

# Admixture mapping: from paradigms of race and ethnicity to population history

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**Abstract** Admixture mapping is a whole genome association strategy that takes advantage of population history—or genetic ancestry—to map genes for complex diseases. However, because it uses racial/ethnic groupings to examine differential disease risk, admixture mapping raises ethical and social concerns. While there has been much theoretical commentary regarding the ethical and social implications of population-based genetic research, empirical data from stakeholders most closely involved with these studies is limited. One of the first admixture mapping studies carried out was a scan for Multiple Sclerosis (MS) risk factors in an African-American population. Applying qualitative research methods, we used this example to explore developing views, experiences and perceptions of the ethical and social implications of admixture mapping and other population-based research—their value, risks and benefits, and the future prospects of the field. Additionally, we sought to understand how social

and ethical risks might be mitigated, and the benefits of this research optimized. We draw on in-depth, one-on-one interviews with leading population geneticists, genome scientists, bioethicists, and African-Americans with MS. Here we present our findings from this unique group of key informants and stakeholders.

**Keywords** Admixture mapping · African-Americans · Multiple sclerosis · Population-based genetic research · Race · Ancestry

## Introduction

Untangling the genetic, environmental and behavioural etiologies of complex disease is becoming a research challenge of global scope. Since the completion of the Human Genome Project, the ongoing development of population-based genomic resources (The International HapMap Consortium 2003; Seguin et al. 2008) is opening up greater opportunities than ever before for pursuing this goal (Botstein and Risch 2003; Daar and Singer 2005). Much of this work relies on studying genetic variation between groups defined by commonly used racial/ethnic labels. Thus, the potential to raise ethical and social problems—for example exacerbating racial/ethnic discrimination and reifying notions of group difference—has been widely discussed [for review see (Caulfield et al. 2009)]. Controversy on the inter-relationship of genetics, social identity and health, and their implications seemed to peak about 5 years ago [for example and review, see the Nature Genetics supplement ‘Genetics for the Human Race’ and commentary surrounding the FDA approval of the first ethnic-specific drug (Sankar and Kahn 2005)]. However, since then and despite the debate, population-

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based genetic studies have flourished, indicating these issues may now be more germane than ever.

A key development in the last 5 years has been technology allowing high resolution analysis of population genetic structure (Li et al. 2008). This reiterated earlier discoveries suggesting that one dimension of genetic structuring in the human population falls along geographic or continental lines (Rosenberg et al. 2002). Thus, although human populations are overwhelmingly similar (Cavalli-Sforza and Piazza 1975; Jorde et al. 2001), a subset of genetic variants differ in frequency between groups. This understanding laid the theoretical and practical foundation for geographical ancestry-based approaches using ancestrally-informative genetic markers (AIMs) (Stephens et al. 1994; Collins-Schramm et al. 2002). One example of their application is admixture mapping (also known as ‘mapping by admixture linkage disequilibrium’ or MALD), a whole genome association strategy that takes advantage of the mixing of geographically-distinct ancestral populations, to map variants for complex traits (Box 1) (McKeigue 1997; Smith and O’Brien 2005; Zhu et al. 2008). Used in concert with other approaches, admixture mapping is starting to generate important scientific insights (Reich et al. 2005; Freedman et al. 2006; Kao et al. 2008; Kopp et al. 2008; Cree et al. 2009).

Despite extensive literature on the ethical and social implications of population-based genetic research (Lee et al. 2001; Burchard et al. 2003; Cooper et al. 2003; Duster 2005), there is limited empirical data from stakeholders most closely associated with these studies (Smart et al. 2006; Fullwiley 2007). One of the first admixture mapping studies carried out was a scan for multiple sclerosis (MS) risk factors in an African-American population (Reich et al. 2005) (Box 2). Applying qualitative research methods, we used this example to explore developing views, experiences and perceptions of the ethical and social implications of admixture mapping and other population-based research—their value, risks and benefits, and the future prospects of the field. Additionally, we sought to understand how social and ethical risks might be mitigated, and the benefits of this research optimized.

To this end, we interviewed a group of key informants with intimate knowledge of, and/or experience with, admixture mapping and other population-based genetic research. We consulted key scientists on the African-American MS admixture study research team; other leading geneticists or genome scientists; experts in bioethics and law; and finally, to further explore the themes arising, African-Americans with MS. Excluding the latter group, these interviewees are representative of those playing a pivotal role in shaping the direction of current population-based genetic research. Now, at a time when new technologies are resolving genetic diversity at ever greater

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### Box 1 What is admixture mapping?

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Genetic admixture occurs when two or more populations that have been separated over long periods of history—often by geography—come into contact and intermix. For example, the genomes of many African-Americans, as members of one recently admixed population in the Americas, are a mosaic of variable proportions of what can be classified as European and West African ancestry (Reich et al. 2005). Admixture mapping relies on distinguishing these chromosomal segments of different ancestry, by the statistical enumeration of hundreds of ancestrally informative markers (AIMs) (Stephens et al. 1994; Collins-Schramm et al. 2002; Zhu et al. 2008). In recently admixed populations these ancestral segments are extremely long, requiring substantially fewer markers for scanning the entire genome than other whole genome association studies (GWAS). This characteristic makes admixture mapping more economical, more efficient, and theoretically a more powerful method for identifying common risk factors for complex disease (Stephens et al. 1994; McKeigue 1997; Collins-Schramm et al. 2002; Hoggart et al. 2004). However, admixture mapping only has statistical power to identify genetic variants that are differentially distributed across populations (Rife 1954; Chakraborty and Weiss 1988; Stephens et al. 1994; McKeigue 1997), and relatively few variants vary in frequency across human groups (Cavalli-Sforza and Piazza 1975; Jorde et al. 2001). Thus, admixture mapping is a more specialized method, and likely will only be useful for gene-hunting in a subset of complex diseases and traits. Nevertheless, the method has the potential for expansion and improvement. Most notably, many recently admixed groups exist worldwide, for which sets of informative AIMs—or admixture mapping panels—have not yet been constructed. Similarly, there are a considerable number of complex diseases which differ in prevalence across populations (McKeigue 1997; Smith and O’Brien 2005). In some cases, genetic factors may play a role. Thus, admixture mapping in combination with other methods may be of considerable use going forward.

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resolutions, gauging the mindset of these actors is both timely and important.

### Methods

For this study we used qualitative research methods: in-depth semi-structured interviews, followed by thematic data analysis (Braun and Clarke 2006) as previously described (Seguin et al. 2008).

#### Study sample and research design

We identified the African-American MS admixture study as a recent and early example of a genomic mapping strategy utilizing new population/ancestry-based genetic methodologies. Twenty-three key informants, including two African-Americans with MS, were identified through purposive and snowball sampling.

The interviews were conducted in three phases. To begin, we invited members of the African-American MS admixture study research team—who had designed and implemented the study, and/or worked closely with

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**Box 2** The African-American multiple sclerosis admixture mapping study
 

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MS was an ideal disease in which to test the proof of concept for admixture mapping (Reich et al. 2005). It is a complex disorder with strong evidence of heritable components. However before the African-American admixture mapping project, several decades of concerted research efforts had not revealed new risk loci. Most importantly with respect to admixture mapping, MS has a markedly different population prevalence, being extremely rare in sub-Saharan African groups and predominant in populations of Northern European descent. In the US, African-Americans, have a half to a third the relative risk of developing MS as do European Americans (Wallin et al. 2004). Based on this well-characterized epidemiology, and the fact that African-Americans are of mixed European and West African ancestry, the hypothesis of the MS admixture study was that genetic risk factors in African-Americans with MS should be of higher frequency in genomic regions inherited from their European ancestors. Thus, to localize these risk factors, admixture mapping scans through the entire genome of African-Americans with MS searching for regions where the proportion of European ancestry is higher than average.

To actualize the MS project (Reich et al. 2005), researchers at the Harvard/MIT 's Broad Institute who conceived the admixture study, partnered with the MS Genetics Group at the University of California at San Francisco (see: <http://www.neurology.ucsf.edu/msdb/>). This group had been gathering self-identified African-American MS cases and controls for some years. The admixture mapping study produced encouraging results—it identified a novel MS risk locus, which was indeed associated with a local increase in European ancestry. Researchers are now fine-mapping the locus to pinpoint the genetic variant(s) responsible for the admixture signal, and it is hoped, to identify a disease-associated gene, novel molecular mechanisms, and ultimately, a druggable target for therapeutic intervention.

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African-Americans with MS and controls—to participate in the study. Three of the lead scientists on the project agreed to be interviewed. In the course of these interviewees we gathered initial study information and ideas.

In the second phase of interviews we used purposive and snowball sampling to identify individuals who would have knowledge and informed perspectives on the MS admixture study, and population-based genetic research. We also used literature searches to identify potential interviewees, converging on a number of the same individuals. This group consisted of other geneticists using admixture mapping or ancestry/population-based approaches in ethnic minorities, and bioethicists/experts in bioethics and law. These individuals were selected to gain representation on both sides, or 'professional standpoints', in the race/ethnicity and genetics debate (Lee et al. 2001; Burchard et al. 2003; Cooper et al. 2003; Duster 2005; Holden 2008). Our Research Ethics Board precluded interviewing the African-American patients and controls whose DNA samples were actually scanned in this particular MS admixture mapping study. To address this limitation, we endeavoured to get a sense of the

perspectives of these research participants, and other African-American and Hispanic/Latino individuals who have participated in other admixture mapping studies, by interviewing researchers (bioethicists and geneticists) who have directly interacted with them. This was an important consideration in the selection of some of our interviewees. This second phase of interviews was used to expand, diversify and validate the issues identified in the first phase.

Finally, to further investigate and to validate these perspectives, we interviewed two African-Americans with MS in a third phase of interviews. These individuals, who had not participated in the MS admixture study, were identified through internet searches for support groups for African-Americans with MS. One said she had heard of the admixture mapping technique, but not of the African-American MS Admixture study. The other was not aware of either. Thus, their knowledge and understanding of admixture mapping was limited. Nevertheless, these individuals were able to validate and expand on relevant information identified in previous interviews.

In total, we interviewed key geneticists on the African-American MS admixture mapping project (3) in a first phase, followed by other geneticists/genome scientists using admixture mapping, ancestry and population-based approaches (9) and experts in bioethics, or legal scholars (9) in a second phase, and finally African-Americans with MS (2). Overall, our study interviewees represented a diversity of ethnicities, and relevant disciplinary backgrounds (Lee et al. 2001; Burchard et al. 2003; Cooper et al. 2003; Duster 2005; Holden 2008), working in the United States and Canada.

#### Data collection

In-depth interviews with key informants were conducted between August 2007 and March 2010. Interviewees were asked semi-structured open-ended questions during face-to-face or telephone interviews that lasted between 45 and 90 min. Interview guides were developed through our reading of the academic literature; questions focussed on exploring experiences and perspectives on (1) the actual preparation, implementation and reporting of the MS admixture study; (2) ethical, legal, social or cultural issues raised by the MS study, other admixture mapping studies, and population-based genetic research in general; (3) strategies for mitigating the ethical, social or cultural risks of these studies; (4) opinions on the value, benefits, risks and future prospects of admixture mapping, as well as on population-based genetic investigations in general. An iterative data analysis process was employed where key issues raised by interviewees were fed into subsequent interviews. In qualitative research the dataset is considered complete when a point of theoretical saturation is

reached—meaning no new major ideas, information or themes are emerging from the interviews. This point was reached at 21 interviews with the key informants. Interviews with African-Americans with MS then served to validate these themes. Interview data was corroborated using documents such as study consent forms and information materials provided by interviewees, and publically-available materials as were relevant to study questions.

#### Data analysis

All interviews were digitally-recorded and transcribed verbatim. These data were analysed using thematic analysis methods (Ryan and Bernard 2003; Braun and Clarke 2006), which are well-suited to the analysis of semi-structured interview data. The process consists of 7 key phases: (1) familiarization—in which interview data were read in-depth multiple times; (2) generating initial codes—identifying pieces of data (passages of text) relating to a common theme or idea; (3) searching for themes and verifying them across the entire dataset; (4) identifying relationships between codes, patterns and distinct differences between subgroups of ideas; (5) defining and naming themes; (6) re-reading the interviews and modifying codes based on emerging themes; and finally (7) mapping, and interpreting the overall narrative identified from the data. Atlas Ti 5.2 software was used to organize this process. To maximize the comprehensiveness and validity of our analysis, interview data were compared and triangulated with information gathered from key documents, and were considered in context of the literature.

#### Ethics consideration

The study was approved by Research Services, Ethics Review Unit of the University of Toronto. All interviewees provided written informed consent.

### Results

Our analysis identified a number of key themes and sub-themes. We present the following, which were the most compelling with respect to our research questions; (1) admixture mapping evokes sensitivities associated with race; (2) the tendency to see things in terms of race and ethnicity; and (3) the importance of moving beyond race. The importance of community engagement (as a mechanism for mitigating the ethical and social risks of population-based genetic studies) was also a key theme in the dataset. However, due to space constriction we have not reported it herein.

We also note that a few interviewees touched on social and ethical issues beyond race-related themes. These were; the need to protect the privacy of research participants, and the confidentiality of their genetic data; the need to raise awareness in the general population of the benefits of genetic research participation; and the ethical implications of creating unrealistic expectations of imminent health benefits from the research being conducted during the process of engaging and recruiting participants. Although these are all important issues, they were framed by interviewees as more general matters with respect to genetic research, rather than being specific to admixture mapping studies. Perhaps for this reason, they were not the subject of lengthy or in depth focus, by those that raised them.

Admixture mapping evokes sensitivities associated with race

#### *Historical and cultural sensitivities*

As might be anticipated, when asked about the ethical and social implications of admixture mapping, the use of race/ethnicity to group research participants, and to locate disease-associated genes was a major focus, and source of concern in almost all of our interviews. As such, interviewees—African Americans with MS, geneticists and bioethicists—said the MS admixture study had the potential to provoke sensitivities stemming from present and historical instances of racial inequity and mistreatment, in the United States.

In particular, the Tuskegee Syphilis Study (Gamble 1997) was cited by many interviewees as being infamous amongst African-Americans, and a key signifier of ‘the bad things that could happen’ out of participating in biomedical studies. As such, many interviewees felt that there is widespread distrust of the biomedical research establishment within the African-American community. Several bioethicists and the African Americans with MS we spoke to suggested that studies investigating a genetic basis for racial/ethnic differences between African-Americans and European Americans may raise particularly deep-seated concerns about the motives for the research, and the potential misuse or racial discrimination that could result from participation.

#### *Population prevalence of MS—stereotyping and inequities*

Our analysis indicated that studying MS, which is often stereotyped as a ‘white disease’, in an African-American population, raises multiple race/ethnicity-related issues. Geneticists on the African-American MS admixture study said a major concern for them was the possibility that African-Americans might view the study as exploitative,



given that MS is far more common in European groups. African-Americans with MS we spoke to confirmed that there is heightened potential for community members to take offense at such a study. They reiterated that there is a general wariness toward research participation amongst African-Americans. However, the other major theme in their interviews was a sense of injustice at inequities in MS research, treatment, outreach and education between European populations, and minorities. Many interviewees noted that historically, MS research has focussed on high prevalence groups. Likewise, geneticists who have interacted with African-Americans with MS also reported that community members expressed frustration—particularly because the MS phenotype is more severe in African-Americans, than in individuals of Northern European descent.

Our African-American interviewees expressed a strong desire to redress inequities in research, including genetic research, for MS and other conditions affecting their community. However, while they were keen advocates for increased involvement of African-Americans in studies, they emphasized that establishing the trust-worthiness of researchers is an absolutely fundamental pre-requisite for participation. Thus, one African-American with MS said:

Doctors and scientists need to learn how to address their patients' concerns and communicate the validity of such a study in a social context that makes their patients feel comfortable. This should be an integral part of their research, not just numbers and data but people.

These sentiments were reiterated by a number of other interviewees who had interacted directly with African-American communities involved in the MS and other admixture studies. Finally, geneticists on the MS admixture project reported that they have not received negative feedback about the study from African-Americans. They attributed this to careful presentation of the study to potential participants, careful research reporting, the implementation of community engagement sessions, and most importantly, to the clear relevance of this admixture mapping study to African-Americans with MS.

The tendency to see things in terms of race and ethnicity

#### *Conflating ancestry with race*

Geneticists we spoke to were quick to emphasize that admixture mapping is about ancestry—meaning, the patterns of genomic variation shaped by population history—not race. Thus, one geneticist using admixture mapping said:

For me the key word is ancestry. I am looking at ancestry as a tool to discover genes, that's all that I'm doing... when you uncouple the issue of ancestry, where the genes of your ancestors, 5, 6 generations are coming from, then it is becoming a research tool and that's all. And then is when it's becoming useful.

However, they acknowledged that concepts of race, ethnicity and ancestry are overlapping, and said they felt the three are very much conflated in the minds of the public, the media, and even many scientists. No interviewee questioned the veracity of ancestral patterning of human genetic diversity. Rather, our analysis indicated that the key ethical issue highlighted by admixture mapping is the tendency for society to understand population-based genetic research in terms of race and ethnicity. Geneticists and bioethicists we spoke to pointed out that the underlying premise of admixture mapping—that genetic variants are differentially distributed across population groups—is easily misinterpreted in ways that objectify race and encourage stereotyping. For example, the labelling of risk alleles with ancestry (see Box 1) can easily lead to the misconception that a detected genetic risk variant is ubiquitous and exclusive to a particular 'racial' or ethnic population. Thus, one bioethicist said:

There are some things that are more common in some populations than others and I don't see anything wrong with studying that. I think the problem is when we imply that these genes or these variants are unique to a particular population, as if all the people in that population have them and all those in another population do not.

Most of our interviewees said that the social and ethical risks of population-based genetic research, including admixture mapping, are strongly influenced by the way that studies are interpreted, reported and ultimately transmitted through the media to the public. As such, many interviewees—including many of the geneticists themselves—noted that geneticists need to take particular care with the interpretation and presentation of admixture mapping studies to minimize the risk of direct social harms to research populations through racial stereotyping and stigmatization, and more broadly to society through the reification of race/ethnicity.

Stigmatization and stereotyping were highlighted in our analysis as serious concerns—researchers working with African-American cohorts reported that members are highly sensitized to the potential for these harms. This view was also emphasized by the African Americans with MS we spoke to. However, geneticists who have presented admixture mapping to African-American communities reported that cohort members, and in one case the

community ethics advisory board, were comfortable that admixture mapping was appropriate once the rationale for its use and the underlying science were described. Rather than being concerned about the methodology itself, their focus was on preventing misuse of the data. Thus, one researcher working with African-American groups said:

all cohort responses that we have got in public meetings have been basically, “We are not afraid of information. What we are concerned about is irresponsible interpretation of information”. And so, there has not been a great concern about admixture mapping, per se, but rather for the potential for misinterpretation.

To date, most if not all other admixture mapping studies have focussed on diseases that are recognized major health issues of, and often more prevalent in, African-American communities (see for example, Zhu et al. 2005; Freedman et al. 2006; Kao et al. 2008). In the past, instances of group stigmatization have resulted from association with a disease-causing variant, after discovery studies in the group in question (Brandt-Rauf et al. 2006). However, the African-American MS project presents a different paradigm in that the detected risk locus is associated with European, rather than African ancestry. Theoretically then, said some interviewees, the MS study posed less of a risk of stigmatization to African-American groups. We asked geneticists about the difference in ethical implications between the MS study and other studies such as the African-American prostate cancer admixture study (Freedman et al. 2006), where the self-identified ethnic identity of the research population was the same as that of the population of highest disease prevalence. Geneticists who commented on this, said they are not different in principle—they felt both studies are simply using population history to identify genetic risk factors. Rather, several interviewees—including bioethicists and geneticists—pointed out these two study designs highlight how socio-cultural meanings can affect the way the public, the media and even scientists relate to genetic data—and also the importance of thinking about, and reporting, admixture mapping studies without objectifying race and ethnicity.

#### *‘Reifying race’ or starting from race?*

Opinions on whether admixture mapping ‘reifies race’ varied markedly amongst our interviewees, and were not clearly polarized by discipline as might have been expected (Burchard et al. 2003; Duster 2005; Holden 2008). A number of geneticists flatly disagreed with the notion that admixture mapping promotes ‘racialized’ understandings. Instead, they pointed out that it contributes to deconstructing these concepts by revealing the variety of

ancestries present within what are commonly conceived of as genetically homogenous ‘races’.

Meanwhile, other interviewees, including bioethicists and some geneticists, were adamant that any genetic studies grouping participants by race/ethnicity, reinforce the idea of these groupings as biologically ‘real’, and genetically distinct. Bioethicists reiterated that there is a contrast between geneticists’ professional interpretations of genetic ancestry-based activities, and non-geneticists’ interpretations of this work. They noted the latter tend to gravitate towards familiar frameworks of race, despite attempts to represent it in more neutral terms. Thus, it was said that despite drawing attention to the ancestral diversity within populations, admixture mapping may inadvertently highlight the salience of race/ethnicity. As such, a few interviewees pointed out that the AIMS currently used to label ancestry correspond to canonical ‘racial’ groups—African, European, Asian etc. They suggested that the act of classifying and labelling genomic segments acts to infer that these groups once existed as ‘pure’ populations. One geneticist underlined this, saying that when he returns genetic ancestry estimates to research participants, they invariably focus on ‘the numbers’—their African, European, Native American percentages, rather than appreciating the ‘estimate’ qualifier. Thus, taken together a number of interviewees felt that a major drawback of admixture mapping is that rather than disrupting concepts of race, it seems to begin with and reiterate them. In contrast, however, several interviewees suggested that debates about the reification of race have little relevance outside academic circles. They were of the opinion that most of the general public already believes in racial biological differences.

#### *A dominant cultural paradigm*

A number of interviewees felt there is an exaggerated focus on comparing races (and other pre-existing social groups) within contemporary genetic research. Thus, one geneticist said:

There’s strong evidence of racial bias that’s internal to the discipline that hasn’t been addressed within an ethical framework...and I feel like geneticists have been woefully—the genetics community—has been woefully inadequate in addressing that.

Most interviewees held that such a bias was unconscious on the part of most geneticists, the result of immersion within a highly ‘racialized’ cultural paradigm in North America. Several bioethicists noted that geneticists would be naive to believe that they are immune to such broader societal perspectives. Many interviewees mentioned the importance of the media in influencing public understanding of scientific information. However, most

emphasized that the greatest responsibility rests on geneticists to critically examine the assumptions underlying the design (the research questions asked, the populations sampled and names given to them) and the interpretation of their studies, and also to be attentive to how findings are communicated through the media to society at large. Thus, while interviewees agreed on the value of continued population-based studies, including admixture mapping, most heavily underscored the need to proceed with critical self-awareness and great care. One ethicist said:

Admixture mapping is a legitimate method, with limitations...I don't think studying populations reifies race, I think the ways studies are done sometimes reifies race, I think how studies are interpreted sometimes reifies race.

### The importance of moving beyond race

All of the geneticists we interviewed employ categories of race/ethnicity in their genetic studies. Nevertheless, most expressed discomfort with use of race, and cited social or scientific imperatives to move beyond reliance on such social identity categories for the following; (1) in genetic research, as a proxy for genetic similarity; (2) conceptually, as a framework for understanding human genomic variation; and (3) clinically, to define disease risk and drug response. Many interviewees also said that they felt the tension and differences of approaches between social and basic scientists, and the socio-political divisiveness that are evoked by race, are a hindrance to scientific, as well as social progress.

However, while looking ahead to an era where the importance of race is de-emphasized socially and clinically, many interviewees saw population-based studies in which social identity is carefully employed, as a transitional step toward this goal. One geneticist whose work focuses on African-Americans stipulated he does not study them assuming they are a homogenous group. Likewise, several geneticists specified that the aim of their work in populations is to deconstruct racial health disparities to their genetic, environmental and behavioural components. They emphasized that these groupings, and AIMs, should be regarded as research tools—a practical means to capture disparities between populations, and facilitate identification of the ultimate causative factors, with a view ultimately to reduce inequities. As such, these tools can be used well, or otherwise. Interviewees strongly cautioned against '*stopping at race*', where social identity is used—or implied—to be the explanation for disease risk or drug response in research reporting (for further discussion see, Braun et al. 2007; Ellison et al. 2007; Caulfield et al. 2009). Thus, our interviewees were opposed to the idea of 'race-based' medicine.

A good number of interviewees—including bioethicists and geneticists—were pessimistic that admixture and other population-based genetic studies per se, in the absence of societal policies and interventions, could improve the social problems associated with race. However, they—like many other interviewees—were strong advocates for concerted efforts to 'move beyond race'. Taken together, our data suggest that population-based genetic studies now need to be pushed to '*the next level*', beyond unquestioning reliance on social identity alone. Recommendations for doing so, summarized from our analysis, are presented in Table 1.

### *Ancestry—rather than race*

Most of our interviewees made a distinction between 'race' as a socio-cultural construct, and 'ancestry'—which they called a 'more biological', empirically-quantifiable measure, that sidesteps the ethical controversies associated with race. Further, geneticists cited the practical application of employing ancestry, through the use of AIMs, in their studies. Thus, they stressed that considering and accounting for variable ancestry within populations, is becoming an absolute necessity within contemporary genetic research in order to correctly analyze genomic data.

A number of geneticists and genome scientists also speculated on how genomic advances are beginning to affect our self-identity, and societal concepts of race. They said they felt that racial categories are becoming 'out-moded'. Said one geneticist, 'I think ethnicity/race is being redefined and...I think that we are very rapidly being—coming to be seen as—overlapping, admixed populations, that all have some things in common'. Several interviews noted that personal direct-to-consumer ancestry-testing in particular, is contributing to shifting public understanding, and dissolving classical notions about racial boundaries. Overall however, our analysis underscored the relative and time-dependent nature of racial, ethnic and genetic ancestry categories. Thus, multiple bioethicists and geneticists noted that the continental identities assigned to genetic ancestries reflect our contemporary perspective on global populations. As such, one geneticist summed up the use of these systems pointing out, '... you know any of these models that consider different parts of the world are false, in that we're really all African -all the evidence points towards a common human origin in East Africa'.

### *Anchoring population genetics in ancestry*

Many interviewees cited the promise of population-based studies to extend understandings of human disease, physiology, identity and relatedness, and of our species' place in the greater web of life on earth. However, to maximize

**Table 1** Recommendations from our analysis for moving beyond frameworks based on race, in population-based genetic studies**Study framework and design**

Consider study designs and groupings that do not rely on race/ethnicity; for example, genotype, disease subtype corrected for genetic ancestry etc., as appropriate to the research question.

Do not use race/ethnicity as an explanation for biological outcomes; endeavour to identify the ultimate determinants—genetic, environmental, behavioural etc—of the complex disease or trait in question.

Design inter-disciplinary studies to investigate the full-spectrum of determinants of complex phenotype— environmental, behavioural and genetic- and the interactions among them.

Where applicable, extend the breadth and depth of human genomic variation studies, encompassing systematic sampling across socio-political boundaries, within and across socially-identified groups.

**Research interpretation, communication and follow-up**

Avoid objectifying race/ethnicity in interpreting admixture mapping and other population-based studies. For example, in reporting admixture mapping make it clear that the detected risk alleles occur across 'racial'/ethnic boundaries; and emphasize that population history, rather than genetic differences between groups, is being used to localize variants more efficiently.

Critically examine assumptions about race and ethnicity, including both overt and implicit messages, when designing, interpreting and communicating studies.

Take into account historical and socio-cultural perspectives on human difference/race/ethnicity.

Provide a population history and bio-geographic ancestry-based framework for population-based genetic studies.

Conduct follow-up studies in multiple populations to validate results from population-specific investigations, and to fully understand how the variant(s) influence the complex trait in question.

**Education, training and outreach**

Include on research teams individuals with expertise in (1) historical and socio-cultural perspectives on human difference/race/ethnicity; (2) effective engagement of non-scientist audiences.

Promote the social awareness of geneticists and the media, and greater engagement between these groups.

Encourage the genetic literacy of research communities and the public—with relevant stakeholders including social scientists, bioethicists, the media, and the public themselves involved, in addition to geneticists.

Create opportunities for open public discourse about the nature of human genomic variation, social identity and health disparities.

these benefits and minimize social and ethical harms, interviewees emphasized the importance of promoting public understanding of genomic diversity that goes beyond simplistic stereotypes. To do so, the need for a more nuanced, informed approach to communication and representation of research findings, particularly by geneticists, was underscored. For example, several geneticists suggested that when addressing the public or the press, researchers should begin by situating their research in a global, evolutionary context—emphasizing the recent common origin of the human species, the genetic similarity between groups, and explaining the reason for phenotypic differences between individuals of varying geographical ancestries. As such, the lead author on the MS study has explained the admixture method in the press by saying, “We are asking, if you trace a segment of DNA back six generations, where did it live, in West Africa or Europe?” (see <http://genepath.med.harvard.edu/~reich/>). Thus, more proactive communication of research findings, education of research populations and the public, and increased opportunities for public discussion of the links between 'racial'/ethnic identity, genetics and health disparities were emphasized as important strategies by most interviewees. Some suggested that popular media such as the television series *African-American Lives* (see: <http://www.pbs.org/wnet/aalives/>), and the availability of personal ancestry services, are also good exemplars. Likewise, several geneticists particularly emphasized the ongoing value of providing such genetics education during community engagement sessions. Nevertheless, our data indicate such educational activities need to be expanded, and should be an ongoing and iterative process.

**Discussion**

In this study we draw on key informants in the field of population-based genetic research to document developing perspectives on the ethical and social implications of admixture mapping, and other genetic studies using social identity. Our data underscores persistent concerns about the ethical and social risks of this research, but they also reveal hopefulness about the potential opportunity offered for biomedical, and even social, progress. Clearly, our findings reflect the views of a relatively small sample, of which many have vested interests in genetic research. However, we report themes which could be further examined in larger and more diverse groups of stakeholders, including non-scientists and members of minority groups. Similarly, admixture mapping raises social, ethical and other non-



science issues beyond those directly relating to race and ethnicity. We have reported key themes from our interviews herein. That the other issues were not major taking points may reflect the strong feelings that issues of race evoke, and the tendency for these to override other issues, at least initially, in discussions about population-based genetic research, and perhaps particularly in North America. Similarly, it should be noted genetic ancestry testing was not the focus of this study. However, genetic ancestry testing, which uses similar technology to admixture mapping raises many similar, and some distinct, socio-ethical, and also economic issues. Notably the advertisement and return of genetic ancestry testing can represent a key teachable moment with regards to genetics, population history and social identity. These issues could be profitably examined in future study.

Our analysis suggests that stakeholders are aware that population-based studies, including admixture mapping, currently rely heavily on socially-constructed concepts of human groupings, and that they are cognizant of the inherent risks. However, it seems geneticists and research participants employ or tolerate these constructs to attain what they see as greater public good: better biomedical knowledge and more nuanced understanding of human genomic diversity. As such, the desire to ‘move beyond’ race was a dominant theme in our dataset. This finding may reflect some degree of participant bias. However, it is significant as it may indicate a ‘readiness for change’ amongst geneticists, and the likelihood of their uptaking future policy aimed at minimizing the socio-ethical risks and maximizing the benefits of population-based studies.

The use of social identity in studies can have unanticipated consequences (for review, see Caulfield et al. 2009, and refs therein). As such, a key contention arising in our data was whether or not admixture mapping (and more generally, genetic research that uses social identity) can assist in moving beyond race. Our analysis suggests this issue to some degree turns on how studies are designed and conducted, and particularly how they are interpreted and communicated to society. Each stage should be implemented with the intention to avoid objectifying social identity including race/ethnicity, and also ancestry. Nevertheless, as many commentators have noted (for review, see Caulfield et al. 2009), and as reiterated by our data, it is extremely difficult to compartmentalize scientific meanings and uses of groupings like race or ethnicity from their social resonances. As such, our study underlines the need for deepening public understanding of genetics and ancestry, and for sustained and conscientious efforts toward challenging and deconstructing stereotypes. How this could be best achieved warrants further in-depth investigation. However, while others have published suggestions for the use of race/ethnicity in biomedical research

(Kaplan and Bennett 2003; Condit 2007; Caulfield et al. 2009), we provide recommendations for ‘moving beyond race’ (Table 1).

Our data suggested that it is incumbent on geneticists, as the producers of genetic knowledge, to take a leading role in acting on these recommendations. However, multiple players influence the creation of scientific knowledge, and its translation, dissemination, and assimilation into popular consciousness. Thus, the goal of moving beyond race is a shared responsibility, and should be ‘co-cultivated’ by all stakeholders—including social scientists, bioethicists, research funding bodies, journal editorial boards, the media and the public—in addition to geneticists. More open discourse and engagement, and setting and aligning of goals among these parties, are needed. This could play out in multiple ways. For example, increased collaboration of social scientists with basic scientists could synergize on dissecting biological from environmental determinants of health disparities, and on translating the findings into policy to redress inequities. They might also foster greater recognition of non-genetic modifiers of phenotype, and facilitate better management of socio-ethical issues and community engagement. Similarly, interdisciplinary professional development workshops between geneticists and media could promote engagement, instruct on more nuanced research reporting, and raise awareness of the societal implications of their work.

An important recommendation arising from our data was to endeavour to interpret admixture mapping, and other population-specific investigations, without objectifying race/ethnicity. However, the findings of these studies will often be most applicable to the community in which the research was done. As others have commented (Dunston 2000; Sharp and Foster 2002), and our data reinforced, the self-identity of research populations will be an absolutely meaningful aspect of the study to them (see for example, Jackson Heart Study at <http://jhs.jsums.edu/jhsinfo/>). Our analysis emphasized how social meanings are evoked, and how they must be addressed alongside the genetics in doing population-based genetics. Thus, the need for ongoing community engagement—including involvement in the research planning and execution, and consultation with respect to its interpretation—and the vital importance of researchers (or members of the research team) having the skill set to communicate with lay audiences about their work, are absolutely fundamental to maximizing the benefits of these studies.

Many interviewees pointed out that grounding population-based studies within a framework of population history and geographical origin, rather than race/ethnicity, would assist in redressing some of the ethical and social concerns arising from this research. In addition, with regard to admixture mapping, the AIMs used in genetic

studies may soon distinguish groupings on a finer scale than the current continentally-aligned versions (Novembre et al. 2008)—thus contributing to deconstructing racial preconceptions.

With the rapidly growing public health importance of complex disease and increasing focus on genomics, both developed and developing countries are undertaking population-based initiatives including admixture mapping (Smith et al. 2001; Mao et al. 2007; Seguin et al. 2008; Xu and Jin 2008). While personalized or ‘individualized’ genomics has been widely discussed as the ultimate goal of this work, detected variants will nevertheless fall into genetic sub-populations, some of which may correlate with social identity (Palmieri et al. 2008; Lahn and Eisenstein 2009; Li et al. 2009). In addition, the risk associated with particular genotypes may vary with race/ethnicity (Christensen et al. 2008). This may be due to the ancestral genetic background on which the risk factor occurs—what has been referred to as ‘statistical race’ (Lee 2009). Equally, it may be due to socio-cultural or environmental factors associated with the individual’s phenotypic or self-identified race/ethnicity. This complexity underlines the importance of studying the effects of risk variants across populations of varying geographic ancestry and environments, and reiterates the utility of admixed populations in this regard (Cooper et al. 2008; Behar et al. 2010). It also underscores the urgent need to develop effective communication and education strategies for clinicians, the media, research participants, and the public about what genetic variation and ancestry mean, and do not mean, with respect to race.

As more admixture and ancestry-based studies are published, developing views on these activities, and their implications, should be monitored. Racial/ethnic discrimination is a challenge facing societies globally, and if not checked may translate to inequities in the development of new treatments, and their application. Our study suggests the potential of admixture mapping, and other ancestry and population-based genetic studies, to contribute to improved social understanding, as well as biomedical progress. A pragmatic approach—recognizing, accounting for, taking advantage of and openly talking about the history of populations when doing these studies—will allow us to reach these goals more efficiently. Throughout, an ongoing commitment to challenging assumptions about race and ethnicity, thoughtful self-awareness and strong ethical leadership from geneticists, bioethicists and from communities themselves must be essential components of this work.

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