].	737 EUs, 58 ACs, 2 ASs; and 715 ACs, 18 ASs, 95 EUs	D	Functional variation in *CYP2C9* affects interindividual warfarin dosing[81,82] but has not been demonstrated to account for differences between populations. Differing average body weight may account for some of the differences between EUs and ASs[83].
Alpha-adrenoceptor blocker	Prazosin	More effective in EUs than AAs for hypertension[76].	1,105	B	Nonadrenergic mechanisms contribute more to blood pressure maintenance in AAs than in EUs[20].
Thiazide (diuretic)	Hydrochlorothiazide	Greater systolic and diastolic blood pressure responses in AAs than in EUs[84].	225 AAs, 280 EUs	B	Probably related to lower bioactivity of endogenous nitric oxide in AAs than in EUs[21].
Calcium-channel blocker	Diltiazem	More effective in AAs than in EUs for hypertension[76].	1,105	B	Probably related to increased predisposition of AAs to the salt-sensitive form of essential hypertension[85].
Beta-adrenoceptor gonist	Isoproterenol	Attenuated vasodilation in normotensive AAs compared with EUs[86–88]. Average dose giving heart rate increase of 25 beats per min is more than 2 times higher in AAs than in EUs[89].	27 AAs, 27 EUs; 18 AAs, 18 EUs; 9 AAs, 13 EUs; and 16	C	Attenuated responses to multiple vasodilators commonly observed in AAs[66]. Mechanisms not fully understood.
Glucocorticoid	Methylprednisolone	Adverse effects (steroid-associated diabetes) more common in AAs than in EUs[90].	9 AAs, 9 EUs	C	Also altered pharmacokinetics between AAs and EUs[90].
Hepatitis antiviral treatment	Ribavirin (interferon alpha)	AAs have lower rate of response to treatment than do EUs[91].	100 AAs, 100 EUs	B	May be due to differing immune abilities. AAs produce more cytokine than do EUs, and EU responders produce less than EU nonresponders[92].
	Interferon	Poorer response in AAs than in EUs[92,93].	4,031 AAs, 62 EUs		

Table 1 (continued)

Drug class	Examples	Difference in response	Sample size	Is the difference real?	Evidence
Prostaglandin analog	Travoprost	Response greater in AAs than in EUs for ocular hypertension[94].	1,381	D	Not replicated, no supporting evidence.
Cytotoxic agents	6-MP, methotrexate and other ALL agents	Significant difference in response by ethnicity for childhood ALL: ASs > EUs> HIs > AAs[95]. EUs have better survival than do AAs and HIs[96]. AA, HI and AI children with ALL have worse survival than do EU and AS/PI children[97].	6,703 EUs, 1,071 HIs, 506 AAs, 167 ASs; 4,061 EUs, 518 AAs, 507 HIs; and 4,952	D	Probably due to differences in quality of health care or therapy.
	Docetaxol and Carboplatin	Greater response in ASs than in EUs with advanced non-small cell lung cancer[98].	68	D	Not replicated. No intermediate phenotypes to support result.
Insulin	Insulin	Insulin sensitivity significantly lower in HIs and AAs than in EUs, and greater acute insulin response in AAs than in HIs[99].	14 EUs, 15 AAs, 28 HIs	C	Differences remain after adjusting for body fat. Results well replicated[99].
Antipsychotic	Haloperidol	ASs with schizophrenia had a significantly higher rating for extrapyramidal symptoms at fixed dose and significantly lower mean required dose than did EUs[100]. Extrapyramidal side effects higher in Chinese than non-Chinese individuals[101].	13 EUs, 16 ASs; and 32 Chinese, 32 non-Chinese	C	No significant difference in haloperidol serum concentrations, although EUs have greater reduced haloperidol concentrations[101].
	Clozapine	ASs showed a greater change than EUs in total scores of the 8-item Brief Psychiatric Rating Scale while receiving a significantly lower mean dose of Clozapine and were significantly more likely to experience anticholinergic and other side effects[102].	17 ASs, 17 EUs	D	Although a relevant drug target polymorphism differs in frequency between EUs and ASs[6] (HTR2A H452Y), it has not been reliably associated with response in both populations.
	Chlorpromazine	EUs received significantly larger maintenance doses than did either ASs or HIs[103].		D	Probably due to different prescribing practices.
	Various	AAs given higher doses than were EUs[104–107].	442; 173; 76 AAs, 88 EUs; and 293	D	
Analgesic	Morphine	Reduction in blood pressure was greater in EUs than in Chinese[108]. AIs more susceptible to depression of respiratory response than EUs[109].	8 Chinese, 8 EUs; and 22 EUs, 22 AIs	D	Conflicting results[16].

If the difference between racial or ethnic groups seems to be real, then it is graded according to how likely it is to have a physiological or genetic basis, as follows: A, there is an indication of genetic causation; B, the association has a reasonable underlying physiological basis; C, the difference is consistently shown but no physiological basis has been demonstrated; D, possibly false positive claim. Racial or ethnic groups: AA, African American; AC, Afro-Caribbean; AI, American Indian and Alaskan Native; AS, Asian; EU of European ancestry; HI, Hispanic; PI, Pacific Islander. ALL, acute lymphoblastic leukemia; INR, International Normalized Ratio (for blood clotting time); NA, not applicable.

one study found significant differences in response to treatment of childhood acute lymphoblastic leukemia among racial or ethnic groups, with greatest response in Asians, followed by Europeans, Hispanics and African Americans[34]. Other investigators, however, found no difference in outcome when African Americans and Europeans Americans were given equal access to the most advanced therapies[35]. It was suggested that the conflicting findings were "possibly due to the specialized referral base of the unique practice of St Jude's Hospital [where the latter study took place], which attracts patients from an 8-state area and provides therapy at no cost to the patient's family"[34]. Nevertheless, there are gene variants that influence drug response that differ among racial or ethnic groups. It is therefore impossible to rule out the existence of such variation, as some investigators seem to have implied. For example, Cooper et al. stated, "Race-specific therapy draws its rationale from the presumption that the frequencies of genetic variants influencing the efficacy of the drug are substantially different among races. This result is hard to demonstrate for any class of drugs, including those used to treat heart failure"[12]. First, therapeutic response may differ among racial or ethnic groups either because of average genetic or environmental differences. Thus, race-specific therapy does not draw its rationale from a presumption of genetic differences. In the case of BiDil, it is not currently known

whether it works differently in African Americans and European Americans because of genetics, environment or both. Second, there is no shortage of gene variants known to influence drug response that have substantial differences in frequency among racial or ethnic groups.

Despite the limited information currently available, we can draw three general conclusions about genetic contributions to differences in drug response. First, genetic differences among groups are graded, as opposed to dichotomous. Second, when genetic factors have a role, identifying the genetic factors themselves so that they can be considered directly will reduce the need to consider race or ethnicity as a loose proxy for predicting drug response. For example, we noted that most individuals from the Arabian Peninsula would respond to codeine, whereas up to 10% of North Europeans would not. A simple genetic test would indicate who would respond, regardless of geographic ancestry. Third, many differences in drug response associated with race or ethnicity are due to environmental correlates rather than population genetic differences. This implies that even when the genetic structure of a test population is taken into account, it may still be appropriate to consider race or ethnicity as a variable in order to take account of the environmental correlations[17].

Pharmacogenetic diagnostics

One common view of the role of pharmacogenetics is that it should provide diagnostic analyses that allow matching of medicines with the genetic makeup of an individual, to ensure use of medicines most likely to be effective and least likely to produce adverse drug reactions (ADRs). This role of pharmacogenetics is best exemplified by a diagnostic test for low-activity variants of the gene *TPMT*, which encodes an enzyme that metabolizes thiopurines, which are used to treat acute lymphoblastic leukemia, rheumatoid arthritis and inflammatory bowel disease[36]. Individuals with intermediate or deficient activity (partially predictable from *TPMT* genotype) risk toxicity at standard doses and must take smaller doses. Another example is the *ALOX5* promoter polymorphism. Here, genotype predicts response to leukotriene receptor antagonists[37]. Individuals without leukotriene activity will not respond as well. Unlike the *TPMT* diagnostic test, this analysis is not currently used in the clinic, probably because nonresponders do not suffer adverse effects from an ineffective drug.

For pharmacogenetic diagnostics to be useful, they must be sufficiently specific and sensitive. This will be a difficult challenge. The predictive values of pharmacogenetic tests will often be low[38], whereas prediction of an ADR, for example, may have very stringent requirements. Ideally, a test for an ADR will have high positive and negative predictive values (the proportion of people with a positive test who will experience an ADR when the drug is administered and the proportion of people with a negative test who will not have an ADR, respectively). For a severe ADR, a high negative predictive value is essential. In some cases, however, positive predictive value will also be important, for example, when alternative medicines are available. Unless there is a high positive predictive value, many individuals will be misclassified as likely to have the ADR and therefore may not get the best treatment.

Will pharmacogenetic tests be equally predictive across different ethnic groups? There are two different reasons why a diagnostic test might perform differently among racial or ethnic groups. The first and most fundamental reason is that underlying physiology may differ among racial or ethnic groups. For example, the variant that influences response to a drug in one racial or ethnic group might not have the same effect, on average, in another group because of different gene-gene or gene-environment interactions. For example, the 3435C→T polymorphism in *ABCB1* has been variably associated with altered drug response[39,40], pharmacokinetics and P-glycoprotein expression[41], but the correlation between the polymorphism and P-glycoprotein levels is not consistent across ethnic groups[42,43]. If 3435C→T is the causal polymorphism (and this has not been proven), then this could be an example of physiological differences across ethnic groups. The second, and perhaps more likely, reason is that the diagnostic test uses a proxy, for example, if it is based on linkage disequilibrium (LD). LD is the nonrandom association of alleles at different polymorphic sites in the genome, and levels are often high across long genomic stretches, making it hard to know whether an associated variant is causal or just a marker for (*i.e.*, usually inherited with) the causal variant. The predictive value of an LD diagnostic test will depend on the degree of association between the markers and the underlying causal variants, and there is considerable variation in the pattern of LD among populations[44]. Unfortunately, diagnostic tests that are based on markers serving as proxies for the causal variants will generally have different predictive properties among different racial or ethnic groups.

One recent example provides a stark warning about the applicability of diagnostic tests across racial or ethnic groups. Abacavir is an effective antiretroviral drug used to treat HIV-1 infection. Approximately 5% of people treated with Abacavir develop a hypersensitivity reaction that requires them to stop taking the drug. Pharmacogenetic studies have identified multiple markers in the human leukocyte antigen (HLA)-B chromosomal region, including HLA-B*5701, that are associated with hypersensitivity to Abacavir in European Americans[45–47] but not in African Americans[46]. Therefore, a pharmacogenetic diagnostic test using this allele would have no predictive value in African Americans. In this case, it is not clear whether Abacavir hypersensitivity has different underlying causes in African Americans versus European Americans. The HLA-B alleles are situated in a tract of ~~200 kb with extensive LD, and is not clear which variants within this tract are responsible for the association in Europeans and Hispanics. Considerably larger association studies or functional studies will be required to determine whether the HLA-B*5701 allele or an associated variant is responsible for the ADR.

These considerations also suggest that in the near term at least, pharmacogenetic diagnostics should rely on validated causal variants rather than either single markers as proxies or genome-wide SNP profiles, both of which will usually rely on LD to generate associations between the markers and the drug responses. Because the degree and pattern of LD typically vary among populations, LD marker-based tests will often need to be adjusted for different racial or ethnic groups. This requires large, expensive studies of many populations.

Genetic subclassification of disease

Common diseases result from complex interactions between genetic and environmental factors. As more is learned about the genetic bases of common diseases, such diseases may be divided into distinct subclasses with similar phenotypes but different underlying genetic bases. In many cases, specific drugs are indicated for specific subtypes of a disease: for example, Herceptin is indicated for the subpopulation of individuals with breast cancer who express *ERBB2*, and Gleevec is indicated for individuals with chronic myeloid leukemia resulting from the *BCR-ABL1* gene fusion. Similarly, two recent studies identified mutations in *EGFR* in lung cancers, which predict response to the tyrosine kinase inhibitor gefitinib (also known by the trade name Iressa)[48,49].

It is unclear how often the underlying genetic bases of disease differ among racial or ethnic groups, but this may occur for some diseases. For example, susceptibility to Crohn disease is associated with three polymorphisms in *CARD15* in European Americans[8], but none of these variants was present in a sample of Japanese individuals with Crohn disease[50]. Another example is a *CCR5* variant that protects against HIV infection and progression. Up to 25% of European Americans are heterozygous with respect to this variant, but it is practically absent in other ethnic groups[51]. The *EGFR* mutations that predict response to gefitinib are more frequent in Japanese individuals, possibly explaining their increased responsiveness.

Even when a genetic variant associated with disease susceptibility is present in multiple ethnic groups, it may have different effects. For example the E4 variant of *APOE* is associated with a substantially increased risk of Alzheimer disease[52], which varies among racial or ethnic groups. Homozygosity with respect to the E4 allele increases the risk of Alzheimer disease by a factor of 33 in Japanese, 15 in European Americans and 6 in African Americans[53]. A more recent study also found differential effects of the E4 allele between Europeans Americans and African Americans[54]. It is impossible to determine from current evidence whether these differences reflect an interaction of *APOE* with genetic background or with environment.

To the extent that progress in understanding the genetic bases of common disease is faster in some ethnic groups than in others, the

ability to genetically subclassify diseases might proceed faster in some groups than others, meaning that treatment can be made more precise in these groups. In this context, it may be a concern that the HapMap project is not sufficiently inclusive.

The HapMap Project is an international research effort to describe the common patterns of human genetic variation in order to facilitate future studies that relate genetic variation to health and disease. The project currently includes European Americans, Africans (the Yoruba in Ibadan, Nigeria), Japanese and Han Chinese but excludes Native Americans and Pacific Islanders, two of the five racial categories indicated by the US Food and Drug Administration and argued by some to be the principal determinants of the geographic component of human genetic variation[17]. Exclusion of Native Americans in particular seems inconsistent with the policy of the US National Institutes of Health to include minorities in biomedical research (there ~4.3 million Native Americans or Native Americans in combination with one or more other races in the US, making up 1.5% of the total population; http://www.census.gov/Press-Release/www/releases/archives/facts_for_features/001492.html). The decision to exclude Native Americans was made after consultation with some representatives of the Native American health research community, who cited concerns about HapMap data being used to facilitate population history studies and comparisons among populations[55]. In a broader sense, given the genetic diversity among African populations, it would almost certainly have been more informative to choose a second African population as opposed to a second East Asian one.

Drug pipeline pharmacogenetics

In some ways the use of pharmacogenetics during the development of potential new therapies generates the most serious concerns because of its potential to influence the medicines that are brought to market. In the past, the basic model in drug development was to find drugs that are as widely applicable as possible, hence the effort to prove efficacy in large, expensive phase 3 trials. Now there is interest in carrying out smaller, less expensive trials using genetics[56]. Although the idea of focusing clinical trials on subgroups of individuals is not new, as stratification by disease subtype has always been a goal of medical research[57], the use of genetics in this context is new. Pharmaceutical companies have long tended, when possible, not to pursue compounds known to be metabolized largely by highly polymorphic systems, such as *CYP2D6*, but pharmacogenetics has otherwise had a small role in drug development. Increasingly, however, there is interest in the use of systematic genetic analyses to identify the genetic causes of variable responses during the evaluation of new chemical entities. Widespread use of such reverse genetic strategies could result in important changes in drug development, including reliance on more focused clinical trials[56].

Early identification of a marker for drug response could lead to smaller phase 3 trials involving those individuals who are more likely to respond. Efficacy pharmacogenetics might lower the cost of phase 3 clinical trials if randomization could be applied to a population of individuals in whom the drug is effective selected in phase 2 trials[56]. This would result in individuals with unfavorable genetic profiles being excluded from trials, even though a proportion of them would probably respond to the drug (albeit less frequently than the target population). There is a risk of creating 'orphan genotypes' that are left untreated for either scientific (difficult to treat) or economic (too small to be economically viable) reasons. Many genetic variants, including DME polymorphisms and drug target polymorphisms, vary in frequency among populations. If a marker for efficacy has low prevalence in a certain ethnic population, that population may be excluded from research or treatment.

How to represent human population genetic structure

It is difficult to address concerns about differences among racial or ethnic groups if there is no agreement about what constitutes a group. This is a contentious issue, and there seems to be little hope the community will soon reach a consensus[14,17]. It may be helpful, therefore, to begin with some areas of general agreement. Most importantly, no matter how groups are defined, most of the genetic variation in the species is due to differences among individuals within groups, not to differences between groups. It is also agreed, however, that individuals with the same geographic ancestry are more similar, on average, than individuals with different geographic ancestries.

The main areas of dispute are how to represent that portion of our overall variability that does correlate with geography, and how important this portion of our variation is in medicine. Risch and colleagues[17] proposed using five racial groups in biomedical research based on continental ancestry. Although this method is easy to implement, it is unclear how well it captures human population structure. A second method, called explicit genetic inference, ignores geographic, racial or ethnic labels and instead groups similar individuals using genetic data[58]. There has been debate about how well self-identified ethnicity corresponds with explicit genetic inference and, more generally, how well we understand the global pattern of human genetic diversity[17,58]. Our view is that worldwide patterns of genetic variation are not well known. Data from Rosenberg and colleagues seem to support the scheme proposed by Risch and colleagues of a small number of groups corresponding largely to continent of origin; in a sample of 1,056 individuals from 52 populations they identified six main genetic clusters, five of which correspond to geographic regions[59]. Although the sample set they used is referred to as a 'diversity panel', geographic sampling is far from comprehensive. The results would be far more graded between groupings, and the groupings themselves might fade or multiply, if more comprehensive samples were analyzed.

Even when there is a generally good correspondence between self-identified ethnicity and explicit genetic inference, we believe that there are contexts where it is still advisable to obtain the most precise information possible about genetic structure. For example, in evaluating new medicines, it would be straightforward to include explicit genetic inference as part of the overall analyses, with a negligible increase in cost and complexity. Groups identified by ethnic or racial labels (or genetics) may themselves be internally structured genetically. This structure would be hard to represent with ethnic labels but is straightforward to represent using genetic inference. For example, estimates of the proportion of European ancestry in African Americans average ~21%, but there is a wide range of ancestry proportions among individuals[60].

The importance of group differences in medical genetics has been the subject of much debate. Cooper and colleagues argue that race is not an adequate proxy for choosing a drug[12]. Although it is true that individual genotype will always be more informative than racial or ethnic labels (for genetic effects), we believe that in some cases, race and ethnicity may be useful biological proxies for the underlying genetic variation. There are many examples of variants that are known to influence drug response and that differ substantially among racial or ethnic groups. Because there are many other variants that are not known, some drug response will correlate with racial or ethnic groups, some of which may be relevant to the selection of treatment alternatives. This source of genetic variation can and should be represented during our period of ignorance of the underlying causal factors. In some settings, this may be best done by explicit genetic inference (*e.g.*, during the evaluation of new medicines), whereas in other settings, self-identified racial or ethnic labels may need to suffice (*e.g.*, routine clinical practice, where explicit genetic inference is not currently practical).

Conclusions

Our aim was to outline how advances in genetics could contribute, even if modestly, to disparities in the quality of health care among different racial or ethnic groups. To the extent that this is agreed to be a serious concern, the solution is straightforward: more and better research in those groups that have been traditionally under-represented in clinical and other biomedical studies. The US National Institutes of Health specifically requires "members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects" (http://grants2.nih.gov/grants/policy/emprograms/overview/women-and-mi.htm). In this spirit, Francis Collins, the director of the US National Human Genome Research Institute, recently outlined a case for a large-scale prospective cohort study in the US to identify genetic and environmental influences on disease, and specifically called for oversampling in ethnic minority groups[61]. Similar European efforts have, however, simply ignored the issue. The UK Biobank project (http://www.ukbiobank.ac.uk/), for example, is sampling minorities in proportion to their representation. This effectively excludes minorities, as the numbers collected will be too small to allow identification of gene-environment interactions specific to the minority groups. We would like to see this decision reconsidered. We welcome the recent proposal from Howard University to begin the Genomic Research in the African Diaspora, which aims to identify and characterize genetic polymorphisms in African Americans and their ancestral populations (http://www.genomecenter.howard.edu/grad.htm).

More specifically, it is important to carry out basic pharmacogenetics research in as broad a range of ethnic groups as possible. It is nevertheless inevitable that diagnostic tests will often be identified in specific ethnic groups, and in these cases, it is essential that the diagnostic be tested explicitly in other ethnic groups, as scientists from GlaxoSmithKline did with Abacavir[46]. In this context, one valuable tool may be the use of healthy volunteers in those cases where drugs can be safely administered, or where probe drugs may indicate the effect of a gene variant on transport or metabolism. The use of healthy volunteers would also facilitate efforts to ensure that functional variation at relevant genes is equally well described in all racial or ethnic groups. Finally, even greater efforts are required to expand the diversity of drug trial populations. The results of such trials could also be interpreted with more clarity, and the effects of genetic structure more systematically assessed, if genetic structure were routinely analyzed in drug trials[58].

Overall, it is difficult to say whether advances in genomic medicine will exacerbate or attenuate health disparities. It seems that no matter how research is done, most medicines will tend to work similarly among different human populations. Because of our youth as a species, most human genetic variation comes from an ancestral source population and is present in most current racial or ethnic groups. But rough statistical similarity in how medicines work among racial or ethnic groups is not always good enough. For example, in the American context, it is both morally and politically unacceptable for the public and private sectors to follow a research agenda leading to medicines that are 5% more effective in European Americans than in African Americans. This sort of an outcome is possible unless there are more explicit efforts are made to ensure that medicines are inclusive.

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