

## GENETICS

# The Illusive Gold Standard in Genetic Ancestry Testing

Sandra Soo-Jin Lee,<sup>1\*</sup> Deborah A. Bolnick,<sup>2</sup> Troy Duster,<sup>3,4</sup> Pilar Ossorio,<sup>5</sup> Kimberly TallBear<sup>6</sup>

Genetic ancestry testing is being applied in areas as diverse as forensics, genealogical research, immigration control, and biomedical research (1–3). Use of ancestry as a potential risk factor for disease is entrenched in clinical decision-making (4), so it is not surprising that techniques to determine genetic ancestry are increasingly deployed to identify genetic variants associated with disease and drug response (5). Recently, direct-to-consumer (DTC) personal genomics companies have used ancestry information to calculate individual risk profiles for a range of diseases and traits.

Despite the proliferation of companies providing genetic ancestry information, DTC genetic ancestry tests fall into an unregulated no-man's land, with little oversight and few industry guidelines to ensure the quality, validity, and interpretation of information sold. Scholars and scientists have therefore urged the genetics community to take a leadership role in offering guidance to the DTC genetic ancestry market (6, 7).

In November 2008, the American Society of Human Genetics (ASHG) issued recommendations on ancestry testing that emphasized the need for greater responsibility, research, explanatory clarity, collaboration, and accountability by DTC companies, academia, and potential consumers (8). While highlighting the clinical implications of ancestry testing, the statement also discussed limitations to the scientific approaches used to infer genetic ancestry, including the incomplete representation of human genetic diversity in existing databases, the false assumption that contemporary groups are reliable substitutes for ancestral populations, and the lack of transparency regarding the statistical methods that companies use to determine test results.

<sup>1</sup>Stanford Center for Biomedical Ethics, Stanford University Medical School, Palo Alto, CA 94304, USA. <sup>2</sup>Department of Anthropology, University of Texas, Austin, TX 78712, USA. <sup>3</sup>Department of Sociology, New York University, New York, NY 10012, USA. <sup>4</sup>Department of Sociology, University of California, Berkeley, CA 94720, USA. <sup>5</sup>University of Wisconsin Law School, Madison, WI 53706, USA. <sup>6</sup>Department of Environmental Science, Policy and Management, University of California, Berkeley, CA 94720, USA.

\*Author for correspondence. E-mail: sandra.lee@stanford.edu

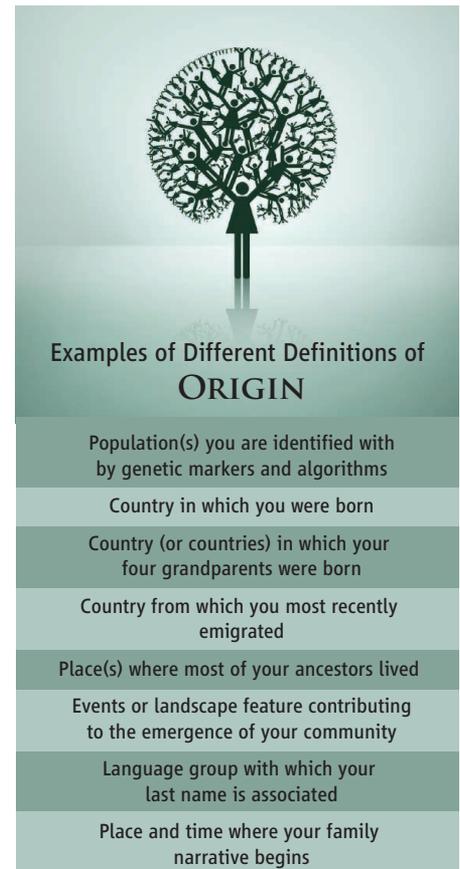
The ASHG statement identifies key issues surrounding the science of ancestry estimation and represents an important first step. However, an effective public policy for the growing market of genetic ancestry tests must build on the ASHG's recommendations and must generate specific mechanisms and approaches. Questions that remain include these: (i) In practice, what do responsibility and accountability mean for academia, industry, and consumers? (ii) How can diverse stakeholders reach a common understanding of the limitations of genetic ancestry tests and their broader implications for human identity? (iii) What role should governmental agencies play in creating infrastructure that effectively addresses the most challenging issues related to DTC genetic ancestry tests?

## Mutual Responsibility and Accountability

The ASHG sees academia, industry, and potential consumers as sharing responsibility for conveying and understanding the limitations of genetic ancestry testing. But what do responsibility and accountability mean in human population genetics? This question is critical because the limitations of ancestry testing are entrenched in a broader set of issues that emerge well before these tests reach market. In particular, ethical questions about the collection and use of DNA samples must be resolved before researchers are permitted to sample many of the populations needed to approximate the full range of human genetic diversity. Historically, relations between researchers and study populations have ranged from open negotiations to opportunism, misunderstandings, and even duplicity (9).

The importance of this issue is illustrated by the recent decision of the Arizona Court of Appeals to reinstate the 2004 lawsuit of the Havasupai Tribe against the Arizona Board of Regents (10). The Havasupai originally consented to have Arizona State University researchers collect DNA samples for diabetes research, but the samples were used without permission to study schizophrenia, inbreeding, and prehistoric human migration from Asia (11). One Havasupai allegation is that ASU's ethics oversight was negligent. However, in many

New regulations on disclosure, authority, and responsibility would shape how genetic ancestry tests are used.



instances, research can be compliant with existing human subjects protections yet fail to recognize long-standing differences in access to institutional and legal power, as well as questions about who holds authority to determine future uses of samples (12). The Havasupai case is not the only instance of Native American samples collected with consent only for health research, but then used to pursue other areas of inquiry that were not originally identified. Samples taken and traded under less stringent ethical regimes still remain in scientists' collections and may be used for purposes beyond the original research questions (13, 14). It is a scientific imperative that we enact enforceable policies that determine what constitutes responsible and accountable collection and secondary use of DNA samples.

Current guidelines issued by the Office for Human Research Protections (OHRP),

U.S. Department of Health and Human Services (DHHS), do not classify research involving previously collected samples that have been delinked from individually identifiable private information as “human subjects research” and, thus, do not specify requirements for informed consent in such research (15). With application of ancestry informative markers (AIMs), though, population-specific labels may be ascribed to anonymized DNA samples. Such samples, now identifiable to a politically and socially salient group, may be used to answer questions that were never approved when the group initially donated samples. Such practices fall outside current ethical oversight. The National Bioethics Advisory Commission has urged consideration of whether research on stored tissue would examine traits with political, economic, or cultural significance and could affect subjects’ communities, but this recommendation has not been taken up by the OHRP (16). ASHG and other governing bodies should formulate policies to guide ethical collection, use, and repatriation (where appropriate) of biological samples.

### Finding Common Language

The high stakes of genetic ancestry research require innovative approaches to dialogue, collaboration, and power-sharing between academia, industry, consumers, and community groups (especially those that have been disenfranchised from the research process) (9, 17, 18). A first step may be joint creation of a vernacular that characterizes key concepts like probability, association, origin, and ancestry to help minimize variability that exists in how such concepts are understood across fields, communities, and governmental and commercial entities with different vantage points.

For example, the term “origin” is not transparently or consistently defined. To a geneticist, origin might refer to ancestral populations inferred for an individual on the basis of specific genetic markers, specific algorithms for assessing genetic similarity, and specific reference populations. To a casual consumer, origin might mean “the country where I was born,” “the country (or countries) where my grandparents were born,” “the place or language group where my last name originated,” or “the place and/or time where my family narrative begins” (see table, page 38). To a Native American, origin might also signify the landscape feature or event where his or her people emerged or acquired their identity.

Even accepting a genetic or genealogical conception of origin, should each identi-

able ancestor or genealogical line be considered an origin? Population origins are rarely defined with that kind of multiplicity in mind. Given that each person may have many ancestors from the same place, does one have more ancestors than origins? Which biogeographical point in the genealogical line of an individual or population do we pinpoint as the origin? What is the rationale for naming ancient genetic lineages according to more recent and shifting ethnic, national, racial, or tribal categories? What are the implications of considering one contemporary population to be the ancestral origin of another?

There are no clear answers to these questions. However, recognizing that key terms can have disparate meanings for different groups will be a critical step toward effective dialogue. Refining a genetic vernacular requires educating both scientists and non-scientists and will depend on incorporating the multiple spheres of expert knowledge of human relatedness. Efforts by genetic researchers and other scholars, community groups, regulators, and industry partners to share their varied understandings may help stem miscommunication and increase rigor.

### A Role for Leadership

Human genetic variation research is a continuously shifting landscape. This dynamic marketplace puts in stark relief the limitations of categorical thinking about how genetic information is produced and applied. Genetic ancestry information can rarely be compartmentalized as either clinically relevant or merely historical. Nor is there a bright line between academia and industry because genetic researchers in universities increasingly collaborate with and move into industry. Even notions of the greater “public” are blurred as consumers of genetic products start their own companies (19).

Given the very different interests of the various stakeholders, resolution of differences will not be an easy, much less voluntary, process. For instance, the ASHG statement calls for greater transparency, but private sector providers of ancestry testing have proprietary reasons for keeping secret their own particular combinations of key technology, software, and population sampling procedures, and many are unwilling to disclose the size and composition of their reference populations. Without mechanisms to enforce transparency, it is difficult to assess the scientific basis for specific assertions of biogeographical ancestry.

Federal agencies such as the Federal Trade Commission, the Food and Drug Administration, and the Centers for Disease Con-

trol and Prevention could play pivotal roles in setting industry standards for what constitutes responsible and accountable practices. These agencies can promote the dialogue and research necessary to discover common language and to identify best practices for presenting the limitations of current genomic technologies and the risks associated with over-extrapolating or misinterpreting genetic ancestry results. New regulations on such matters will help shape how practitioners are able to communicate genetic ancestry testing results to consumers. How these regulations will be put in place is going to be a struggle between various parties that have shown little indication that there will be a compromise that will be acceptable to all. Political will and leadership toward addressing fundamental differences in perspectives may ultimately determine whether a gold standard for genetic ancestry testing can be achieved.

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