Back with a Vengeance: the Reemergence of a Biological Conceptualization of Race in Research on Race/Ethnic Disparities in Health

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Over the last five years, literature on the role of race in biomedicine has exploded. Articles detailing differences in allele frequencies between 'racial' groups have become commonplace in the journal *Nature-Genetics*. The clinical relevance of race/ancestry groupings has been debated in the pages of the *Journal of the American Medical Association (JAMA)* and in the *Annals of Internal Medicine*. The latest issue of the *New England Journal of Medicine* contained a full feature article, one letter and one commentary, all positing a genetic connection between race and disease. The recent approval by the Federal Drug Administration (FDA) of BiDil, a heart failure medication patented exclusively for African-Americans, likely marks the beginning of new era of race-based pharmaceuticals and clinical care. It would not be an exaggeration to say that we are currently on the forefront of a new wave of scientific endeavors, fueled largely by developments in the Human Genome Project (HGP), which will alter the fields of anthropology, population genetics, epidemiology, demography, and medicine for years to come. But to argue that the current developments aimed at elucidating a genetic basis of race/ethnic disparities in health, constitute an entirely new phenomenon, would be to ignore the weight of history connecting race, genes, and disease.

This paper aims to review the major new developments in research on population genetics/biomedicine and race/ethnicity. In doing so, I hope to highlight the importance of critical reflection at every stage of the research process in studies of race/ethnic disparities in health. Throughout the paper, I adopt a constructivist approach to science, recognizing that, just as there are complex interactive feedback loops between biology and culture, there are also feedback loops between *biologists* and culture (Reardon 2005). As much as we might want to pretend otherwise, there are no clear lines between the factual and ideological or between scientific data and cultural bias. Historians of science have been making this point for quite some time and researchers examining the intersection of race, genes, and disease are no exception to this rule, in fact they may just be the embodiment of it.

What are the Claims?

The Human Genome Project (HGP) and its related spin-offs(e.g. the Human Haplotype Map (HapMap) project) are the engines behind the current increase in race-gene-disease research. There are three main claims that have been put forth in the literature. They rest on the premise that an understanding of population genetic structure can: 1) assist in inferring human evolutionary history; 2) help to identify medically important genotypes that vary in frequency across populations; and 3) help to elucidate the basis for racial disparities in health. These three claims are different but also inter-related. Demographers, and those who study racial/ethnic disparities in health, are most interested in Claim 3. But as we shall see, empirical evidence for Claim 3 is highly dependent on understandings put forth in Claims 1 and 2.

Claim 1: Ancestral Origins

The possibility that geographic ancestries of individuals can be inferred from genetic markers has received a great deal of attention in both the popular and academic press. In a recent PBS special hosted by Henry Louis Gates, the chair of the African Studies department at Harvard University, nine prominent African-Americans, including Oprah Winfrey and Gates himself, were genotyped to determine their ancestral origins. The first method commonly used traces an individual's ancestors through analysis of Y chromosome DNA, which follows the paternal line, i.e. one's father's father's DNA. The second method uses mitochondrial DNA analysis (mtDNA) and traces ancestry via the maternal line. If one traces both lines back six generations, an individual will be linked to 2 of his/her 64 great-great-great-great grandparents. The other 62, while equal contributors to our genetic make-up, are not accessed (Duster 2006). As a way to fill in these holes, a third technology has been developed that attempts to ascertain ancestry through admixture mapping with genetic markers such as ancestry informative markers (AIMs). AIMs examine a groups' relative sharedness of genetic markers found on the autosomes (the nonsex chromosomes inherited from both parents). AIMs are shared across all human populations (with one known

exception) but they differ in frequency between predefined "populations." Geneticists examine the rate of incidence across different groups, rather than the presence or absence of specific alleles, to determine population clusters and an individual's placement within them.

In the PBS special, Gates has several prominent geneticists use these three technologies to trace the ancestry of the participants back to particular regions in Africa, and in most cases, back to regions in Europe. In discovering his genetic origins, Gates declared the technology "a miracle," even though he wasn't thrilled with the results (it turns out that 50 percent of his ancestors are likely European). But Troy Duster, past president of the American Sociological Association, who has monitored issues surrounding race and genetics, was less impressed. In a critical assessment of the program, Duster questioned the validity of "the miracle," arguing that admixture mapping is highly sensitive to several methodological decisions (Duster 2006). With AIMs technology, an individual's ancestry is ascertained by comparing their genetic make-up to that of reference populations, which consist of DNA databanks of relatively small groups of contemporary people. In using these contemporary groups to stand in for populations from centuries ago, geneticists make many untested assumptions about ancient migrations, reproductive practices, and the demographic effects of historical events. AIMs technology also reduces all shared genotypes to "inherited direct ancestry" ignoring the very real possibility that no direct ancestry is responsible for the shared genetic material, e.g. similar traits can result from convergent adaptation rather than from genetic relatedness (Graves 2005). Reflecting a common human ancestry and high gene flow rates, an analysis of individuals from 32 different populations estimated a rate of continent of origin misclassification of around 27 percent, with the rate being constant whether allocation is based on autosomal or Y-chromosome polymorphisms (Romualdi et al. 2002). According to Duster, a more accurate claim of an individual's ancestry ascertained by admixture analysis would be: "[i]t is possible that while the Native American groups we sampled did not share your pattern of markers, others might since these markers do not exclusively belong to any one group of our existing racial, ethnic,

linguistic, or tribal typologies" (Duster 2006). But to do so would definitely diminish the aspect of "miraculousness" that gives the computer-generated data its appearance of precision; a precision that Duster notes is dangerously seductive.

Duster's critique of the validity of admixture mapping for ascertaining individual ancestry taps into a larger debate over the judiciousness of positing population structure from the genetic data of selectively sampled individuals. Instead of trying to assign individuals to pre-defined groups on the basis of their genotype, as described above, other researchers have attempted to identify population groups on the basis of individual genotypes, i.e. to cluster genotypes of individuals until a certain number of genetically homogenous groups are defined. The program STRUCTURE is most often used to infer the number of such groups and assigns individuals to each of them on the basis of probabilities estimated from a set of independently transmitted loci (Rosenberg et al. 2002). The reliability of the results from such analysis has been hotly debated in several recent exchanges (Rosenberg et al. 2005; Serre and Pääbo 2004).

One camp argues that although genetic differences between human groups are relatively small, these differences can be used to situate many individuals within broad, geographically-based groupings (Bamshad et al. 2003; Bamshad et al. 2004; Risch 2006; Rosenberg et al. 2003; Shriver and Kittles 2004; Shriver et al. 2005; Tang et al. 2005). Their premise is that the genetic information from a subset of individuals (who have had their self-identified racial designations removed), can be analyzed, e.g. with a program such as STRUCTURE, and with this information, the individuals can be sorted into genetic groupings that closely match known racial/ethnic groupings.

Several other studies debate the reliability of these exercises in genetic sorting and argue that population substructure is highly dependent on sample selection and methodological decisions; factors that translate into substantial differences in how populations are sorted (Graves 2005; Kittles and Weiss 2003; Olson 2005; Ossorio and Duster 2005; Pfaff et al. 2004; Romualdi et al. 2002; Serre and Pääbo 2004). An analysis of

two different Alu-insertion data sets (Alu8 and Alu21, compromising information on 8 and 21 loci, respectively, for 32 different populations) used the program STRUCTURE and produced markedly different results. Not only was the number of groups produced different between the two data sets, but the geographical ranges did not overlap (Romualdi et al. 2002). An analysis by Wilson et al. of 16 chromosome 1 microsatellites and 23 X-linked microsatellites in eight different population samples used the program STRUCTURE and also failed to find an "obvious natural clustering scheme" (Wilson et al. 2001). Serre and Pääbo went even further and used STRUCTURE to compare the results of a re-analysis of a population-based dataset with a geography-based data set (Serre and Pääbo 2004). The population-based genotype data were from 89 individuals sampled from 15 populations, and they determined that Bayesian analytic software would classify 83 percent of the individuals as belonging to 1 of 2 inferred populations (African individuals vs. non-African individuals). The geography-based data were from 90 different individuals sampled from 52 populations that were more geographically contiguous, and the same analysis failed to discern any discrete clusters. Instead, all of the individuals were estimated to be 40-50 percent admixed between the two inferred populations, with no qualitative difference between Africans and non-Africans.

This last analysis, along with that of Wilson et al, has been the subject of considerable criticism. A recent article co-written by the creators of the STRUCTURE program issued a direct rebuttal to the Serre and Pääbo analysis (Rosenberg et al. 2005). They examined the influence of several study design variables that have often been implicated in the critiques against STRUCTURE results, e.g. sample size, number of loci, number of clusters, assumptions about correlations in allele frequencies across populations, and the geographic dispersion of the sample. The authors find that each of these variables did have an effect on the extent of clusteredness found in the data. But they dismiss the main critique of Serre and Pääbo, namely that a sample with more random geographic distribution leads to reduced clusteredness. Instead they argue that if sufficient data is used,

the geographic distribution of the sample should have no effect on the results. The largest difference in results concerned the choice of a correlation model, i.e. whether the model stipulates that the allele frequencies in the inferred populations at each locus are correlated with each other or not. Rosenberg et al. argue that allele frequencies should be expected to be correlated, on the basis of the shared decent of all human populations from the same set of ancestral groups. Serre and Pääbo argue that allele frequencies should be allowed to be independent of each other based on a model in which colonizations of various parts of the world originated from ancestral populations that were subject to genetic drift. Each set of authors bases their decisions on different theories of human evolution. Interestingly, in this case, the point of disagreement supersedes the genetic information available and remains entangled with substantially different interpretations of the human evolutionary record.

The main point of detailing these current debates is simply to call attention to the fact that they exist; that there is substantial disagreement as to how human genetic variation is structured and the ways to capture this variation. Reviewing the main contentions in these debates is worthwhile in the midst of a flood of recent articles appearing in journals ranging from strictly clinical venues to journals focused on the human genome that all posit a genetic basis to race/ethnic groups. Most researchers working in this area would agree that, with the right number of cases and markers, ancestry can be determined with a certain level of confidence and genetic clusters can be ascertained (Olson 2005). But there still remains debate over the accuracy of these assessments and their ultimate meaning. Because human genetic variation is not categorically distributed, any attempts to partition it are going to necessitate decisions that will invariably affect the results. One side of the debate argues that even accounting for these types of decisions, individuals can successfully be partitioned into genetic clusters that match major geographic (and usually race/ethnic) population subdivisions. The other side of the debate is more measured in their assessment. This side readily acknowledges the existence of human genetic (and obviously biological) variation but argues that the bulk of human variation is continuously distributed and, as a result, any

categorization schema attempting to meaningfully partition that variation will necessarily create artificial truncations. It is for this reason, they argue, that attempts to allocate individuals into ancestry groupings based on genetic information have yielded varying results that are highly dependent on methodological design.

In addition to debates over how meaningful partitions between populations are constructed, questions arise over what these divisions mean (Barr 2005). Clearly, ascertaining the structure of human genetic variation speaks directly to questions regarding human history and historical patterns of migration. Molecular anthropology is a burgeoning field that will likely shed new light on issues of human evolution (Templeton 1999). But questions of ancestry and historical population movements are not the only ones being asked here. Rosenberg et al. have been very vocal that their findings of natural clusterings of humans into distinct genetic subgroups will tell us something meaningful about disease. This leads us to Claim 2, namely that population genetic structure can help to identify medically important genotypes that vary in frequency across populations.

Claim 2: Race, Genes, and Disease

The debate over the distribution of human genetic variation spills over into the second claim prominent in current research, namely that population structure, and specifically a racialized categorization of population structure, can be leveraged to understand the genetic basis of disease (Burchard et al. 2003; Mountain and Risch 2004; Risch 2006; Shriver 1997). The reasoning follows that *if* an individual's race/ancestry can be determined by genetic data *and* race/ancestry groups can be defined or described genetically (as specified by Claim 1), then race/ancestry may be related to important genetic differences in disease. There are two justifications for this claim. The first, which falls under Claim 2, is that race/ancestry is useful for medicine because it will improve the efficiency with which medically important correlations between genes and diseases can be identified. The second justification, although related, is different in that it utilizes a disparities framework to argue

that using race/ancestry to understand the genetic basis of disease will be useful in explaining race/ethnic disparities in health. This section will focus on the former justification.

We are currently in an incipient state of knowledge regarding the human genome and its relationship to pathophysiology. Roughly 20 years since the birth of the field of modern clinical molecular genetics, little is known regarding the genetic basis of disease, excepting a handful of monogenic diseases. Despite early hopes to the contrary (at least on behalf of the public), thus far, findings from the Human Genome Project have been felt in basic, rather than therapeutic, biomedical research. Barring direct functional information that leads scientists to disease-causing genes, scientists have begun to search for the genes associated with disease indirectly using epidemiological methods. These include conventional case-control gene-association studies, linkage analysis, and high density genome scans that are dependent on linkage disequilibrium. The strengths and limitations of each of these strategies has been debated, with views changing in response to new data releases, new innovations in computational genetics, new insights from the HGP, and the development of more refined research questions (see Risch 2000 for a discussion).

As more researchers attempt to study continuous 'polygenic' variation, i.e. the type associated with common complex diseases, genome-wide association studies are becoming increasingly common. Genome-wide association studies have become entangled in the issue of race/ethnicity in several ways. One such entanglement involves case-control association studies and the issue of population genetic substructure. The usual notion of association mapping is to find linkage disequilibrium between polymorphic markers and particular phenotypes, such as the presence of a disease.[1] But association studies can produce spurious results if cases and controls have differing allele frequencies for genes that are not related to

[1] Linkage disequilibrium is defined as a point where alleles occur together more often than can be accounted for by chance. The presence of LD indicates that the two alleles are physically close on the DNA strand. (http://www.doegenomes.org/)

the disease being studied (Tang et al. 2005).[2] It is for this reason that many researchers argue that genetic studies should focus on only one "population" or should control for population substructure, either with self-identified race/ethnicity or biogeogrpahical ancestry, as estimated by genetic clustering analysis (as explained in Claim 1).

Beyond controlling for the possibility of population substructure, others have argued that race/ethnicity can be useful for shedding light on gene-gene or gene-environment interactions (Salari et al. 2005). These researchers have attempted to leverage genetic differences between particular "populations" in their hunt for candidate genes with a method called admixture mapping (Patterson et al. 2004; Shriver et al. 2005; Smith et al. 2004; Tang et al. 2005). In admixture mapping, genome-spanning markers that differ in frequency between different groups are selected. Genetic studies that use admixture linkage disequilibrium can then search for disease alleles with fewer markers than would be needed in a direct or haplotype scan (nearly 1 percent as many) (Patterson et al. 2004). The idea is that in populations that have descended from the recent "mixing" of groups from multiple parts of the world, the same chromosomal regions containing variants contributing to disease risk, will also contain an overrepresentation of "ancestry" from whichever population has a higher proportion of risk alleles at the locus. Patterson et al. (2004) give the example of multiple sclerosis which is more prevalent in people with European ancestry. To identify gene variants that might contribute to the disease, African American patients with MS would have their genomes scanned searching for regions where the proportion of European ancestry is higher (or lower) than average. A powerful study requires a map of thousands of markers known to have substantial differences in frequency across populations.

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[2] The magnitude of this problem in genetic association studies is subject to debate (see Thomas and Witte 2002 and Wacholder, Rothman and Caporaso 2002).

Thomas, D. C., and J. S. Witte. 2002. "Point: Population stratification: A problem for case-control studies of candidate-gene associations?" *Cancer Epidemiology Biomarkers & Prevention* 11:505-512,
Wacholder, S., N. Rothman, and N. Caporaso. 2002. "Counterpoint: Bias from population stratification is not a major threat to the validity of conclusions from epidemiological studies of common polymorphisms and cancer." *Cancer Epidemiology Biomarkers & Prevention* 11:513-520.).

Applications

Despite the enthusiasm for admixture mapping, the few existing studies that go beyond estimating admixture levels to try to correlate them to phenotypic variation, have been underwhelming in their analysis and findings. One such study by Salari and colleagues (2005), attempts to leverage different rates of "admixture" between Mexicans and Puerto Ricans to determine if the proportion of a particular ancestry is significantly associated with asthma-related phenotypes. The reasoning is that markers informative for ancestry may be in linkage disequilibrium (LD) across large distances. So the enhanced LD in admixed populations may be used to identify alleles that underlie a genetically determined difference in phenotype between two "ancestral populations." Because admixture analysis simply relies on estimating significant associations between two factors (estimated ancestry and phenotype), no prior specification of potential physiological pathways or genetic understanding of disease is necessary. In some ways this is the strength of admixture mapping and the rationale behind all genetic association studies. On the other hand, failure to identify specific genomic regions and the absence of testable hypotheses regarding disease progression and physiological processes often leaves admixture studies susceptible to individual bias and uncritical acceptance of random associations between "population" membership and particular genetic markers.

The same caveats apply to admixture analysis that that were identified in the discussion of Claim 1. One of the main assumptions of admixture mapping is that ancestry of alleles at each locus can be assigned to one of the two founding populations. But the reality is that there are no existing "ancestrally distinct" populations upon which to anchor an analysis (Olson 2005). As a result, assignment of alleles to parent populations can become very problematic (Kittles and Weiss 2003). In addition, the alleles used in the AIMs technology are located in regions of the genome that do not code for functional molecules, such as proteins. The genetic information that allows us to identify ancestry with a certain level of confidence, "may be discordant with particular phenotypic traits, since much of the

classification salience originates from DNA that does not influence phenotype" (Graves 2005). This point is an important one because it draws attention to the discordant nature of human variation. Traits that arouse under selective pressure are clinally distributed in response to the presence of the selective force that dictated their development. Their distribution does not necessarily reflect the distribution of neutral polymorphisms (e.g. AIMs which are useful for predicting group membership) nor do their distributions necessarily correspond with each other (see Frank 2001).

The utility of admixture analysis is highly dependent on the genetic architecture of common diseases, such as asthma. It has yet to be determined if disease variants that differ in frequency between populations are common or not, i.e. the common disease/common variant hypothesis (Hinds et al. 2005). Even if there is some utility in admixture mapping, it remains susceptible to confounding if there is a correlation between individual admixture and non-genetic factors, which is often the case (Olson 2005).

The weight of these issues comes to bear on the findings section of the Salari article. The authors used 44 AIMs to estimate individual admixture levels, albeit with large standard errors. As expected, self-identified Mexican-American individuals had larger ancestry estimates of European and Native-American ancestry while the Puerto Rican subjects showed more African ancestry. What separates this analysis from those that focus exclusively on estimating ancestry (as seen in Claim 1) is that, upon determining admixture levels, the authors attempt to link this variation to phenotypic variation. This move represents the leap from using genetic information to learn something about human population history to using population affiliation to learn something about disease. To test for an association the authors use logistic regression with the maximum likelihood estimate of individual ancestry as the predictor of three different asthma-related phenotypes. The analysis is susceptible to all the usual critiques of regression, including the problems with appropriately accounting for known contributors to the outcome. The only control variables included in the equation are birthplace and exposure to second-hand smoke in the

household. For Mexicans, a census-tract level variable of neighborhood income is also included but its estimate is not reported. The absence of known correlates of asthma means that any relationship between the admixture measure and the outcome could be spurious and correlated to omitted variables.

Only one significant relationship emerges, between proportion European ancestry and baseline forced expiratory volume (pre-FEV). The authors conclude that a 10 percent increase in European ancestry is associated with a decrease of 1.7 percent decrease in baseline forced expiratory volume. The odd sounding tone of this finding (what is a 10 percent increase in European ancestry?) is never contextualized because there is never an attempt to articulate why we would expect certain ancestry estimates to be correlated with asthma. The portion of the analysis that attempts to correlate the individual AIMs markers and asthma phenotypes is no help either since only three of the markers are nominally associated with pre-FEV. The absence of any significant correlations between the AIMs markers and an asthma phenotype is not surprising in light of the fact that most AIMs markers do not influence phenotype (Graves 2005). Even the cornerstone of admixture mapping, that genetic association studies in admixed populations may be biased because of population substructure, only receives nominal support here.

The authors are forthright in acknowledging that there are unmeasured environmental factors that likely vary with proportion of European ancestry. Yet they eventually conclude that, "observation of greater asthma severity in individuals with higher European ancestry suggests that one or more alleles at higher frequency among Europeans may increase asthma severity in Mexican-American populations" (84). This is in spite of the fact that their unstable estimate of ancestry was only associated with one phenotype (no relationship was found between ancestry and forced expiratory volume (FEV) or drug responsiveness (ΔFEV)), in one population (no significant association were found in Puerto Rican subjects), and none of their genetic markers was significantly associated with their phenotypic outcome.

A comparable exercise conducted by Tang and colleagues in the case of hypertension resulted in strikingly similar findings (Tang et al. 2005). While subjects were successfully clustered using genetic cluster analysis into groups that matched with self-reported race, no relationship was found between the allele frequency levels associated with particular race/ethnic groups and hypertension. Yet as in the case of Salari and colleagues, Tang et al. continue to hold fast to the contention that admixture will potentially tell us something about disease, arguing that the topic, "merits additional scrutiny" (274).

There is considerable variability in the attention given to potential biomedical mechanisms in existing admixture analysis. A key distinction is between those studies that at least hypothesize an etiologic pathway and those that simply hunt around for significant associations between alleles with differing frequency rates between race/ethnic groups and some phenotypic trait. In a recent article appearing in *Nature Genetics*, Helgadottir et al. argue that they have identified an allele that confers a "ethnicity-specific" risk of myocardial infarction (Helgadottir et al. 2006). First, the authors demonstrate in an Icelandic cohort that a haplotype (HapK) confers a modest risk of more severe MI phenotypes, i.e. MI with additional cardiovascular diseases (no significant differences were found between only MI and any of the haploytypes they tested). HapK spans the LTA4H gene encoding leukotriene A4 hydrolase, a protein in the same biochemical pathway as another gene encoding a protein already known to be associated with MI. The authors hypothesize that the risk of severe MI is mediated through upregulation of the leukotriene pathway (LTB4, the main product of the LTA4H enzyme).[3]

At this point, the researchers perform a replication study in three U.S. cohorts (recruited from Philadelphia, Cleveland, and Atlanta). They found that HapK was not as common in the African-Americans recruits (although there was some variation across U.S. sites) but the

[3] The idea is that LTB4 produced through activation of the leukotriene pathway may amplify inflammatory responses in the arterial wall, by mediating chemotaxis and thereby promoting adhesion of leukocytes to the vascular endothelium and transmigration.

association with severe MI phenotypes was stronger in the African-Americans than in the White subjects. In order to test the contention that the greater risk of HapK in African-Americans is due to increased European ancestry, they conduct an admixture analysis in much the same way as the previous examples.[4] As in the aforementioned cases, no association was found between increased European ancestry and the relationship between HapK and severe MI. The authors conclude that the increased risk among African-Americans "suggests a strong interaction between HapK and other genetic variants and/*or non-genetic risk factors* that are more common in African-Americans than in European Americans or Icelanders" (71: emphasis added). There is ample evidence of the existence of substantial differences in non-genetic risk factors between African-Americans and Whites. But instead of stressing the potential role of non-genetic factors in contributing to the relationship between HapK and increased risk of MI in African-Americans, the authors instead choose to highlight that their results, "emphasize that although genetic differences between human continental groups are small, some of these differences may nonetheless contribute to ethnicity-based health disparities" (71).

The Helgadottir et al. analysis was unique in that it was considerably more thorough in specifying potential pathways through which particular haplotypes may be associated with phenotypic outcomes. Yet it still foundered when the researchers were called upon to explain differences in prevalence and risk between racial groups. In the end, the authors gloss over the role of nongenetic factors and stress genetic differences between groups. Their emphasis appears oddly misplaced, particularly in light of their own findings which suggest no difference in admixture levels and increased MI risk.

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[4] It is not clear why the authors would expect European ancestry to confer a greater risk of MI among African-Americans instead of just greater prevalence of HapK among those African-Americans with higher "European" estimates. The analysis demonstrates that African-American carriers of HapK did have, on average, more "European" ancestry than those who did not carry HapK. But controlling for European ancestry estimates among the African-American sample had no effect on the association between HapK and MI.

Up to this point, the articles reviewed here have been restricted to those that: 1) estimate ancestry from AIMs or other allele markers, 2) correlate individual ancestry proportions with phenotypic variation, 3) correlate ancestry markers directly with phenotypic variation, and 4) (in a much smaller number of cases) hypothesize the metabolic pathways through which genetic variants are correlated to phenotypic variation and how/why these might vary between population groups. On the whole, this literature is limited by several assumptions but still holds promise for identifying alleles and their relationship to phenotypic variation *if* standards can be maintained regarding: 1) specification of pathways (at the very least hypothesized), 2) increased attention to interactions with non-genetic factors, and 3) an appreciation of the assumptions inherent in work that involves relying on unknown factors such as the structure of human genetic variation.

Where the literature becomes infinitesimally less sophisticated is when the focus shifts from one that is attempting to understand the genetic basis of disease to one that tries to understand the genetic basis of *group differences* in disease.[5]

Claim 3: Race, Genes and Disparities in Health

Positing a genetic explanation for racial/ethnic disparities in health is not a new trend. For quite some time, researchers who work on racial/ethnic disparities in health have either advocated for, or against, a genetic explanation for health disparities. What is new and has changed the parameters of the debate is the recent influx of genetic data. While it remains to be seen which side will prevail, the struggle is somewhat stacked against the anti-race/genetics side in that they are unlikely to be proficient users of the new genetic data. On the other hand, Ossorio and Duster argue that setting up the debate as a binary "us versus them" dynamic is misplaced (Ossorio and Duster 2005). In lieu of debating whether or not

[5] Clearly these two endeavors are closely related but I would argue that there are explicit differences in the way particular research questions are framed, addressed, and analyzed that distinguish many of the existing studies.

racial groupings can be discerned from genetic data, and if so, then arguing that race should be used in science and medicine, Duster and Ossario argue that a third option exists. They say that race can be best understood as, "a set of social processes with biological feedback that require empirical investigation." This third option will lead to thinking of disparities as a consequence of differential treatment and experiences rather than an independent cause of differential outcomes. Whether this third option takes hold in the research community is yet to be seen. Working against it is the extreme difficulty in locating gene-environment interactions. In the interim, it is useful to trace several examples that illustrate many of the inherent pitfalls associated with research on genetics and health disparities.

An example of a fairly nuanced invocation of a genetic explanation for health disparities is exemplified in a recent *New England Journal of Medicine* article examining different rates of lung cancer among 5 different race/ethnic groups (African-American, Japanese-American, Latino, Native Hawaiian and non-Latino White) (Haiman et al. 2006). Exemplifying the standard procedure used in nearly all past work, different risks are observed between the different racial/ethnic groups, bivariate associations are re-estimated net of a certain number of controls, and the remaining risk is attributed to a variety of possible mechanisms, including genetic differences between groups. In this particular case, African-Americans and Native Hawaiians who are moderate smokers (<30 cigarettes per day) are found to be significantly more likely to experience smoking-related lung cancer. Controls are included for occupation, level of education, and dietary intake of fruits and vegetables, yet the association remains. Interestingly, among those who smoked more than 30 cigarettes per day or those who never smoked, the risk of lung cancer was similar across the five racial/ethnic groups. The authors conclude that one explanation for the increased risk of lung cancer among African-Americans and Native-Hawaiians moderate smokers is that they are "constitutionally more susceptible to the effects of tobacco carcinogens." It is not clear exactly what is meant by "constitutionally" although the word "genetic" does not appear anywhere in the article. Instead, the authors raise the possibility that differences in smoking

behaviors across race/ethnic groups, such as type of cigarettes smoked or way cigarette is smoked, may be factors in the association between lung cancer and African-American and Hawaiian affiliation. They also suggest that there may be metabolic differences between different race/ethnic groups but refrain from implicating genetic differences as the source of differences. This is important because it is much more inline with what many critics have advocated (Frank 2001; Krieger 2005) in terms of exploring physiological differences between groups instead of genetic ones.

In many ways, the *New England Journal of Medicine* article represents the status quo in biomedical research on health disparities in that a difference in a particular health outcome is specified (e.g. lung cancer), attempts are made to account for the difference using statistical methods that "control for" various confounders (e.g. education, diet), and then any residual effect is attributed to "constitutional" differences between groups. However, in other ways the article represents an improvement over the status quo in that it does not directly attribute the residual difference to genetics but instead presents several hypotheses related to behavioral and physiological processes.

Yet the appearance of a more physiologically-oriented perspective, as opposed to a strict genetic one, is quickly done away with an editorial directly following the *New England Journal* piece. Neil Risch, a leading geneticist who has been a vocal advocate for the practical applications of studying race and genetics, makes the case in his editorial that genetics are likely to have played a role in the association between African-American/Hawaiian race/ethnic affiliation and lung cancer (Risch 2006). To assess this possibility, Risch takes us back to admixture mapping and advocates that the authors utilize admixture analysis to examine correlations between ancestry estimates and the lung cancer. To bolster this suggestion he references yet another letter in the same issue of the journal that makes the now familiar case for the correspondence between self-reported ancestry and genetic clusters (Sinha et al. 2006). Through his editorial, Risch succeeds in turning an article on disparities

that had no explicit genetic content into one that makes a direct connection between genes and race.

Risch ends by appealing to the very premise of health disparities research, namely health equality. He argues that, "denying the existence of racial or ethnic differences in gene frequencies…is unlikely to benefit minority populations" (410). To bolster the claim that focusing on gene differences between racial/groups will benefit minority populations he cites an example of patients with colon cancer who receive irinotecan as treatment. Patients who are homozygous for deficiency alleles of the enzyme uirdine diphosphate glucuronosyltransferase isoform 1A1 may experience severe side effects from irinotecan. As a result all patients who are eligible for irinotecan are recommended to undergo genetic testing for homozygosity for deficiency alleles (Innocenti et al. 2004). Importantly, in the case of irinotecan, testing is done for the specific genetic variant that is known to result in an adverse reaction. Race/ethnic group membership is not a factor in determining if irinotecan is an appropriate treatment for sufferers of colon cancer. Yet this does not stop Risch from appropriating this example to make a connection between race/ethnic group membership, gene variants, and adverse drug response. He goes on to cite a litany of differences in the frequency of deficiency alleles across race/ethnic groups, completely ignoring the fact that if the deficiency allele is identified and has been connected to a particular adverse drug reaction, as in the case of irinotecan, then genetic testing should be conducted for the presence of that particular deficiency allele, irrespective of race/ethnic affiliation.

The Case of BiDil

No case illustrates the pitfalls inherent in investigations that attempt to link race/ethnicity, genes, and disease than the case of BiDil, the first drug in the U.S. to be based on a patent formulated in terms of its benefit to a specific racial or ethnic group. BiDil, a combination of hydralazine and isosorbide dinitrate (H/I), was approved by the Federal Drug Administration (FDA) last June 23rd to treat heart failure in African-Americans

exclusively. The FDA's approval of BiDil relied heavily on the results of the African-American Heart Failure Trial (A-HeFT) published in the *New England Journal of Medicine* in November 2004 (Taylor, Cohn and Worcel 2005). The trial involved 1050 self-identified Blacks with moderate to severe heart failure. All were treated with standard therapy (ace-inhibitors and beta blockers) and randomized to either BiDil or placebo. The trial was halted early due to a higher mortality in the placebo group compared to the group receiving BiDil, 54 deaths (10.2%) compared to 32 deaths (6.2%), respectively. The response of Whites or other groups with heart failure receiving current standard therapy remains unknown because only Blacks were included in the A-HeFT trial.

Jonathan Kahn, a law professor at Hamline University, has closely and critically followed the process of bringing BiDil to market and he argues that it is one of the most egregious cases of manipulating science to serve commercial interests (Kahn 2004; Kahn 2003; Kahn 2005; Sankar and Kahn 2005). According to Kahn, BiDil has set in motion a trend in the pharmaceutical industry of turning widely used and cost-effective generics into patented expensive drugs in the name of health disparities.

In short, BiDil is a combination of two genetic drugs that is likely to be beneficial to all patients suffering from heart failure. Early studies of heart failure treatment conducted in the 1980s by the Veteran's Administration included both Blacks and Whites and showed great promise for combining H/I (what is now BiDil) with enalapril (an angiotensin converting enzyme that is now the standard therapy for heart failure for all race/ethnic groups) (Cohn et al. 1986; Cohn et al. 1991). Up until this point in its development, BiDil was not a race-specific drug and its advocates argued that it would work effectively in all individuals experiencing heart failure. BiDil only morphed into an African-American-specific drug *after* it failed to receive initial support from the FDA in 1996 (the FDA failed to approve it; not because it failed to work in the older VA trials, but because the trials themselves were found to be inadequate according to current criteria for new drug approval). At this point, no funds were raised to conduct a more rigorous trial of BiDil that would meet

FDA criteria for new drug approval because BiDil only combined two generic drugs and generics that do not combine differently are not profitable.

It is only at this point that the researchers returned to their VA data and began to exploit race/ethnic differences in response to treatment. A 1999 paper published in the *Journal of Cardiac Failure* found significant differences in response to H/I in the 49 African-Americans who were placed on H/I in the first VA trial (Carson et al. 1999). The same month that this article appeared, the pharmaceutical company Nitromed purchased the intellectual property rights for BiDil and 34 million dollars were raised in private venture capital financing to conduct the confirmatory trial now known as A-HeFT. According to Kahn, the question of whether H/I helps heart patients was never the question of the A-HeFT trial, for this had already been demonstrated in the earlier VA trials for *all* heart failure patients. The point of A-HeFT was to prove BiDil's efficacy in such a way that patent law could protect it and a new drug application (NDA) could succeed. That "way" was by positing race/ethnic differences in the genetic basis for disease.

In the weeks following A-HeFT, NitroMed stock more than tripled in value and then again following the publication of the results in the *New England Journal of Medicine*, the stock soared. NitroMed has predicted that BiDil will have eventually have revenues that will top 1 billion annually. These estimates are based on the cost of taking BiDil at $10.80 per day. The cost of generic equivalent is about $1.50 per day (Sankar and Kahn 2005). In the A-HeFT trial, the two generic components, hydralazine and isosorbide dinitrate, were explicitly tested in doses that are not available in its generic components. The key here is that the race-specific patent will prevent insurers from recommending to physicians that they use generic substitutes to save money. Generic manufacturers can still sell H/I separately but they will not be able to advertise them as treatments for heart failure. The new race-specific patent protects NitroMed until 2020, 13 years beyond the general methods patent supporting BiDil which expires in 2007.

Kahn argues that the primary forces driving the re-invention of BiDil as a race-specific drug were legal and commercial rather than biomedical (Kahn 2004). This observation ignores the current climate in biomedical and clinical research which has embraced the notion that estimated genetic differences between race/ethnic groups likely have clinical applications. The logic behind AHeFT is that African-Americans have lower levels of nitric oxide in their blood. As a result, BiDil is hypothesized to work more efficaciously in African-Americans because the isosorbide is a nitric oxide donor and the hydralazine is an anti-oxidant, which may enhance the efficacy of nitrates (Taylor, Cohn and Worcel 2005). But instead of making lower levels of nitric oxide the determining factor for admission into the trial, it was whether or not you self-identified as Black. In a recent editorial that appeared in the Annals of Internal Medicine, Barr (2006) suggests that decreased levels of nitric oxide are also a principal contributor to vascular damage associated with diabetes. One alternative explanation for the higher rates of vascular nitric oxide activity in Blacks is the higher rate of diabetes among Blacks in the U.S. Indeed, the prevalence of diabetes among patients in the treatment group of the A-HeFT trial was statistically significantly greater than among the patients in the control group and was substantially greater than that among all patients with congestive heart failure (CHF). Barr suggests that H/I will likely be of benefit to all populations of patients with CHF and high rates of coexistent diabetes, regardless of individual racial affiliation. Conversely, H/I might be less useful for CHF with patients who do not have impairment of endothelial nitric oxide associated with diabetes. Whether this assessment is correct or not, the point Barr makes is one that has been made repeatedly by many observing the headlong rush into race-specific pharmaceutical trials. Factors that vary at the level of the individual likely contribute to the apparent racial differences in response to treatment. So entry in race-specific trials assumes some inherent factor in the patient that influences response goes with being Black instead of defining the factor so that the results can be generalized to other sub-groups that share that factor (Cooper and Psaty 2005).

A further case against using self-identified race as a treatment criteria for heart failure is made by a meta-analysis of fifteen different anti-hypertensive drugs (Sehgal 2004). The analysis demonstrate that while, on average, Blacks and Whites differ in their response to specific antihypertensive drugs, there is wide variation in drug-associated changes in blood pressure within each racial group. The percentage of Whites and Blacks with similar drug-associated changes in systolic blood pressure ranged from 83% to 93%. The authors conclude that small differences among thousands of patients will say little about how a particular patient will respond.

A second often-cited study by Wilson et al. examined polymorphisms in drug metabolizing enzymes (Wilson et al. 2001). He found statistically significant variation in allele frequency according to self-identified racial group and according to genetic clusters estimated from the program STRUCTURE. However, neither group membership category (either self-identified or estimated from genetic data) was sufficiently precise to make them clinically useful in guiding choices of drugs. What this analysis demonstrates is the difficulty of translating differences among groups into a test that has adequate predictive value to help with clinical decisions. It is impossible for "race to provide both perfect sensitivity and specificity for the presence of a DNA sequence variant." [6]

The clinical implications of the BiDil controversy are the most pressing, especially in light of compelling research that suggests that many non-African-American patients will miss out on receiving a beneficial treatment that would likely help their condition.[7] Another, less direct, implication of BiDil is what it means for disparities research. BiDil biologizes race by suggesting that African-Americans benefit from a drug in ways that Whites do not because of unspecified characteristics inherent to being Black. BiDil also illustrates how

[6] An important distinction is between differential group drug response and differential frequency of adverse drug reactions. Adverse drug reactions are likely to be caused by mutations that are associated with toxic effects. These tend to be rare and rare variants are more likely to be group-specific. .According to Cooper and Pasty (2005), only when inter-ethnic contrasts in allele prevalence reach levels of 90 percent versus 10 percent does ethnicity serve as a clinically useful diagnostic predictor of potential drug response.

[7] Unless of course Nitromed is successful in promoting "off-label" uses of BiDil which it is indeed pursuing.

using race as a biological proxy creates the impression that the best way to address health disparities is through commercial drug development. This is not to ignore the glaring absence of African-Americans in biomedical and clinical research, historically and continuing into the present. In fact, the historical absence/mistreatment of Blacks in clinical research has not escaped the attention of the manufacturers of BiDil, who have capitalized on this history to promote their product and to form strategic alliances with the Association of Black Cardiologists, the Congressional Black Caucus, and most recently with the NAACP. In a partnership labeled "Campaign for Health Justice," NitroMed argues that their development of the BiDil drug illustrates the struggle for equal access and equal medical outcomes for all populations. Given the profit margins of BiDil, i.e. potentially 1 billion dollar annual profits, the complete appropriation of the health disparities discourse to promote BiDil appears somewhat disingenuous.

Important to demographers who study race/ethnic disparities in health, the appropriation of the health disparities discourse by the pharmaceutical industry represents a shift away from research on the non-genetic sources of health disparities. According to some researchers, the success of BiDil with the FDA represents a changed political and social climate that prioritizes genetic explanations at the expense of political, social and economic causes of health disparities. Yet according to others, the exact opposite is true, so that, "all too frequently there is an eagerness to impugn psychosocial factors as the major explanation for any observed differences…in Blacks" (Yancy 2002 as quoted in Kahn 2004). Even as both sides of the debate over the cause of health disparities argue over whose explanation is given precedent, the fact remains that an "infrastructure of racialization" is currently taking place in biomedicine and drug development (Lee 2005).

What does this all mean for demographers?

The main premise behind the delivery of race-based pharmaceuticals is that more effective health care can be tailored to an individual patient based upon the patient's

membership in a particular population group (usually defined in race/ethnic terms). A similar logic is present in the research that posits genetic differences as a source of health disparities between race/ethnic groups. Interestingly, the understanding that group membership has the potential to influence individual health actually has its roots in the field of population health and has been closely tied to the demographic tradition. Historically, a population perspective has involved recognition of the social, economic and environmental contexts that influence individual health outcomes and also shape population distributions. Yet in its more recent permutation, as advocated by NitroMed and others, the "population perspective" has become exceedingly narrow. In the context of the current biomedical research, membership in a particular race/ancestry group has become important *only* to the extent that this membership acts as a marker for shared genetic heritage. This purely genetic conceptualization of population membership is excessively restrictive and represents a hijacking of the traditional population perspective.

Sir Geoffrey Rose articulated one of the first formulations of a comprehensive population perspective in a landmark article titled "Sick Individuals and Sick Populations" (Rose 1985) According to Berkman and Kawachi, Rose's crucial insight was that "an individual's risk of illness cannot be considered in isolation from the disease risk of the population to which they belong" (Berkman and Kawachi 2000). Rose and the many social epidemiologists and demographers that have followed him have advocated for recognizing that individual lives are socially patterned in ways that affect health outcomes. This has involved stressing the importance of understanding disease causation *as well as* disease distribution. I would argue that as demographers who study race/ethnic disparities in health increasingly find themselves surrounded by an "infrastructure of racialization," we would do well to remember the core tenets of a population health perspective. But in doing so, we must not ignore the claims made by those interested in researching shared genetic heritage within race/ethnic groups. If history has told us anything, it is that blindly claiming that race is socially constructed without attempting to understand the biological variation

that very clearly distinguishes population groups, only serves to isolate social scientists further from large swaths of the health disparities research community, particularly those in biomedicine. Instead, demographers, sociologists, and anthropologists, must continue to engage in these crucial debates over the factors contributing to population health disparities.

Fear and Political Correctness in Existing Debates

One of the more insidious features of the debate over the place for genetics in research on race/ethnic disparities in health involves the invocation of the idea of "forbidden knowledge" (Kempner, Perlis and Merz 2005). It has often been claimed that one of the reasons that disparities research has not privileged genetic explanations is because of a "fear" of doing so. A *New York Times* article published earlier last year profiled a young Harvard economist studying race/ethnic differences in test scores (Dubner 2005). In explaining his research, the researcher noted, "I want to have an honest discussion about race in a time and a place where I don't think we can. Blacks and Whites are both to blame. As soon as you say something like, 'Well, could the Black-White test-score gap be genetics?' everybody gets tensed up. But why shouldn't that be on the table?" The implication from his statement is that absence of a genetic argument in explaining racial disparities across a range of outcomes is due to a fear of articulating that explanation and not because the explanation itself may not be valid. Nancy Krieger (2005) extends this example to the debates over race, genetics, and health disparities, which are often framed as, "a matter of "politically correct" unscientific ideology vs. scientific yet "politically incorrect" expertise rooted in biological facts" (2155).

The idea that scientific thinking must choose between biology and social explanations is not a new polemic but instead one that has surfaced repeatedly throughout history. The cyclical nature of many of these debates is closely connected to the cultural context from which they cannot be separated. An illustration of this fact is found in the previously mentioned *New York Times* article profiling the career of Roland Fryer. After

arguing that Fryer can ask the "tough" questions, the reporter goes on to explain why: "(F)ryer is Black. Fryer well appreciates that he can raise questions that most White scholars wouldn't dare. His collaborators, most of whom are White, appreciate this, too. "Absolutely, there's an insulation effect," says the Harvard economist Edward L. Glaeser. "There's no question that working with Roland is somewhat liberating." Again referencing the idea of "forbidden knowledge," these remarks illustrate the (mis)understanding that the only reason genetic explanations for race/ethnic differences are not more fully explored is because researchers are not "allowed" to do so and that only Black researchers have the cultural capital to ask these particular research questions. More broadly, these comments highlight an underlying reality in the debates over the place for genetics in health disparities research, namely that they are taking place in a racialized society, with racialized actors, and racialized agendas.

According to Ossorio and Duster (2005), "Each succeeding generation of researchers believes that contemporary scientific views of race transcend the current social milieu" (115). Clearly, this has never been, nor ever will be, the case for the very simple reason that science is a product of culture. At the same time, critical, open, visible, informed research that utilizes a population health perspective will go a long way in setting the course for more productive future research agendas on racial/ethnic disparities in health.

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