Published in final edited form as:
Per Med. 2012 November ; 9(8): 839–847. doi:10.2217/PME.12.100.

Why personalized medicine will fail if we stay the course

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Abstract

Genomic science and associated technologies are providing scientists and clinicians with novel insights that are transforming the delivery of healthcare and the overall well-being of society. However, these insights inform us that historical population sampling approaches for investigating rare and common genetic variations are not representative of the complex ancestral backgrounds of today's patients. In order for personalized medicine to be meaningful and applicable to the global populations, we will need to know how common and rare genetic variants found in different parts of the world influence health and drug response. This article demonstrates the importance of increasing ethnic and racial diversity among participants in genomic research, highlights areas of opportunity for improving our understanding of genomic diversity among populations, and provides examples of successful models that help to resolve these concerns.

Keywords

diversity; ethnicity; genomic medicine; global populations; personalized medicine

As scientists continue to unravel the information encoded in our genomes, clinical decision-making will increasingly incorporate human genetic variation in the hope of tailoring therapies to maximize efficacy and reduce adverse drug effects [1,2]. This medical utopia is generally referred to as personalized medicine, a concept that is as old as the practice of medicine itself [3]. However, the definition of personalized medicine has been revitalized and expanded in the genomic era with the growing inventory of human genetic variation. Therefore, for the purposes of this perspective, we acknowledge that personalized medicine is a dynamic and broad term used to describe the incorporation of patients' genomic profiles, family history and other health details into clinical decision-making. As such, the present-day practice of personalized medicine employs genetic-screening and -testing technologies aimed at providing physicians with sharper insights into a variety of clinical scenarios. For example, pharmacogenomics, the study of gene–drug interactions, has already begun to influence prescribing methods for pharmaceutical drugs known to have variable responses based on patients' genetic profiles [4].

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Financial & competing interests disclosure The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
No writing assistance was utilized in the production of this manuscript.

Genomic, and especially pharmacogenomic, data continue to drive a paradigm shift in medical practice; however, the path to personalized medicine is not without obstacles. Soon after the completion of the human genome project in 2003, for instance, scholars and international advisory bodies argued that entire populations would be neglected by pharmaceutical companies seeking to profit at the expense of individuals with rare genetic variations [5–8]. Similarly, when discoveries in genetics started to signal the shift in focus from one-size-fits-all medicine to individualized treatment, it was argued that the application of personalized medicine would be limited to patients with well-understood genotypes. If these predictions are correct – and the forecasts seem to be coming true – disparate access to routine and cutting-edge treatment will continue to foster healthcare inequalities in medicine. Furthermore, challenges to access may extend far beyond questions about who can afford genetic testing, DNA microarray analysis and high-throughput sequencing technologies.

We argue that the potential strengths of personalized medicine could also be undermined by the lack of inclusion of genetically diverse human populations. Specifically, genomic research has not been evolving congruently with the genetic make up of our global society. This is not to say that the scientific literature has been devoid of efforts to draw awareness to this problem (e.g., pharmacogenomics of neglected diseases [9]), but rather that these calls for change have been, for the most part, unheard or ignored. To ensure the long-term success of personalized medicine, researchers and providers will need to identify and examine genetic variations among a wide range of human populations with ancestry from different parts of the world. Otherwise, we are risking the eventual bimodal classification of patients: those whose genetic variations we understand clinically and everyone else. This breakdown could create health burdens that discriminate across populations and ethnic identities. In this perspective, we illuminate the link between current failures to include all populations in genomic research and the potential failure of personalized medicine to apply to all individuals who make up our genetically diverse human race.

Moving beyond race to guide individualized treatment

The CDC reports that adverse drug reactions (ADRs) cause 700,000 visits to the emergency department and 120,000 hospitalizations annually [101]. Although knowledge gained in genomics has advanced our understanding of biology, the promise of personalized medicine continues to appear far off. Pharmacogenomic information has been added to over 70 drug labels [101], but the studies on which label information are based have mostly focused on European populations. Meanwhile, African populations, who have the greatest genetic variation resulting in more haplo types, lower levels of linkage disequilibrium, more divergent patterns of linkage disequilibrium and more complex patterns of population substructure, are grossly underrepresented in the genomic studies that inform pharmaceutical guidance [10]. The result is that clinicians may rely too heavily on data obtained from Europeans to make clinical decisions for Africans and other non-European populations. In addition, this inadequate representation of global populations in the cataloging of genetic variation is hindering the need to move away from the use of group labels such as race, which is often a poor proxy for genetic ancestry.

Studies that expand our knowledge of the genetic variants and corresponding phenotypic features that contribute to disease and treatment outcomes will be necessary to make our genomic interventions more precise and relevant to all populations. A significant proportion of ADRs could be prevented, for example, if investigators and physicians had a more robust understanding of the distribution of human genetic variation across our genomically diverse global populations [11]. A powerful example of pharmacogenomic data used to avoid life-threatening ADRs is the association of the *HLA-B*1502* allele with carbamazepine-induced

Stevens–Johnson syndrome and toxic epidermal necrosis. This allele highlights the power of pharmacogenomics (and the need for inclusion of global populations) illustrated by its striking association in Han Chinese patients (44 out of 44) that experienced carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrosis [12]. Moreover, it is estimated that nearly 60% of ADRs are potentially linked to variations in phase I drug-metabolizing enzymes [13], of which hundreds of genes have been identified, with some functional variants already making their way to US FDA drug labels [102]. Clearly, the impact on reducing ADRs will be driven largely by the implementation of pharmacogenomic data.

Inclusionary policies at leading research institutions, such as the NIH and the FDA, aim to increase ethnic diversity in biomedical research. For example, the NIH and FDA have taken steps to help facilitate the recruitment of research participants from different gender, racial and age groups in studies funded by their agencies. Furthermore, if the evidence supports a difference in response among these groups, the NIH requires researchers to assess how demographic factors affect research outcomes. Similarly, the FDA requires sponsors of new drug applications to “include summaries of effectiveness and safety data for important demographic subgroups, including racial subgroups” and to annually tabulate the number of research participants in each group. Still, underrepresented groups remain poorly defined [14] and insufficiently engaged [15]. Research on European populations to the exclusion of others continues to predominate genetic studies. Furthermore, as per agency requirements, investigators may classify study participants using only six racial categories devised by the US Office of Management and Budget (i.e., American–Indian/Alaska Native, Asian, black/African–American, Native Hawaiian/other Pacific Islander and white). Meanwhile, when recording ethnicity, investigators may choose among two options: `Hispanic/Latino' and `not Hispanic/Latino.'

Resistance to these categories has been widely reported in the USA. While the Office of Management and Budget labels [103] have technical benefits for staff at the Department of Health and Human Services (i.e., allowing them to share data in standardized and consistent formats), they fail within the context of our ethnically diverse nation where people are increasingly classifying themselves in more complex ways. An increasing number of adults are choosing to identify with ethnicities that go beyond the designated ethnic labels provided on the US census form. The US Census Bureau also reported in 2012 that more than half of all children in America under the age of 1 year are underrepresented minorities [104]. It is strikingly obvious that the census checkboxes available to USA residents are outdated and inadequate descriptors of the ethnic populations that participate in research. Gaps in research outcomes are created by the repeated overreliance on broad racial and ethnic categories, as well as the inadequate examination of important health indicators, such as socioeconomic contributors to disease and the role of gene–environment interactions.

Fortunately, next-generation sequencing technologies offer investigators an opportunity to record and assess human variation on unprecedented levels, providing us with new opportunities to include more diverse populations in research [10]. In addition, as international genomic projects begin to bear fruit, we are offered a new way of viewing diversity among individuals and global populations; a potential solution to the inadequate enrollment and engagement of diverse communities in research. Specifically, the 1000 Genomes Project has surpassed its namesake with well over 1000 human genomes sequenced [105]. Initial analyses such as principal components analysis describe the relationship of these populations to be largely reflected by geopolitical boundaries. However, nuances arise when describing populations intracontinentally, for example, or when deciphering the relationship of admixed populations. One of the best examples that highlights the variation of a given population is African–Americans. African and European

ancestry in self-identified African–Americans can vary wildly with proportions of European ancestry spanning the full range of variation, which can have significant impact on how we identify disease loci [16]. Broad ranges of variation have also been found in other admixed populations such as individuals from Mexico. When considering parental populations, groups from continental Africa have acquired vastly different genetic profiles due in part to culture, geography or simply a longer evolutionary history resulting in more complex patterns of genetic variation. With growing interest in understanding how low-frequency and rare variants influence complex diseases, risks and variable drug responses [17], the inadequacies of large umbrella population labels (e.g., `blacks' or `Hispanics') have become glaring. A recent study detailing the examination of rare functional variants specifically in the context of drug target genes concluded that there is a substantial amount of rare variation that is likely to be population specific providing further support for the inclusion of diverse groups in genomic research [18].

The implications of this phenomenon have been examined in Brazil and other populations that self-identify with a particular race. Several studies have shown, for instance, that there is a disassociation between Brazilians' self-reported `color' on census forms and their genomic ancestry [19]. Others have noted that the term, `Caucasian' can be misleading because it fails to account for white patients with founder populations that carry disease-specific alleles, such as French Canadians or Ashkenazi Jews [20]. Ultimately, race and ethnicity are poor proxies for individual genetic variation [21]. Moreover, these categories are heavily influenced by ideological concepts, vulnerable to political and social exploitation, and are often inconsistent with one's individual genetic make up. The complexities of race and the acknowledgement of many other factors that need to be taken into consideration have given rise to new paradigms such as ethnogenetic layering, which provides an “alternative to the current reliance of the biological racial paradigm in public health, epidemiology, and biomedicine” by integrating “information on relevant geographic, environmental, cultural, genetic, historical and demographic variables needed to understand local group expressions of disease inequities” [22].

Furthermore, studies that include adequate African–American representation often do so to compare this population with those of European ancestry, to develop a race-based drug, such as BiDil® (Arbor Pharmaceuticals, GA, USA; the first race-based drug approved by the FDA) [23], or to engage in other practices that result in gaps in knowledge about non-African–American and nonwhite populations. These concerns intersect with existing public policies that could lead to health disparities [24]. Currently, drug manufacturers only describe observed phenomena on a drug label and must present substantial evidence to support each indication. With few pharmacogenomic variants meeting this criterion, the burden is on the clinician to assess the efficacy and safety of medication with possible but unclear pharmacogemonic implications for patient care. This phenomenon creates yet another potential obstacle to implementation given that genetics and genomics has been slowly adopted by medical training curricula.

Informing genomic research with ethnically diverse cohorts

Although race and ethnicity are inadequate proxies for individual genetic variation, the success of personalized medicine will depend on how well we understand genetic variation among ethnically diverse populations [25,26]. Genetics have played a role in clinical decision-making for many years. For example, recording a patient's family history provides a useful perspective of heritable traits that may provide clues into disease susceptibility and may even inform appropriate treatment regimens. However, in the past decade, family history has been increasingly supplemented by specific genetics and genomics information that can help predict the onset of disease as well as guide drug prescription. To continue on

this path to fully understanding disease and treating people with diverse ancestry, researchers must capture genetic variation across the globe, expand upon the data sets that inform genomic medicine and translate these findings into clinical care.

To date, the successful translation of human genetic variation into an actionable component of clinical care has been largely bolstered by the rapid growth of genome-wide association studies (GWASs), which are published at a dizzying pace and proven to be a methodological workhorse in the effort to uncover genetic variants associated with disease and disease-related traits [27]. With just under 100 GWASs published prior to 2008, the current catalog lists nearly 1300 publications as of June 2012 [106]. These publications have reported on phenotypes ranging from cancers to cardiovascular diseases, to metabolic and mental-health disorders, to behavioral traits and almost everything in between. In short, the successes of GWASs have opened the door to translating these observed genetic differences into a critical component of medical care.

Furthermore, the number of potential genetic risk factors identified by GWASs provides insight into the etiology of a variety of common complex human diseases and disorders. Case–control and cohort studies have expanded from hundreds to thousands, and even hundreds of thousands of participants, in order to tease out genetic variants contributing to the onset of diseases, which include those with significant public health implications. Although several problems have been noted. First, most GWASs, and other linkage and candidate-gene studies, have focused on European-ancestry populations with approximately 90% of GWASs relying on participants of European ancestry [25,28]. Second, the rate of discovery for significantly associated variants has disproportionately outpaced the identification of functional variants, which have a better chance of explaining genetic influences on disease outcome. There are arguments made for and against a number of strategies to address this dilemma, which is sometimes called the `missing heritability' of complex diseases [29]. Potential strategies include supporting more family studies, further examining rare variants and leveraging animal models. We argue that studies of genetic variation in diverse populations are also an important strategy given that disease-associated variants may be population specific or their frequencies may vary widely across global populations [30]. The absence of multiple global ethnicities in genetic association studies have previously illustrated the effects of incorrectly assuming that populations of the same shared ancestry are sufficient for comprehensively identifying important genetic markers associated with a particular disease trait [26]. While our focus in this perspective is to describe the impact of surveying and understanding the scope of genomic variation, it is worth noting that the lack of phenotype and epidemiological data may be equally detrimental and must be considered when seeking to include multiple global populations in future studies.

A potential tipping point in the utility of genomic information in clinical care and, ultimately, personalized medicine, is the field of pharmacogenomics [31–34]. Prescribing the appropriate drug is an art of medicine often dictated by feedback from the patient, which may include a trial-and-error approach that could bring about painful and sometimes fatal side effects. Just as genetic variants are being linked to disease susceptibility, there are increasing data published on the ability to predict drug response based on known positions in the human genome. The development of gene chips specifically designed to assess polymorphic alleles of drug-metabolizing enzymes and other genes involved in the absorption, distribution, metabolism and excretion (ADME) of drugs offers an alternative in identifying variants useful in a clinical setting [35]. Interrogating ADME-specific or -related variants can be viewed as an expansion of the candidate-gene approach (i.e., multiple candidate genes) and may have advantages over GWASs, which are agnostic surveys of a representation of the total genetic variation in the human genome.

Pharmacogenomics provides an exciting area of research with a potentially quicker translational turnaround. Unlike most GWAS-identified risk loci with unclear functional implications, pharmacogenomic variants associated with drug response tend to have immediate clinical relevance [36]. A genetic test of select pharmacogenomic variants can help identify the appropriate drug that will get the patient on the road to recovery faster and more safely. Importantly, pharmacogenomics is also an opportunity to illustrate the impact of human genetic variation in the context of global populations. Despite the successes in GWASs, the slow pace to include multiple populations has left an abundance of information in the dark. However, because the translation of GWAS results remains slow, the clinical impact is yet to be determined. If an ethnic monolithic approach is also taken with pharmacogenomics, then a divide is created from the start and the benefit is clearly relegated to some and not to all. Therefore, in order to appreciate the impact of global genetic variation, multiple populations with different ancestral backgrounds must be studied.

As Table 1 demonstrates, it is shortsighted to think that a population of a single shared ancestry is sufficient to explain human genetic variation as a whole. Using a measure of population differentiation (F_{ST}) [37], we demonstrate the relationship of minor allele frequencies between global populations of variants within known ADME genes (Table 1). As expected, population differentiation is high at many positions when comparing African-ancestry populations with other continental populations [38]. However, illustrating the point further are the several dozen sites with moderate-to-strong population differences exhibited within African-ancestry pairwise comparisons. Clearly, a group label of `black', for example, is insufficient in clinical decision-making when considering the pharmacogenomic variation observed in multiple populations of African ancestry. Globally, similar complexities are observed in countries of rich admixture such as Brazil, where F_{ST} analyses highlight the challenges in nation-wide drug selection [39]. Thus, inferring the genetic make up of patients based on the ethnic or racial groups with which they identify could have serious health implications for patients. In addition, broader concerns for regulatory actions such as drug assessment, particularly for countries lacking extensive pharmacogenomic data, are warranted [40].

Engaging underrepresented populations in genomic research

Of the global ethnicities poorly represented in genetic research, samples from the oldest populations with the greatest amount of genetic variation (i.e., individuals of African ancestry) are at the top of the list. Foregoing the debate for a moment that African populations (as others) should be considered for genetics research based purely on the argument of equality, a logical scientific approach towards understanding the scope and depth of human genetic variation would be to start at the birthplace of mankind. However, it is clear that this has not been the strategy of the global scientific communities for multiple reasons, including economic, political and scientific. For example, dozens of gene chips that provide a means to interrogate the human genome have come to market over the past decade. However, the genetic variation captured on these chips overwhelmingly represents variation found in European-ancestry populations despite the African continent containing the highest amount of genetic diversity. It was only in 2011 that a gene chip was designed to specifically maximize coverage of alleles common and rare to African populations [107]. The lack of appropriate genomic tools provides further disincentive to include poorly represented global populations. It is important to note that calls for the inclusion of global populations are not fleeting cries of political correctness but rather necessary alternatives in order to comprehensively inform disease/trait etiology [15].

Examples of successful models

Significant efforts to bring Africa into the conversation have been made possible by initiatives such as the International HapMap Project [108] and the 1000 Genomes Project [105] but the full potential of these data sets is slowly being realized. Meanwhile, smaller consortia and even smaller collaborative projects are beginning to leverage global populations in genetics studies. For example, the genetic architecture of non-European-ancestry populations proved fruitful in their contribution to narrowing disease-associated loci and uncovering novel variants [41–43]. These findings were based on cohorts of non-European ancestry individuals that have contributed to our understanding of human genetic variation. Specifically, the HUFS trial successfully recruited thousands of African–Americans from the Washington (DC, USA) metropolitan area [44]. Samples from the HUFS trial participants provided data for novel discovery or replication of genetic variants associated with metabolic disorders, cardiovascular disease, kidney disease and related traits based on GWASs, linkage studies and admixture mapping [41,44,45]. Similarly, the AADM study has recruited over 6000 sub-Saharan Africans primarily from Ghana, Nigeria and Kenya [46]. Initial findings utilizing AADM study samples were born from linkage studies but are now moving towards GWASs of common complex diseases such as hypertension, obesity and Type 2 diabetes [47–49]. In addition, the two GWASs addressing major public health issues in Africa, malaria and tuberculosis, were made possible by networks established within Africa – the MalariaGen [109] and the African TB Genetics consortia, respectively [50–52].

The success stories of genetic variation studies across global populations must also be matched with the reality of implementation. Addressing disparities of representation in genomic studies is certainly an important and large part of the solution; however, if no infrastructure is available as part of the translational pipeline then these efforts will fall short. The Human Heredity and Health in Africa (H3 Africa) initiative [110] is an excellent example of efforts to develop a framework designed to integrate biomedical research into public health strategies to positively impact African populations. Efforts such as H3 Africa are especially needed in countries lacking adequate health-delivery systems.

Role of community engagement

International successes such as those from Africa described above exemplify an understanding of community engagement. The legwork carried out, speaking with elders, approaching community liaisons, getting `in the trenches' and fully engaging local scientists, went a long way towards building trust. Another important component was making sure individuals understood the premise of the study and what exactly their role would be and what would be gained from participating. This was wonderfully illustrated by the informed consent process tailored to Ethiopian participants in a project aimed at understanding the geochemical disease podoconiosis [53]. Not only were the findings ground-breaking in that the study shed significant light on the genetic basis of podoconiosis [54], but these significant efforts were put forth to acknowledge that a different process was needed to educate and inform such a unique international community [55].

Although the added precautions needed to properly engage and demonstrate respect for different communities may seem burdensome and economically challenging, it is required to build trusting relationships that will ensure long-term participation in genomic research by all types of people [56,57]. Historically, research involving indigenous populations, for example, has failed to observe long-held indigenous values and beliefs [58], leading to a legacy of mistrust of research institutions by Native American communities [56]. Culturally sensitive policies and general openness among investigators to establish partnerships with such communities when possible could help facilitate further collaborative efforts that

enhance our understanding of human genetic variation globally [59]. Such efforts could have profound positive effects on the clinical application of personalized medicine in the future.

Conclusion

To ensure that tomorrow's medicine and technology will serve all human populations, broadening ethnic participation in genomic studies is a social and a scientific imperative. This strategy of more inclusivity will serve to capture more of the genotype–phenotype correlations necessary to effectively translate observations into clinical practice. Furthermore, the assumption that a single population is sufficient for genetic association studies is increasingly defunct, especially as rare functional variants not necessarily shared across populations may uncover novel insights into drug targets and, ultimately, drug development [18]. The excuse that participant recruitment (domestically or internationally) is a bottleneck too difficult to overcome is losing validity. Inclusion of global populations in genomic (biomedical) research can no longer be an afterthought.

Future perspective

Given the exponential drop in cost and increase in speed of sequencing a human genome, the future of personalized medicine will include routine use of genomic information for tailored prevention, early detection of disease and individualized drug therapy. However, the amount of clinically useful variants will still be modest compared with the vast amount of data obtained from genetic association studies that leverage known common and rare variation, exome and whole-genome sequencing. Health professionals will be faced with the constant challenge of discussing genetic test results with patients, evaluating comparative-effectiveness research (i.e., comparing genetic testing vs traditional treatments) and translating probability scores for disease susceptibility into practical clinical decision-making. Global populations will have a larger representation in genomic databases allowing for greater contributions to genomics research and the understanding of human genetic variation. This much needed inclusion will avoid implications such as poor adoption by healthcare companies and their failure to reimburse providers for genetic tests for variants not considered `mainstream', which may ultimately lead to poorer health outcomes due to inferior or less efficacious treatments for individuals of certain populations. However, challenges to remain vigilant in ensuring representation of global ethnicities will surface in the continued pursuit of understanding the human genome. For example, epigenetics will be at the forefront as we look beyond genomic sequences and attempt to characterize elements acting on DNA. This emerging field will bring us again to a crossroads and, hopefully, past experiences will guide researchers to be more inclusive in the design of relevant studies. Likewise, functional studies of discovered variants associated with disease traits will be another opportunity to showcase the benefits of studying multiple ethnicities as we seek to translate findings from the bench to the bedside. The future will reflect a global society that is highly interconnected providing the proper foundation to shed old paradigms and adopt new motivations for investigating human genetic variation in the hope of bringing personalized medicine to all.

Acknowledgments

The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official view of the NIH.

This work was supported in part by the Intramural Research Program of the Center for Research on Genomics and Global Health (CRGGH). The CRGGH is supported by funds from the Office of the Director, National Institute of Diabetes and Digestive and Kidney diseases (NIDDK) and National Human Genome Research Institute (NHGRI) at the NIH (Z01HG200362).

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Executive summary

Promise of personalized medicine

- Traditional medical practice involving family history and lifestyle data will be enhanced with the use of genomic technology.
- Genetic testing and screening technologies aim to make prevention, diagnosis and treatment strategies more efficient and effective.
- The current genetic profiling of diseases, tumors and individuals has led to ground-breaking drug therapy and treatment strategies.

Genomic diversity of individuals

- We live in a multiethnic society with a growing number of admixed populations.
- Although patients may identify with one or two ethnicities, genetic data often tells a complex story about their genetic ancestry.
- All individuals, regardless of ethnicity, may carry genetic variations that correspond with rare alleles found in understudied populations.

Maximizing the relevancy of genomic research

- Historically, genetic association studies have focused narrowly on segments of European populations, leading to outcomes that only serve a portion of the global population.
- Translation of population-level data may include nuances that are overgeneralized in a clinical setting.
- Failure to research genetically diverse populations as we prepare for the era of personalized medicine could lead to disparate applications of genomic technology among all populations.

Genomic research models for the future

- Small collaborative projects are providing excellent examples of research occurring among genomically diverse groups.
- Cohorts of individuals from non-European ancestry populations are providing novel insights into genotype–phenotype associations.
- Genomic science and medicine will benefit greatly from the inclusion of multiple global populations.

Table 1

Pairwise comparisons of population differentiation for pharmacogenomically related SNPs among global populations.

F_{ST}	Intercontinental pairwise comparisons†			Intracontinental pairwise comparisons†			
	AFR/EUR	*AFR/EAS*	*AFR/AMR*	*AFR*	*EUR*	*EAS*	*AMR*
0 to <0.05	26,642	14,564	17,069	26,326	7741	2208	2674
0.05 to <0.15	9055	6176	4936	529	171	10	49
0.15 to <0.25	2409	1756	1287	23	0	0	0
≥0.25	1666	1330	567	6	0	0	0
Total comparisons	39,770	23,821	23,858	26,884	7912	2218	2723

F_{ST} values from 0 to 0.05 indicate little population differentiation; values between 0.05 and 0.15 indicate moderate population differentiation; values between 0.15 and 0.25 indicate large population differentiation; and values above 0.25 indicate very large population differentiation.

†F_{ST} values were calculated for a pharmacogenomic SNP panel (1156 variants selected from Affymetrix DMET™ Plus, CA, USA) between or within eight AFR ancestry populations (Yoruba in Ibadan, Nigeria; Luhya in Webuye, Kenya; Maasai in Kinyawa, Kenya; AFR ancestry in southwest USA; Igbo from Nigeria; Akan from Ghana; Gaa-Adangbe from Ghana; and African-Americans from the metropolitan Washington, DC, USA area), five EUR ancestry populations (UT, USA residents with northern and western EUR ancestry from the Centre d'Etude du Polymorphisme Humain [CEPH] collection; Toscans in Italy; British from England and Scotland; Finnish from Finland; and Iberian populations in Spain), three EAS ancestry populations (Han Chinese in Beijing, China; Han Chinese south; and Japanese in Tokyo, Japan) and three Latin AMR populations (Mexican ancestry in Los Angeles, CA, USA; Puerto Rican in Puerto Rico; and Columbians in Medellin). AFR: African; AMR: American; EAS: East Asian; EUR: European.