Ethical Dimensions of Disparities in Depression Research and Treatment in the Pharmacogenomic Era

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Introduction

Personalized medicine with its promise of developing interventions tailored to an individual’s health need and genetically related response to treatment might seem a promising antidote to the documented underutilization of standard depression treatments by African Americans. In addition, understanding depression not merely in biochemical terms but also in genetic terms might seem to counter cultural beliefs and stigma that attach to depression when conceived as a mood or behavioral problem under an individual’s control. After all, if there is one thing for which a person is not responsible and cannot be blamed, it is her genes. Nevertheless, for multiple reasons, a personalized medical approach to depression treatment, and its attendant conceptualization of depression and treatment response as genetically influenced, present the risk of exacerbating well-documented disparities in access to, and utilization of, treatment for depression among African-American and Caucasian elderly adults. At the same time, if treatment response is indeed influenced by genetic variation, then the development of effective treatments for depressed minority elders will be all the more important and yet may be impeded by the disparately lower participation rates of racial minority members in research on depression and its treatment. A self-perpetuating and expanding cycle of disparity in effective depression treatment may result.

This paper begins by examining the multidimensional factors associated with disparities in effective treatment of depression among African-American and Caucasian elderly adults. It focuses on the cultural constructs, socioeconomic factors, multiple levels of racism, and stigma attending both mental health issues and older age, and argues that the intersection of these factors may help to explain disparities in the treatment of the depressed elderly. Then, the paper examines the relevance of these factors for ensuring that pharmacogenomic research enrolls and holds the potential to benefit African Americans, as well as Whites. It argues for the scientific and ethical importance of pursuing various paths to address

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multiple levels and sources of stigma and mistrust if pharmacogenomics is to help, rather than exacerbate, disparities in depression treatment. In its final section, seven recommendations are offered to increase the likelihood that developments in pharmacogenomics will reduce disparities in depression treatment.

**Disparities in Diagnosis and Treatment of Depression**

Recent data indicate that while in the U.S. Whites have higher current and lifetime rates of depression than Blacks, depressed African Americans and Caribbean Blacks both tend to have more persistent and severe depression resulting in higher levels of impairment in home, work, and social life than Whites. Although differences among “Black” populations in the U.S. with regard to health conditions and outcomes, as well as sociocultural experiences, should be acknowledged and investigated, well-documented disparities in depression treatment between “Black” populations taken together and their white counterparts are of particular concern.

Older Americans in general are frequently misdiagnosed and undertreated for depression. Among older Americans who suffer from depression, African-American elders are less likely to seek specialized mental health services, but are more likely than other elderly populations to seek depression treatment from a primary care physician. However, primary care physicians recognize and diagnose depression in African Americans, and prescribe antidepressant medications to them, at lower rates than other older Americans. Among African Americans and Caribbean Blacks who have mental health disorders, the oldest and youngest age groups were least likely to utilize any services.

**A Cycle of Disparities in Research Participation and Depression Treatment**

The limited efficacy of currently available treatment in African Americans of any age may also be a factor in their use of depression interventions, though there are conflicting findings regarding the relative efficacy of antidepressants in African Americans and Whites.

Older age may also complicate achieving effective treatment. Treatment of the “old-old,” at least with earlier generation antidepressants, though generally effective, requires a longer period to achieve treatment response and is associated with increased risk of negative side effects, both of which are associated with reduced rates of adherence and effectiveness. Research has also begun to study factors influencing African Americans’ willingness to access psychotherapy and the efficacy of counseling for them. Among African Americans studied, cultural mistrust and rejection of things associated with White culture are strongly associated with preference for an African-American counselor. Disparities of representation in the health care workforce may be particularly acute in mental health services, with 2005 data showing that African Americans comprise 5% of physicians, but only 3% of psychiatrists (per 2002 data) and 2% of psychologists and 4% of social workers (per 2004 data). These disparities may have a disproportionate effect on service utilization and health outcomes, as lack of rapport, trust, empathy, and understanding (i.e., ability to comprehend and relate to patients’ revelations) undermine the effectiveness of a therapeutic relationship.

Similarly, a variety of factors may impede development of more efficacious interventions for African Americans, especially the elderly. The interaction of social, cultural, and historical factors contributes to African-American elders’ reluctance not only to access depression treatment but even to identify themselves as having depression or suffering from a mental illness. These same factors are likely impediments to the involvement of older African Americans in research on depression and treatment response. Indeed, groups frequently underrepresented in medical research include ethnic minorities, women, and the elderly. When a patient falls within several such groups, such as elderly African-American women, the risk that treatments or clinical practice guidelines based on study data will be less applicable to the patient increases exponentially. Thus, it is critical to identify and address factors contributing to such underrep-
presentation in research if effective treatments are to be developed to prevent reinforcing a cycle of African Americans’ reluctance to seek and utilize mental health treatment.

**Contributing Factors in Depression Treatment Disparities and African Americans’ Underrepresentation in Depression Research**

Socioeconomic factors such as lack of insurance, inability to afford copayments for doctors’ visits and medications, and lack of transportation contribute to the differences in accessing depression treatment by African-American elders and white (or other) elders; however, these factors do not fully account for the disparities. In recent years, some research has begun to focus on the role of beliefs, attitudes, and stigma associated with depression treatments in explaining these disparities; yet studies conclude that stigma associated with depression and with particular treatments does not account for disparities in African Americans’ accessing and adhering to treatment regimens. Exploration of the intersection of socioeconomic factors and stigma attending both mental health issues and older age, as well as specific cultural constructs surrounding depression may illuminate the causes of these disparities. Multiple levels of persistent racism and a history of African Americans’ warranted mistrust of the medicoscientific establishment also play a role in depression treatment disparities.

**A History of Mistrust**

Many African Americans have a mistrust of the medical community at multiple levels. This mistrust is predicated upon both personal experience and a history of discrimination, mistreatment, and exploitation perpetrated upon African Americans by members of a once predominantly white male medical establishment. Younger African Americans may have generally positive associations with “Tuskegee” as an institution of higher learning and may have only a vague understanding of the Tuskegee Syphilis Study; indeed, recent studies indicate that the study is not a factor in African Americans’ disinclination regarding research enrollment. Nevertheless, especially for older African Americans, “Tuskegee” may mark a vivid memory of shared cultural experience that evokes negative visceral reactions and mistrust. Moreover, the Tuskegee Syphilis Study is only one among many historical examples that grounds African Americans’ cultural mistrust in an ongoing legacy of exploitation and neglect. In 2001 we witnessed another prominent example: the relative neglect of predominantly African-American postal workers following the anthrax bioterrorism in Washington, D.C. Examination of some African Americans’ responses to what help was offered by government physicians is instructive of the complex way that a history of warranted mistrust fuels suspicions in the face of uncertainty. A Brentwood Post Office worker, for example, quit three days into a prescribed course of Cipro designed to prevent anthrax, saying, “I figure He [God] has a better answer than CDC has….When I wanted to know the long-term side effects of using these drugs, they couldn’t answer….I thought they were using us as guinea pigs….”

Similarly, in the context of depression care, the current reality that pharmacological prescribing for any particular patient remains largely a matter of trial and error may further fuel suspicions grounded in historical mistrust. Claims that a particular intervention (e.g., Celexa) is “worth trying” or is “likely to be helpful in treating” one’s depression are irreducibly probabilistic, epidemiologically based claims. Some commentators have suggested that in the presence of scientific uncertainty, and in light of concern about again being experimented on, some African Americans may be more likely to embrace folk remedies or rely on religious faith than to accept conventional medical interventions. For those who do seek treatment, mistrust may prove a barrier to appropriate diagnosis and effective treatment. Because depression is typically treated with a combination of medication and interactive therapy, mistrust of one’s health care provider would constitute a barrier to an effective therapeutic relationship and may undermine consistent medication adherence.

At the same time, African Americans’ mistrust may be interpreted as a symptom of mental illness and lead to a misdiagnosis of paranoia or paranoid schizophrenia. In turn, fear of being thus diagnosed may prevent African Americans from seeking treatment or being forthcoming with their clinicians. Moreover, African Americans have been targeted by anti-psychiatry movements attempting to fuel distrust of psychiatric and mental health services by means of highly inflammatory charges that psychiatry has racist, genocidal goals involving torturous treatments, attempts at mind control, misdiagnosis of learning disabilities among minority students, and the creation of disorders whose treatment amounts to “mental slavery.” Creating Racism: Psychiatry’s Betrayal, a publication of the “Citizens Commission on Human Rights,” ties psychiatry to mid-20th century eugenic movements in the U.S. and Germany, emphasizes the potential side effects of contemporary pharmacological interventions, and alleges that psychiatry and psychology are “actively and deceptively fostering racism throughout the world.” The “Citizens Commission” is...
a self-described “nonprofit mental health watchdog” group founded in 1969 by the Church of Scientology. Although one of the most prominent participants in the anti-psychology movement, the Church of Scientology is not alone. The “Human Rights Action Coalition” has material on the internet (dating from the late 1990s) that reports its advocacy activities and alleges that “for a long time, African Americans have been primary targets of the mental health system. Organizations like the National Alliance for the Mentally Ill (NAMI), plus federal and state governments, are campaigning NOW to escalate psychiatric oppression of African Americans.”27 These opportunistic anti-psychiatry movements play upon African Americans’ often warranted skepticism of the medical community and serve as an additional cultural barrier to for African Americans of all ages seeking treatment.

Socioeconomic Factors
Socioeconomic factors may operate directly to prevent poor African Americans (and other poor populations) from accessing general health care and mental health services, and also may increase African Americans’ mistrust of entering into the mental health system. Although Medicaid and Medicare provide a mental health safety net to older Americans, resources may be more limited for older adults who are not yet 65. Moreover, multigenerational economic disadvantage may impede older adults’ access to mental health services they can afford, as they may be providing informal childcare or health care-giving. Additionally, the costs of accessing health care services are not merely professional fees, diagnostic tests, and medications; time and costs of transportation may prove prohibitive. Effective treatment for depression frequently involves a combination of pharmacological and psychotherapeutic interventions, and effective “talk therapy” typically involves committing to, and following through on, regular visits with a therapist.28 For depressed individuals the effort necessary to “get it all together” to seek help, especially in the face of economic deterrents, may seem especially daunting.

Socioeconomic factors may, quite reasonably, compound African Americans’ mistrust of coming into contact with health care and other social services. African-American elders report the fear that being diagnosed as mentally ill may result in their involuntary commitment and loss of their home and freedom.29 Such fears may not be unreasonable based upon a cultural mistrust of the medical community in general, fear that engaging with the mental health system may result in a loss of freedom secondary to coercion to participate in, and be compliant with, mental health services, and a specific fear of involuntary commitment.30 Especially for depressed individuals who are not able to access primary care or primary mental health care on a regular basis, the likelihood is increased that they will enter the mental health system in an acute phase that warrants hospitalization. Elders, whose family may be geographically dispersed and whose friends may be in ill health or deceased, may have fewer informal caregivers to call upon to support their efforts to become well without hospitalization. African Americans with high risk comorbidities such as substance abuse, poor health, and/or poverty have an increased risk for depression, and may have fewer socioeconomic support systems, making it more likely that they may be evicted or face foreclosure if institutionalized.31 Finally, in a country that incarcerates African Americans at six times the rate of white Americans,32 it is reasonable for African Americans to attribute particularly negative cultural significance to any involuntary institutionalization. Deprivation of freedom, even ostensibly for one’s own good,33 in a society that condoned slavery of one’s ancestors less than 150 years ago may be fraught with especially negative connotations.

Racism and Its Intersection with Ageism
In addition, for elder African Americans, structural or institutionalized racism is part of their life-long experience. For many, segregated schools and public places, anti-miscegenation laws, and Jim Crowe laws are part of their personal memories. World War II ostensibly integrated African-American and white soldiers, but they returned to largely segregated housing and racially-influenced employment opportunities. In many urban settings, housing — including low-income housing for elders — remains substantially de facto race segregated.34 Such segregated housing is associated with a lack of community-level economic investment and health services, with both market failures and redlining in health care and pharmacy services impeding continuity of depression care.35 Race-based housing segregation is also associated with interpersonal experiences of unfair treatment, which are associated with psychological distress.36 While explicit, legislated racial discrimination has been prohibited, ostensibly race-neutral application of policies and social practices has perpetuated inequality between African Americans and Whites in rates (or levels) of income, home ownership, educational attainment, and employment.

Interpersonal racism — discrimination and disrespect in many obvious or implicit and private, interpersonal ways — has substantial effects on individuals’ daily lives, while internalized racism is inversely related to health. One recent study indicates that per-
ception of racism, particularly in interpersonal health care interactions, is associated with increased mistrust in the health care system. Such findings suggest that mistrust is not an historically induced attribute of individuals or populations, nor even, but the result of personal experience.\textsuperscript{37} 

Racism and ageism may operate for African-American elders as Dorothy Roberts argues racism and sexism operate for women of color: there is not a merely additive effect, but a transformative effect with exponential impact on the lived experience of those occupying several devalued groups.\textsuperscript{38} An older African-American man who, because of his age, no longer seems threatening on a darkened street and no longer prompts a young white woman to cross to the other side of the street, avoids her racist fear only in virtue of being subject to ageist disregard. In viewing an older African-American woman as a matriarchal figure, one may indeed venerate her for her wisdom and life experience, but without specific knowledge of her, such regard is mere ageist, sexist, and racial stereotyping that marks her as beyond her sexual prime and valued primarily in terms of her family or community role. Ageism may cast as beyond their prime a population that because of racism never came into its own and never had access to prime opportunities. Examination of health and health care disparities at the population level affords an opportunity to both tease apart and examine the synergistic interaction of race, age, gender, and socioeconomic, cultural, and economic factors.\textsuperscript{39}

Alternate Explanations of Depression: Aging and Religious Beliefs

The combination of these factors — institutional and interpersonal racism, a history of maltreatment and mistrust vis à vis American health care and research, and, for some, socioeconomic factors — may support the old saw that African Americans, especially older African Americans, have good reason to be depressed. Indeed, being sad, disappointed, and anxious may be quite reasonable responses to the life circumstances and background social conditions of many older African Americans. This fact may complicate their own recognition of the symptoms of clinical depression and may help to explain why African Americans report fewer episodes of Major Depressive Disorder (MDD), but may suffer more chronic depression or dysthymia, as compared to Whites.\textsuperscript{40}

Older adults, and especially African Americans,\textsuperscript{41} may attribute symptoms of depression to normal aging rather than depression, or may attribute some disruptions, for example, of appetite and sleep to medications or other illness. They may delay seeking treat-

ment until the symptoms are severe. Following the loss of a spouse or friends, normal grief, complicated grief, and depression may be difficult to distinguish, though the latter two may benefit from medical intervention. Such events may, in turn, complicate treatment of diagnosed depression. Slowing down or decreased participation in once enjoyed activities, for example, may be perceived as a part of the aging process or as a natural response to the ongoing hardships of life, rather than as symptoms of depression. This naturalizing of depressive symptoms leads to a failure to view them as potentially changeable or treatable. The onward progress of time and aging cannot be halted or reversed; social conditions such as economic hardship or racism are individually insurmountable. So, the depression symptoms attributed to these natural causes, or viewed as natural responses, may be viewed as equally intractable.

In addition, some African Americans have developed belief systems that may serve as barriers to seeking depression treatment. Some attribute mental illness to spiritual problems such as insufficient faith, possession by an occult force, or being under the influence of a spell.\textsuperscript{42} In a study conducted by Marsha Wittink et al., older African Americans reported that depression was a symptom of insufficient or lost spirituality or faith,\textsuperscript{43} and expressed the belief that faith not only is a source of moral strength but also has healing powers. Thus, prayer may be a first course of “treatment” and may delay the seeking of professional medical help for symptoms of depression.\textsuperscript{44} While turning to prayer or spirituality in conjunction with other depression therapies may be appropriate and helpful, the authors suggest that such understandings of the etiology of mental illness stigmatize depression by blaming those who are depressed for their lack of faith and placing the responsibility for their healing upon them. Such self-blame may compound delay or avoidance in seeking mental health treatment, as the depressed may feel even worse in supposedly having to confront or admit their faith-related failings.

Layering of External and Internal Stigmatization

Despite attempts of the past century to explain mental illness in medical, physiological, and specifically neurochemical terms, stigma is still attached to mental illness by people of all sociodemographic characteristics. Depression and dysthymia are no exception, and may even be more challenging for some to recognize as diagnosable and treatable illnesses because their symptoms lie at one end of a spectrum of “normal” emotional responses. Unlike other acute or chronic conditions, mental illness is often perceived by the public as a behavioral issue that is within a person’s
control, thereby further stigmatizing mental illness by casting the sufferer as culpable, blameworthy, and unsympathetic. Whether recognized as having an illness or not, people with mental illness are often assumed to be incompetent, unintelligent, or violent, stigmatizing attributes which can interfere with their ability to secure employment, stable relationships, and housing.

In response to the stigma that may accompany a mental health diagnosis, people with mental illness may internalize the negative stereotypes associated with a psychiatric condition. They “may begin to believe that they are less valued because of their membership within this stigmatized group and may suffer negative emotional reactions such as diminished self-esteem and self-efficacy.” This internalization of social stigma may also lead to social avoidance due to feelings of shame, guilt, hopelessness, decreased self-esteem, and isolation, which in turn may further impede the acquisition of timely and appropriate mental health services and cause an escalation in symptoms. Rather than relieving personal responsibility for one’s mood, inactivity, and other symptoms, the diagnosis of depression may stigmatize those diagnosed. Where for other conditions diagnosis grants permission to occupy the sick role and serves as a gateway to treatment, for depression, diagnosis itself may stigmatize, confirm a negative social role (or impose a new one), and serve as a barrier to seeking treatment.

In the United States generally, old age carries similar negative connotations or stigma. While some cultures venerate old age, the U.S. is in many ways a youth-oriented culture that idealizes independence, action, energy, and productivity. The conditions, qualities, and even virtues associated with older age are often denigrated. Opportunities for new social affiliations and other bases of self-esteem are expected to decline with age. Older women especially experience a decline in their experience of being found physically attractive, which is stigmatizing in a beauty-oriented culture. The elderly are often viewed (stereotyped) as inactive, used up, and unproductive. Aging reminds us of the dependence that all who live long enough will eventually experience. Many feel their current (younger, vital) self-identities threatened by the prospect of their eventual dependency to the point of disparaging growing old. Many of the negative effects of growing older could be mitigated by changed social attitudes and environments, as well as the provision of adequate health care. Instead these negative associations seem to be considered as inevitable as aging itself. One result is that the stigma of old age is often internalized and incorporated into the self-image of the elderly.

Helen Black et al. report that older African-American women experiencing depression may face a particular double bind in acknowledging their symptoms and seeking treatment. Ironically, for some of them, not negative stereotyping, but the positive attitudes and behaviors associated with female role models – e.g., women depicted in African-American history, literature, song, and religions — may constitute a barrier to seeking mental health care. These positive images may create unrealistic expectations that African-American women should care for and inspire others with their strength and fortitude. As a result, “silence and strength regarding depression seem to remain an expectation, if not a cultural ideal” for older African-American women. These expectations, in turn, may serve as both social and internalized barriers to seeking depression treatment, as doing so would risk loss of social regard and sources of self-esteem.

The consequences of not participating in depression research may be even greater, as a lack of appropriate treatment can lead to greater despair and isolation, which can lead to greater depression, which further impedes one’s ability to pursue depression treatment. The prospect of developing personalized medical interventions, or at least interventions tailored to African-American populations, would seem an antidote to this downward spiral of research underrepresentation and subsequent undertreatment. But the participation of African Americans is a prerequisite, and additional factors may serve as barriers to African-American participation in pharmacogenomic research.
From Treatment to Research: Reluctant Participation and Underrepresentation

For all of the historical, cultural, and psychosocial reasons that have been discussed, African Americans, especially the elderly, underutilize depression interventions and are underrepresented in depression research. Their lack of representation in all sorts of clinical trials leads to research findings that are not necessarily generalizable to older African Americans, which in turn decreases the availability of effective medical interventions and leads to poorer overall health outcomes. The consequences of not participating in depression research may be even greater, as a lack of appropriate treatment can lead to greater despair and isolation, which can lead to greater depression, which further impedes one’s ability to pursue depression treatment. The prospect of developing personalized medical interventions, or at least interventions tailored to African-American populations, would seem an antidote to this downward spiral of research underrepresentation and subsequent undertreatment. But the participation of African Americans is a prerequisite, and additional factors may serve as barriers to African-American participation in pharmacogenomic research.

The reasons given by African Americans for not participating in genetic research are similar to those given for not participating in medical research generally: distrust of the medical establishment and fear of being used as “guinea pigs,” lack of knowledge of medical terminology and systems, a perceived risk of minimally invasive procedures, and investigators’ lack of cultural competence in recruitment and research. However, African Americans report additional concerns regarding the potential use of genetic research and information to discriminate against them. Richard Zimmerman et al. suggest that the reluctance of African Americans to participate in genetic research centers on two concerns shared by white counterparts – discrimination in insurance and employment — and one that is distinctive: racially based eugenics. Study respondents report fear that genetic information would be used for population control and genocide by identifying and then not developing treatments for diseases specific to African Americans. Additionally, Lorraine Frazier et al. suggest that “a lack of understanding of genetic concepts,” a fear of having passed on a disease to their offspring, and a “lack of confidence in the interpretation and validity of genetic test results” may contribute to lower participation in genetic research by older Americans in general.

A dearth of research explores whether African Americans’ attitudes toward pharmacogenomic research would differ from their attitudes toward genetic research on disease risk. Some commentators suggest that being identified as a high/fast/effective or low/slow/poor metabolizer, or as a nonresponder, would not be as stigmatizing as being identified as at increased risk for disease. Nor would such information likely carry the same psychological distress as living with that increased disease risk. Nevertheless, expression of concern that genetic information may be used to identify and not seek to treat conditions prevalent among African Americans suggests that African Americans may be suspicious of pharmacogenomics’ research agenda and methods.

Pharmacogenomics, Personalized Medicine, and Problems with Populations

Pharmacogenomics is the study of the relationship between genetic variation among individuals and their drug responses, with the goals of developing new drugs and guiding prescribing practices. Assessment of drug response involves assessment of the drug’s efficacy — the degree of positive response to it — and its toxicity or production of adverse side effects.

Drug response may be affected by myriad factors at various levels ranging from the social and behavioral (e.g., ability to purchase and adhere to prescribed doses) to biological features of individuals (e.g., age and co-morbidities), to specific pharmacokinetic processes, especially drug metabolism. Genetics can more or less directly influence factors at each of these levels; however, pharmacogenomics focuses on genetic variation influencing drug absorption, distribution, metabolism, and elimination.

Genetic variation refers to differences in and between individuals’ genomes, and also to the patterns or frequency of variations in the genomes of groups of individuals. The basic methodology of pharmacogenomics involves sorting people according to their genetic variation and drug responses. The AmpliChip CYP450 Test, produced by Roche and approved by the FDA in 2004, for example, identifies variation in two genes — CYP2D6 and CYP2C19 — which are associated with metabolism of at least 50 drugs. Of relevance for patients with depression is that variation in the CYP2D6 gene can result in low/slow/poor, normal/rapid/ extensive, or ultra-rapid metabolism of some antidepressants. Those who metabolize antidepressants slowly are at increased risk of having the drug remain in their blood for a prolonged period, which in turn increases their risk of adverse side effects. Ultra-rapid metabolizers may not achieve sufficiently high concentrations of the drug in their blood to enjoy any, or the desired level of, therapeutic effect: the drug is metabolized and eliminated too quickly. African Americans, for example, are reported
to have superior and faster response to tricyclic antidepressants than their white counterparts, but also to develop more toxic side-effects, perhaps explained by the higher average concentrations of the drug in their blood.\textsuperscript{61}

Though environmental pressures cause some changes in an individual's genome across her lifetime, an individual's particular set of genetic variations or genotype is the result primarily of inherited genetic contributions. Historically, geography influenced mating and migration patterns with the result that today people with a specific continental ancestry (e.g., Africa) exhibit frequencies of genetic variation that differ from those with a different continental ancestry (e.g., Asia). Members of different ancestry groups are slightly more different from each other than they are from other members of the same population. Pharmacogenomic research reveals and relies upon the fact that genetic variations associated with different drug responses occur in varying frequencies in different continental ancestry groups. However, when enrolling subjects in research and reporting results, pharmacogenomics uses race as a rough approximation for individuals' continental ancestry. Similarly, in the absence of a direct test like the AmpliChip, when clinicians apply pharmacogenomic findings to their patients, they rely on the self-reported or attributed (based on phenotypic characteristics) race of their patients to predict their drug response.

The inferences being made from phenotype/self-report, to race, to continental ancestry, to variation in genotype — both in enrolling research subjects and in treating patients — allow for substantial “slippage.” Because in pharmacogenomic research the pre-existing categories employed — races and to a lesser degree ethnicities — are not genomically defined, “it is important to keep in mind that the ways in which individuals are grouped together determine the genetic frequencies that are attributed to such populations, not that genetic frequencies determine how to group individuals into populations.”\textsuperscript{62} Despite studies showing that self-reported race aligns fairly well with continental ancestry determined by genotype,\textsuperscript{63} racial admixture increasingly complicates attribution or self-report of continental ancestry based on skin pigmentation or received views of family history and ancestral origins.\textsuperscript{64} Even if the “gold standard” of direct genomic testing (e.g., something like the AmpliChip) is employed clinically to determine the presence or absence of a particular genetic variant in a patient, the meaning of the variant will have been established based on studies that employed race (or perhaps continental ancestry) to enroll subjects from whom the probabilities of various genotype-treatment response associations were derived. Imprecision in, imprecision out. Indeed, it is critical to understand that even upon realization of its full promise, personalized medicine will remain probabilistic and epidemiologically-based, just as evidence-based, non-genomic interventions are today: a clinical trial of a new drug yields only an average result across a given population of patients, and a treatment recommendation based on that result still holds only a population-based probability of success in the individual patient. Results of a study with subjects exactly like the current individual in all known relevant ways, including the same relevant genetic variation and environmental factors, would still be only an average result that predicts a specific probability of successful treatment when the intervention is applied in the current individual.

For the foreseeable future, for reasons of cost and the state of the science, clinicians will most often not employ direct genomic testing, but rely on attributed or self-reported race as surrogates for the actual genetic variations of their patients. With identification of an increasing number of genotype-treatment response associations, this will likely change, especially if insurance reimbursement for direct testing for treatment response is shown to be cost effective in avoiding the expenses of adverse consequences or “wasted” medications as clinicians pursue their current trial-and-error approach to finding an effective drug for their patients. Though not singular, current depression treatment is an obvious case of such trial-and-error attempts.

If African Americans — especially those acutely cognizant of the legacy of having been experimented on as “guinea pigs” — interpret clinical uncertainty as evidence of such experimentation (like the postal worker who refused Cipro because the CDC lacked certainty about its effects and effectiveness), pharmacogenomics’ promise of reducing such uncertainty should eventually result in their increased utilization of antidepressants. This positive result assumes, however, that the genetic variations African Americans exhibit are sufficiently well-characterized to ground accurate, clinical meaningful interpretation. Thus far, however, fewer studies of drug response associated with CYP2D6 and CYP2C19 have been undertaken in African Americans and Hispanics than in Whites and Asians.\textsuperscript{65}

In another genetics context — testing for breast cancer risk — we can observe the negative effects of low African-American research participation and relative lack of meaningful genetic information. In the mid-1990s genetic variation in the BRCA1/2 genes were found to be associated with an increased lifetime risk of breast cancer. Yet, a 2005 report by Rita Nanda
et al. begins, “Ten years after *BRCA1* and *BRCA2* were first identified as major breast cancer susceptibility genes, the spectrum of mutations and modifiers of risk among many ethnic minorities remain undefined.”66

The authors conclude that their data “underscore the need for larger studies among minority populations in the United States,” but refer to “documented racial/ethnic disparities in patterns of referral to cancer risk clinics.”67 Of the hundreds of variants in *BRCA1/2* genes that have been identified, over 50% of those detected in African Americans have been found to be family-specific; in those cases breast cancer genetic testing would require complete sequencing of *BRCA1/2*, a more expensive and less accessible undertaking than even the direct *BRCA1/2* testing commercially available from Myriad.68

Social and economic status (SES) is assumed to play an overwhelming role in race-associated health disparities; however, after controlling for SES, racial disparities in health often remain. In identifying racial differences, “race” may correlate with multiple confounding factors — not just continental ancestry, but also multiple aspects of current social environment, and biological adaptive responses (including gene expression) to current and accumulated generational environmental pressures. It is reasonable to suppose that these factors affect the onset and experience of depression, and response to treatment, especially given depression’s association with multiple other conditions and their treatment.

At the same time, discovery that Ashkenazi Jews are ten times more likely to have *BRCA1/2* mutations than the general population illustrates potential repercussions of identifying a socially visible group with particular, meaningful genetic variations. Especially in light of the impact of 20th-century eugenics on Jewish populations, identification of “the Jewish gene for breast cancer” prompted concern about stigmatization and discrimination in insurance and employment and with regard to more informal social affiliations and institutions, such as reduced marriage prospects for Jewish women with “the BRCA gene.”

Despite differences between research on disease risk and on treatment response, and between the stigma and discrimination experienced by both Ashkenazi Jews and African Americans, these social outcomes of *BRCA1/2* research may fuel concerns African Americans report about participation in genetic research. A 2004 meta-analysis, for example, found that two-thirds of 42 gene variants associated with drug response showed a significant difference in frequency between people of African and European ancestry, with those of European ancestry more often having a favorable response.69 If the “nonresponder, difficult to treat genotype” or “prone to side effects genetic variation” were associated with African-American race, these stigmatizing labels could be added to the stigma of race, age, and depression, increasing the burdens of stigma for depressed African American elders. In a similar vein, studies concluding that African Americans need to be treated with higher doses of antipsychotic drugs than other populations would feed anti-psychiatry sentiments and mistrust of psychiatry’s alleged proclivity to diagnose African Americans with paranoia and schizophrenia.70

Perhaps the greatest ethical concern is the possibility that the pharmacogenomic significance of genetic variations that are more prevalent in African Americans would not be pursued. This could be for two reasons. First, there is the difficulty to date of enrolling a sufficient number of African Americans (or more precisely, individuals with the genetic variation of interest) to enable identification of accurate genotype-drug response associations. As a result, in the absence of accurate scientific information, clinicians may rely on unintentional and unchallenged, but racist biases in treating patients.71 Genetics’ and pharmacogenomics’ emphasis on the importance of group differences may — though we know of no empirical research exploring this — reinforce clinicians’ reliance on culturally received views of racial differences, at least until these sciences supply more accurate understandings of population-treatment associations.

A second reason that genetic variations more common among African Americans might not be pursued is the possibility that once the drug response-relevant meanings of a large percentage of genetic variations is established, the profit-oriented motive to character-
ize the meaning of a smaller percentage of variations — or to develop drugs that are effective in individuals exhibiting those genetic variations — could be significantly reduced. If these “orphan genotypes” roughly mapped onto portions of the African-American population, the concern African Americans expressed — that genetic differences would be identified and used to avoid treating conditions of particular interest to them — would be realized. Pharmacogenomics could become one more branch of medicine in which they face health care disparity.

Disparities in depression treatment of older African-American and white adults provide an excellent lens through which to examine the complicated interactions of biologic, social, and environmental factors of which pharmacogenomics must take account. The elderly have been recognized to be hypersensitive to many drugs for multiple biological reasons including the slower absorption and metabolism of drugs and, with the elderly’s increased number of co-morbidities, increased incidence of drug-drug interactions. Social and economic status (SES) is assumed to play an overwhelming role in race-associated health disparities; however, after controlling for SES, racial disparities in health often remain. In identifying racial differences, “race” may correlate with multiple confounding factors — not just continental ancestry, but also multiple aspects of current social environment, and biological adaptive responses (including gene expression) to current and accumulated generational environmental pressures. It is reasonable to suppose that these factors affect the onset and experience of depression, and response to treatment, especially given depression’s association with multiple other conditions and their treatment (e.g., cardiac and kidney disease, obesity, and diabetes). Despite psychiatry’s attempts to standardize diagnostic criteria, variation in diagnosis of depression — and the subjective nature of many clinical and patient-reported assessments of treatment response — confound mental health research in ways and to a degree that do not affect, for example, studies involving hypertension or diabetes. As mentioned, physician prescribing practices and patient adherence to a prescribed regimen — and thus the social, cultural, and economic factors influencing these — also confound pharmacogenomic study of treatment response.

While attempting to control for all of these confounding factors when trying to isolate and identify gene-drug response associations is highly desirable methodologically, it is exceedingly difficult especially in the context of depression research. Moreover, these are factors that will continue to influence the clinical application and patient uptake of pharmacogenomic findings. Therefore, pharmacogenomic research on depression treatment is an arena ripe for development of what has been termed an “integrated science of the determinants of disease” that includes “new integrative, life course and intergenerational scientific models that will seek to understand how the accumulation of social adversities and resources can alter biological processes, including gene expression, to affect health.” Such an integrated research approach would constitute a radical shift from the reductive approaches currently employed in most basic science and clinical research and especially in pharmacogenomics. In the next section we offer recommendations for pharmacogenomics research and its clinical application.

Recommendations for a Pharmacogenomics That Helps to Reduce Health Disparities

1. It is critical to address the multiple barriers to research participation in order to enroll representative populations in research on genetic variation and drug response.

Concern for justice, increased well-being, and good science demands that research populations must be representative of the populations to which findings will be generalized. Depression research and treatment afford a prime example that the underrepresentation to date of older adults and of African Americans leads to study findings that are disproportionately inapplicable to them. Indeed, if pharmacogenomic findings are to benefit minority populations, they will likely need to be overrepresented in order to have adequately powered studies (i.e., adequate numbers to evidence statistically significant effects associated
with genotype). Yet the many reasons for cultural mistrust on the part of African Americans suggest that they may be suspicious of research that oversamples them, i.e., that disproportionately uses them as guinea pigs. Pharmacogenomics thus highlights the urgency of mistrust and barriers to participation. Moreover, pharmacogenomic research reveals that when study populations (e.g., “African Americans” and “Whites”) are inaccurately assumed to be representative of the population(s) to which results will be applied (e.g., Caribbean Blacks, African Americans, European Americans, and admixed populations of African, Caribbean, and European descent), results in clinical application of study findings will likely not be comparable to the research results. Confounding environmental factors, including patient adherence behaviors may be blamed, when imprecise study eligibility criteria would instead be an explanation at least warranting further study.

2. It is critical not to allow reductivist approaches — e.g., a focus on genetic variation and associated drug metabolism, absorption, and elimination — to crowd out attention to systems-level causal contributions to ill health and health disparities (whether these are sociocultural systems, the biopsychosocial whole organism system, or gene-environment interactions). This recommendation is salient at two levels of progress in pharmacogenomics. First, for research, it is critical to recognize that diet, body mass, age, background state of health, environmental stresses, sociocultural conditions, as well as genotype, influence individuals’ drug responses. When trying to understand genotype-phenotype associations, especially when the phenotype is at the micro level of drug response, it is tempting to treat these other personal characteristics and environmental contributions as extraneous factors that must be controlled to eliminate their confounding effect on study results, rather than to view them as relevant contributors to the effect of interest. Especially in depression treatment, where situational influences — like stresses of daily life, past stresses and adaptive responses, and interpersonal therapeutic interventions (even limited interactions with a prescribing psychiatrist or study investigator) — are known to affect mood, it is scientifically and ethically warranted to study those factors, in order to understand both drug response and broader questions of effective depression treatment.

Second, even if accurate, replicable pharmacogenomic findings could be generated without attention to systems-level factors, their clinical application will be undermined by the persistence of barriers to treatment utilization. These barriers operate as mutually reinforcing, cyclical systems. This fact is obvious with regard to sociocultural systems of racism, ageism, socioeconomics, health care, and cultural mistrust.

What is only more recently recognized is how these sociocultural systems influence whole organ systems, for example, through development of both adaptive responses and disease.

3. It follows, then, that an integrated scientific agenda to study the multiple factors associated with multi-factorial complex conditions like depression should be established and socially valued, with adequate funding, prestige in publications, and influence on health care and policy.

The first section of this paper argued that attention to ageism, racism, and the stigma of depression is necessary to conduct depression research that will potentially reduce disparities in depression care. Furthermore, as indicated in the preceding section, without attending to the health-related effects of these and other sociocultural factors, research results will be at best incomplete. Studies increasingly indicate that experiences of racism, ageism, stigmatization, and discrimination — as well as poverty, violence, perceived unfairness, and race — are associated with health status and utilization of health care interventions. Understanding these associations, including the direction of causality (which may, in fact, be bidirectional), is critical to interpreting, replicating, and eventually implementing potentially valuable health-related research findings. Yet, perhaps bedazzled by the apparent clarity of intracellular polymorphisms and proteins, it is easy to neglect the fact that at least across generations, if not lifetimes, these polymorphisms may themselves change in response to the messier inputs of social life in particular environments. In health research generally, even when those interactions are acknowledged, we still have not developed research methods to study interactions at multiple levels — intracellular to inner city — simultaneously.

There is a pressing need to develop such an integrated research infrastructure, as well as integrated multi-level research methods, and models to integrate findings from various kinds of studies. Such an infrastructure will take time to build, require that investigators develop different sets of skills and knowledge, and likely demand changes in research training programs or at least different patterns of collaboration. One-off multi-disciplinary initiatives will not be sufficient; instead, a truly foundational and enduring integrated research infrastructure is required. Within a better integrated infrastructure, comparative effectiveness research might, for example, be valued equally with
the current gold standard of controlled clinical trials. Hypotheses for bench and clinical research might be more directly informed by social science and epidemiological research (and vice versa). Results of employing one methodology might be better integrated with findings generated by other methods to yield new hypotheses and potentially more useful interventions. While precision may increase across some dimensions—e.g., inclusion criteria may move from reliance on self-identified race-based groups to genotype—other research dimensions may become more complicated—e.g., the importance of studying, not just controlling for, culturally influenced beliefs or diet would be recognized and eventually methodologically accommodated. Until such an infrastructure can be realized, perhaps modesty with regard to individual research programs and methods is not merely a desirable half measure, but an actual prerequisite for such future integration.

4. A health disparities impact statement, modeled on environmental impact statements, should accompany research proposals and treatment guidelines reflecting research outcomes.77

As pharmaceutical companies and investigators capitalize on the existence of relevant genetic variations, priority in drug development may be given to one group over another. The convenience and potential profit of focusing on genetic variations known to be meaningful may be exacerbated when those variations are associated with a social group that tends to have greater ability to pay for cutting edge prescription medication, thereby exacerbating health and healthcare disparities associated with SES.

Investigators should be prompted, in the design of their proposals, to anticipate the effect of possible findings on existing health disparities. The 2011 Department of Health and Human Services Action Plan to Reduce Racial and Ethnic Health Disparities states that program grantees “will be required to submit health disparity impact statements as part of their grant applications,” but no detail regarding the content of such plans is provided.78 In various fields—from environmental protection to information technology to military intervention—requirements to develop an impact statement present an opportunity to anticipate effects of proposed action and develop plans to mitigate negative effects. An impact statement typically states the anticipated benefits and harms of an action (e.g., conducting research) on the community (variously and relevantly defined, perhaps by geography, health condition, or sociodemographic features) in which the action is undertaken. It includes a plan to mitigate anticipated harms and enhance benefit. Contemplation of the “ripple effect” of the proposed action beyond the community most directly and obviously affected is encouraged.

A health disparity impact statement might encompass two components: first, plans to assess the impact on existing health disparities of the proposed research, and second, impact of the anticipated outcome of the research. A study enrolling African-American and white elders in a pharmacogenomic study of response to Antidepressant A, for example, might seek to measure—or at least contemplate and prepare for—the effects on disparities in depression treatment of community education regarding depression and genetics and subsequent recruitment activities, and of enrolling individuals not previously receiving depression treatment. There may be effects on other disparities in health care (if recruited individuals are, for example, referred for treatment regarding other conditions evaluated during eligibility screening, e.g., blood pressure control), as well as impact on relevant attitudes such as trust in the health care system and investigators and attitudes toward research participation, mental illness, and genetics. Even if there is no research interest or available funding for measuring/studying

Similar to the “Points to Consider” suggested for Institutional Review Board review of genetic research during the 1990s, the primary goal of developing a health disparities impact statement is to prompt investigators to consider explicitly the impact of their research on health disparities. Doing so may result in direct research attention to these disparities or introduce safeguards within the study, may suggest additional future research questions, or may gradually lead to a less reductionist research paradigm or to a research agenda that explicitly seeks to address health disparities.
such effects of the research process, making the effort to anticipate potential harms and benefits, and consider possible investigator and institutional responses to the effects of research is a matter of practicing sound preventive ethics and raises awareness of the potential impact on health disparities of the research enterprise itself.

The second less obvious, but perhaps more important component of a research project’s health disparity impact statement should include reflection on the effect of anticipated findings of the proposed study. If, for example, the study seeks to establish that Caribbean-American elders metabolize antidepressant A more slowly than their counterparts of European ancestry, the disparity impact statement should address eventual clinical uses of this information (if it were appropriately replicated and validated). Possible health disparity impacts could include effects on access to the drug (for example, if voluntary or mandatory black box warnings or other advisory statements regarding prescribing practices are instituted, or if its status on formularies in health care institutions serving Caribbean-Americans were altered). In addition, self or social attributions of potentially stigmatizing labels of being “difficult-to-treat” might exacerbate existing disparities in depression treatment, while increased clinical vigilance regarding possible adverse reactions may increase patients’ trust in clinicians or increase their mistrust of pharmaceutical interventions. Moreover, the statement should consider the potential impact of failing to achieve the study’s aims, as well as the discovery of incidental findings.

Similar to the “Points to Consider” suggested for Institutional Review Board review of genetic research during the 1990s, the primary goal of developing a health disparities impact statement is to prompt investigators to consider explicitly the impact of their research on health disparities. Doing so may result in direct research attention to these disparities or introduce safeguards within the study, may suggest additional future research questions, or may gradually lead to a less reductionist research paradigm or to a research agenda that explicitly seeks to address health disparities.

Furthermore, development of clinical practice guidelines or a health system’s “formulary” of pharmacogenomic tests should consider whether health disparities will be reduced or increased by particular decisions. An especially strong justification should be required for decisions that would exacerbate health disparities, e.g., by failing to include an antidepressant that is shown to have favorable response primarily among individuals who are systematically undertreated. Requiring a statement of anticipated impact would render the decision-making process and choice-consequence dyads more transparent, provide opportunity for comment and potential remediation, and establish an hypothesis regarding health disparity impact that may be tested as the research or intervention is implemented. Indeed, in the context of health disparities research, the pharmacogenomic enterprise itself becomes part of the environmental context. To the extent that pharmacogenomics appears to exacerbate racism, ageism, or creates a new mode of stigmatization as a “nonresponder” with “recalcitrant” genes, there is reason to believe it will exacerbate health disparities. This is especially important in the context of developing treatments for depression, as the prospect of benefit from treatment — the encouragement or discouragement of patients’ realistic expectations and hope — is relevant to outcome, no matter how low or high-tech the therapeutic modality.

5. Public policy should strive to avoid creation of new genotype-based disparities or so-called orphan genotypes, while employing genomic and other scientific findings to reduce existing disparities.

Identification of genotypes associated with favorable drug responses may lead to the exclusion of those with less favorable genotypes from drug trials, even though some of them would likely respond to the drug. As a result, effective and largely nontoxic interventions may be developed for those with these favorable genotypes or for the majority (and largest market share) of genotypes, thereby leaving those with unfavorable or less prevalent genetic variations with fewer (or no) effective treatments. (Of course, such “minority genotypes” will not necessarily coincide with — or be found in — individuals in socially recognized racial or ethnic minority groups; however, in cases where such a coincidence does occur, health disparities would be exacerbated.) Some have suggested that legislation similar to the Orphan Drug Act of 1983 be enacted to alleviate this problem by providing incentives to companies who would otherwise find research regarding small market share genotypes unprofitable.

Concern for the impact on health disparities should inform the overall pharmacogenomic research agenda, including the temporal and funding priority given to particular questions, choice of study populations, and methods (e.g., genome-wide or candidate gene approaches), as well as specific policies regarding study conduct (e.g., minimization of potential harm to communities as well as individuals, or return of results and incidental findings). Public pressure and policy should encourage market-based pharmaceutical companies to use pharmacogenomics to develop products that reduce disparities. Incentives might be
built into research funding or the drug approval process to direct study to less prevalent genetic variations. Incentives exist and could be harnessed to encourage companies to “rescue” drugs that did not seem promising for treatment of “the general population” but that received favorable treatment responses in some portion of the study population and that, upon further well-designed investigation, might help to reduce health disparities. It must be emphasized that only well-designed studies should be encouraged to examine and rescue such drugs. The first instance of such rescue — the study and FDA approval of BiDil as a “race-specific drug” — is instructive regarding the fallacies and pitfalls to avoid, and illustrates the importance of addressing both African Americans’ mistrust of medical science and barriers to implementation of a nonreductionist research methodology.

Approved and marketed “for the treatment of heart failure in self-identified African-American patients when added to standard heart failure medicines,” BiDil combines in one pill two readily available generic drugs in quantities not available generically. Its approval for race-specific use extended its patent for an additional 13 years, delaying development of a generic, while its lack of direct dosing comparability to its two generic components complicates their prescription as a less expensive alternative. It is suggested that these details of BiDil’s constitution and development were driven by considerations of profit, not science or concern to address health disparities.

Testing of BiDil in a 2001 study enrolling only self-identified African Americans was based on underpowered post hoc subgroup analysis of two non-race-specific trials from the 1980s. That analysis appeared to show that African Americans had benefited from BiDil, while Whites fared better with the ACE inhibitor, enalapril. As with most post hoc subgroup analyses, there is substantial likelihood that statistically significant but arbitrary group differences were generated by chance and that genuine differences between groups were not identified. Despite evidence of baseline differences along multiple sociodemographic and medical dimensions between the self-identifying African Americans and Whites in the 1980s trials, the subsequent focus on racial difference prevented further inquiry into the underlying factors that might be associated with different treatment response. In the rationale for the 2001 single-race study — and implicitly in media reporting of study results and subsequent marketing of BiDil — apparent racial difference was assimilated to, or treated as a marker for, essential biological or genotypic difference, whereas self-reported race could as justifiably have served as a marker for sociodemographic variables and social-environmental exposures. Marketing BiDil as the first drug targeted for African Americans, however, has been a largely ineffective strategy. Perhaps because of African American’s deeply rooted mistrust in the medical-scientific enterprise, it seems that many are skeptical of drugs developed just for them and would prefer to be afforded the same medical care as Whites. There might be greater uptake of BiDil among African Americans if it had been tested as an adjuvant therapy in a general population trial, not only because they might be more trusting of the trial results, but also because the results might have shown the value for all patients of including BiDil, thereby allowing the drug’s patent to expire and reducing its cost through the development of competing generics.

6. In clinical decision making and decisions regarding inclusion of drugs on institutions’ formularies, pharmacogenomic findings regarding treatment response should be used to improve individual care, by directing interventions to those who are likely to respond positively and avoiding the use of interventions in those at increased risk for serious adverse effects; however, care must be taken not to categorically deny an intervention to an individual whose genotype indicates a relatively lower probability of positive treatment response if (a) the intervention is otherwise available, (b) no other intervention has been developed that is deemed (more) effective for individuals with that genetic variation, and (c) the risk or burden of the intervention to the individual — i.e., the probability and magnitude of toxicity — is not unduly burdensome given the possibility of benefit. Moreover, it may be argued that, after a thorough informed consent discussion of risks and potential benefits, the individual should be left to assume those risks and not be denied the opportunity to seek remote benefit when no other good alternative exists, especially when others are offered access to the intervention. At least when the intervention with remote prospect of benefit would be undertaken at her own expense, it would seem quite reasonable to allow the patient to assume the risks. However, most patients — from those with lower socioeconomic status through the middle class — would be hard pressed to afford the full cost of many interventions. Further, for at least some condition-treatment pairs, like pharmacological treatment for depression, the greater risk of adverse responses might increase the likelihood of nonadherence, further limiting the intervention’s already more marginal potential benefit. Moreover, it may seldom be the case that such marginal potential benefit interventions would be entirely at the patient’s own expense. If severe side effects resulted, demands
would likely be placed on the health care institution or insurance plan. It is reasonable for insurers and health plans to consider these costs in making coverage decisions; however, decisions to deny one individual, on the basis of her genotype, an intervention available to others cannot be made lightly or categorically, and appropriate appeal processes should be instituted.

Further, the relevance of existing legislation must be considered. On one hand, it would seem that the Genetic Information Non-discrimination Act of 2008, which bars the use of genetic information to determine health insurance eligibility or coverage terms, would prohibit use of pharmacogenomic test results to deny to a particular patient coverage for a specific antidepressant, for example, when it is part of the plan’s covered package of treatments. On the other hand, it might be possible for health plans to argue that the particular antidepressant is not medically appropriate treatment for an individual whose genotype suggests she is unlikely to respond or will suffer severe side effects. Indeed, insurance companies are permitted minimal access to genetic information (test results or family history information) in order to determine medical need. A woman in her late-20s would not typically be covered for annual mammography; however, a strong family history of breast cancer or positive BRCA1 mutation testing could establish her medical need and grounds for reimbursement. Since an insurer is permitted access to genetic information to make such coverage decisions, by analogy a health plan could presumably use results of pharmacogenomic testing to refuse coverage of the hypothetical antidepressant that has a low probability of effectiveness for the particular patient. Similar considerations could be invoked to interpret provisions of the Health Insurance Portability and Accountability Act of 1996 or the Patient Protection and Affordable Care Act of 2010.

7. **Investigators, clinicians, funding agencies, and the media should employ realistic rhetoric to instill in the public realistic expectations of pharmacogenomics and personalized medicine.**

The mapping of the human genome should not have been sold to Congress and the public with oversimplified descriptions of imminent gene therapy (“we’ll go into the patient’s cells, remove the bad gene, and substitute one that will function properly”). Similarly, continued genetic research, especially studies of genetic variation requiring large participant populations, should not seek support with misleading promises of personalized medicine, such as this widely quoted bit of overselling, which was eventually removed from the Pharmacogenomics Knowledge Base, PharmGKB web-site: “Imagine ... being able to find out how a drug will affect you before you take it. [Imagine] ... receiving a medication that is specifically tailored to treat your disease.” Most people may be disappointed to learn that in order to yield a treatment recommendation, even the future “$1000 gene chip” containing all of their genetic information will still be matched with the best information about how past populations of patients — similar in diagnosis, circumstances, and genes — responded to treatment. Treatment of the individual patient will always be an experiment based on the best (probabilistic) information about what may work and what probably will not.

Most patients believe they are entitled to accurate information from their doctors or researchers; most appreciate a hopeful but realistic approach in the recommendation of treatment. Overselling pharmacogenomics in general media, research recruitment, or clinical consultations is a prescription for disappointment and mistrust. Attempting to develop honest, transparent collaborative research and therapeutic relationships — especially with already mistrustful populations — is necessary not only to redress a history of a medicine that went bad and did wrong. Honesty and realism are also necessary to dispel the mythical image of good medicine as all-knowing and certain of its outcomes. The unfortunate corollary of that image is a belief that uncertainty and probabilistic information are marks of a medicine that is not good — incompetent at best, ill-intentioned at worst. Medicine’s inevitable uncertainties are better tolerated in an environment deemed benign or benevolent, not hostile or uncaring. As developments in genetics and pharmacogenomics make evident the probabilistic basis of medical recommendations, and the epidemiological basis of medical knowledge, an inflated view of medicine’s potential and promise may be as unhelpful as outright mistrust of its motives and methods.

The promise and potential hazards of pharmacogenomics bring into sharp relief the necessity, in order to address health disparities, of understanding and addressing the multiple nuanced barriers to encouraging the research participation of elders, African Americans, and others who have been underrepresented in research. Where stigma of the condition under study combines with other sources of stigma, cultural beliefs, and socioeconomic barriers to diagnosis and treatment, the challenge is especially great. Visibly implementing the recommendations offered may help to avoid pharmacogenomics’ exacerbation of both health disparities and mistrust of research and health care systems.
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References
4. In the balance of this paper, we shall adopt the convention of referring to “African Americans” in discussing these disparities and will use the term to refer to the diverse group of “Black” populations in the U.S. We will specify when data or claims refer to specific populations (e.g., Caribbean Blacks) or to older African Americans. J. Miranda and L. A. Cooper, “Disparities in Care for Depression Among Primary Care Patients,” Journal of General Internal Medicine 19, no. 2 (2004): 120-126; see Simpson et al., supra note 1; Williams et al., supra note 3.
7. Id.; see Das et al., supra note 5.
23. See Sanders, supra note 21.
25. Id.; In The Protest Psychosis, Jonathan Metzel details how schizophrenia became a different, socially constructed diagnosis for African-American and white patients, and specifically how its diagnosis in African Americans – both in individual doctor-patient interactions and at a cultural level – reflects racial tensions, the white establishment’s anxieties about racial difference, and fear of African-American rage in response to a racist culture. J. M. Metzel, The Protest Psychosis: How Schizophrenia Became a Black Disease (Boston: Beacon Press, 2009).


29. See Alvidrez et al., supra note 15.


31. See Das et al., supra note 5.


33. Indeed, among the arguments made for preservation of the institution of slavery was the need of the American Negro for the protection and structure afforded by being the property of Whites, who considered themselves a superior race.


38. See Roberts, supra note 19.


40. See Williams et al., supra note 3.


43. Faith and spirituality as used by Wittink et al. referred to faith in God and the power of spirituality and prayer to heal. The article does not name a specific god, nor does it refer to organized religion. Various Pentecostal traditions embrace the view of faith as potentially healing and of the ability to heal—by whatever means (i.e., traditional medical or not)—as a gift from God. See Wittink et al., supra note 6.

44. See Wittink et al., supra note 6; R. K. Zimmerman, M. Tabbara, and M. F. Nowalk et al., “Racial Differences in Beliefs About Genetic Screening among Patients at Inner-City Neighbor-
focusses on genotypic variations that are not tissue-specific, while p-genomics focuses on gene expression in cells of particular tissues (see Buchanan et al., supra note 57). Because our concerns about research participation apply to both domains, however they are defined, and because our focus is on the eventual clinical use of all such research to reduce health disparities, we employ the term “pharmacogenomics” to refer to the generation and clinical translation of information about genetic variation and treatment response. Rothstein and Epps (M. A. Rothstein and P. G. Epps, “Pharmacogenomics and the (Ir)relevance of Race,” Pharmacogenomics Journal 1, no. 2 (2001): 104-108) define pharmacogenetics as the study of inherited genetic influences on drug response, a conception that may resonate negatively with older adults whom Frazier et al. identified as reluctant to participate in genetic research for fear of learning they have passed on a condition to offspring (see supra note 56).

60. Some include a fourth phenotype: intermediate metabolism (between slow and rapid). See Poolsup et al, supra note 9.

61. Id.


65. See Poolsup et al, supra note 9.


67. Id., at 1930.


70. This finding has been disputed by other studies and also has been attributed to differences in clinicians’ attitudes and prescribing practices, rather than to African Americans’ response to anti-psychotic medications. See Poolsup et al, supra note 9.


72. An additional burden for the elderly African-American population is the fact that depression is associated with these conditions or treatment for them, and African Americans experience these conditions at disproportionate rates. Establishing the efficacy of antidepressants in African Americans, especially those middle-aged and older, is thus a necessary feature of adequately addressing multiple health problems facing an aging African-American population and providing them non-disparate care.

73. See Williams et al, supra note 39, at 91.


75. See Williams et al, supra note 39.

76. Id.

77. This recommendation is made by Brody with regard to other types of research that affect health disparities. L. S. Parker and H. Brody, “Comparative Effectiveness Research and Health Reform: Ethical Issues,” Health Progress 92, no. 5 (2011): 64-71.


82. See Buchanan et al., supra note 57.


84. In the 1980s two trials of BiDil (a combination of isosorbide and hydralazine) failed to establish that its effect was comparable or superior to that of an ACE inhibitor, enalapril, for the treatment of heart failure. Most of those enrolled in the 2001 African-American Heart Failure Trial (A-HeFT) were also using ACE inhibitors or betablockers, or both, so that A-HeFT studied and established the effectiveness of BiDil as an addition to standard therapies, which is not the same question the 1980s trials had examined. Whether adding a combination of isosorbide and hydralazine to the current treatment regimens of non-African-American heart failure patients would be beneficial has not been studied in an all-race trial. Evidence that BiDil works well in African-Americans, but not in Whites, is at best ambiguous. G. T. H. Ellison, J. S. Kaufman, R. F. Head, P. A. Martin, and J. D. Kahn, “Flaws in the U.S. Food and Drug Administration’s Rationale for Supporting the Development and Approval of BiDil as a Treatment for Heart Failure Only in Black Patients,” Journal of Law, Medicine & Ethics 36, no. 3 (2008): 449-457.

85. See Ellison et al., supra note 84.

86. Such sentiments were expressed, for example, at the April 7, 2006 conference, Race, Pharmaceuticals, and Medical Technology, sponsored by the Center for the Study of Diversity in Science, Technology, and Medicine of the Massachusetts Institute of Technology, as reported by University of California Hastings College of the Law professor, Osagie K. Obasogie, available at <http://www.biopoliticaltimes.org/article.php?id=2018> (last visited December 5, 2012).

87. There are apparent incentives not to conduct such a study: BiDil is currently approved for marketing to African-American patients, and other patients may be prescribed BiDil on an off-label basis, thereby expanding its market. The generation of evidence that the combination is beneficial in other populations would actually undermine the rationale for FDA approval of BiDil, its patented status, and its marketing strategy. Ironically, showing that BiDil is suitable for the majority would actually undermine the rationale for FDA approval of BiDil, its patented status, and its marketing strategy. However, showing that BiDil works well in African-Americans, but not in Whites, is at best ambiguous. G. T. H. Ellison, J. S. Kaufman, R. F. Head, P. A. Martin, and J. D. Kahn, “Flaws in the U.S. Food and Drug Administration’s Rationale for Supporting the Development and Approval of BiDil as a Treatment for Heart Failure Only in Black Patients,” Journal of Law, Medicine & Ethics 36, no. 3 (2008): 449-457.