Commentary

Ancestry in translational genomic medicine: handle with care

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Abstract

Disparities in health outcomes of members of different ancestral or ethnic groups can be observed in both developed and developing countries and continue to be a global concern. Genomic medicine can help toward closing this gap by expanding the knowledge on novel alleles related to disease risk and drug response, their frequencies, and their relation with disease and drug-response phenotypes, in as many countries and ethnic groups as possible. Without such knowledge, genomic medicine cannot deliver upon its promise of contributing to health for all. However, the use of ancestry or ethnicity-related genetic information as a selection criterion for assigning varying levels of access to health care is condemnable. Translational genomic medicine will allow for individualized clinical decision making - doing away with the use of race, ethnicity or ancestry as a proxy.

The study of ancestry or ethnicity in biological and clinical sciences continues to raise controversy. In May 2001 the *New England Journal of Medicine* (*NEJM*) published a landmark study reporting that African-American heart failure patients with left ventricular dysfunction did not benefit from the popular angiotensin-converting enzyme inhibitor drug enalapril, while the same drug reduced the heart failure hospitalization risk of Caucasian patients by 44% [1]. The *NEJM* report, which eventually paved the road for the US Food and Drug Administration (FDA) approval of BiDil as the first 'ethnic medicine' four years later, was accompanied by two editorials - a rare practice for the *NEJM* - one heralding it as 'great help to physicians in their attempt to choose the best therapy for heart failure in patients of different races' [2], and the other condemning it and demanding that 'tax-supported trolling of data bases to find racial distinctions in human biology must end' [3]. Large disparities in health outcomes among socioeconomic and ethnic groups remain well documented, even in developed countries, and include drug-response variations due to genetic polymorphisms with different frequencies in different population subgroups [4]. Besides, it is unsurprising that many drugs work better for Caucasian patients, given the fact that a clear majority of clinical trial participants are of European ancestry [5]. Using ancestry or race/ethnicity as a surrogate biomarker for drug choice at the level of the individual is acceptable when this is the only approximation available until better biomarkers for clinical response are discovered and validated [6]. Using ancestry for establishing shortcuts in healthcare policy, however, is not an acceptable practice.

Personalized medicine: the individual in context

In biomedical research, using race and ethnicity for stratification and in the reporting of results is often misleading and may skew scientific outcomes, as outlined by Timothy Caulfield and colleagues' well-thought out manuscript in the

January 2009 issue of *Genome Medicine* [7]. In healthcare policy making, using 'genetic explanations' for ancestry-based provision of services is controversial at the very least. It is a risky practice, potentially leading down the slippery slope of denying individuals equal access to prevention and care based on their ancestral background. At the same time, the current practice of setting specific criteria for the allocation of some healthcare resources, as, for example, determining the eligibility criteria for screening, shows the urgent need for personalized medicine.

An article comparing the cost-effectiveness of colorectal cancer screening in different ethnic groups may illustrate these two aspects [8]. The study examined the cost-effectiveness of various screening methods for colorectal cancer in different population subgroups in the USA, using age, gender and race/ethnicity as classifiers for stratification. The authors concluded that 'the cost-effectiveness of a 35-year screening program in black men beginning at age 45 was ... more cost-effective than screening nonblack women as well as Asian and Latino men beginning at age 50'. However, even if these calculations may be correct, they are utterly insufficient in the era of genomic medicine. More subtle information will be coming, including genetic biomarkers for cancer susceptibility, which we should use in the near future in order not to fall short of due care at the individual level.

Isaac Kohane, in his January 2009 *Genome Medicine* commentary [9], asks 'who are you and whom do you most resemble?' He convincingly argues that personalized decision making requires the combination of information about the population subgroup a person belongs to, along with information about the particular individual. Both genomic and non-genomic information must be taken into account.

When it comes to allocating resources for personalized medicine, the crucial policy discussion remains that of 'whose utilities are being maximized, society's or the patient's' [9]. While the prudent balancing of societal and individual interests when deciding on policy matters always requires tough choices, the patient's ancestry should never be employed for denying access to health services, just as it should never be employed for denying access to education or employment.

Translational genomics and human diversity

One of the greatest threats to human integrity and freedom is the classification of individuals according to their ancestry/race/ethnicity for assigning civil rights and access to societal resources. The risk of harm is even larger when such classifiers are linked to genetic information, given that the latter is permanent, has inherent privacy risks in the age of electronic information management, and has implications for immediate family members [10]. The 20th century has taught us horrifying lessons on the risks that ethnic classification poses to human integrity and freedom - lessons that should not be forgotten when building up for better health care in the 21st century. Translational genomic medicine must strive to achieve so that no one can refer to 'genetic evidence' for supporting healthcare policy guidelines that block the access of individuals to medicines or diagnostic services based on their ancestry. Efforts toward minimizing healthcare disparities between particular communities are imperative. Such efforts should include establishing new links between gene alleles, disease risks and drug-response phenotypes in as many distinct populations as possible. Moreover, different genes, not just different alleles for the same gene, may account for drug response in different ethnic groups. One example is azathioprine-mediated myelotoxicity, which is primarily linked to thiopurine methyltransferase deficiency among Europeans, Africans and Native Americans but to inosine triphosphate pyrophosphatase deficiency among Asians [11]. The translation of such findings into clinical practice can lead to different diagnostic or treatment strategies in different countries, based on considerations related to their major local ethnic populations. But, as Caulfield *et al.* implied [7], how effective can such strategies be in countries with extensive population admixture?

Translational genomic medicine: personalized, multiracial

Humans differ in their disease susceptibility and drug response, with genetic and genomic variations often contributing to such individual differences. Pharmacogenetics, which plays a key role in personalized medicine, studies the heritable variations affecting drug response. Currently, it is the lack of prospective validation studies on genetic markers for drug safety and efficacy, and not a lack of knowledge about ethnic variations, that hinders the wider clinical uptake of pharmacogenetics [12]. If personalized medicine is to succeed as a research discipline and in its clinical application, it must be comprehensive and take into account both heritable and non-heritable factors affecting drug response. This has been the message of personalized medicine from its onset, and it must remain so, putting aside any attempts - be they driven by sheer commercial interests or cost-effectiveness considerations - for the establishment of ancestry/ethnicity as 'easy shortcuts'.

It is time to recognize that 'we are all multiracial, related to each other only to a greater or lesser extent', quoting Aravinda Chakravarti, who claims that we must change our concepts on family, population and race [13]. Consider, for example, that the 44th President of the United States of America, portrayed by the media as an African-American, would be assigned - were he sending his DNA sample to one of the commercial personal genome providers - as Caucasian based on his mitochondrial DNA (having a Caucasian mother), but as an African-American (or rather, of Kenyan

ancestry) based on his Y chromosome. So, genetically speaking, is President Barack Obama an African-American or a Caucasian? Neither. Like all his fellow humans, he is a member of the human race.

Abbreviations

NEJM, *New England Journal of Medicine*.

Competing interests

The authors declare that no conflict of interest exists.

Authors' contributions

Both authors took part in writing the manuscript.

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