



## Ancestry Testing Has Limitations, Genetics Society Warns

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PHILADELPHIA, Nov. 17 -- Inexpensive genetic testing that purportedly traces a person's ancestry to historical figures such as Mongolian warlord Genghis Khan is more titillating than medically relevant, suggested guidelines by the American Society of Human Genetics.

"Consumers, as well as scientists, must remember that ancestry testing inferences are fallible, and that over-interpretation or misinterpretation can happen," said Edward R.B. McCabe, M.D., Ph.D., of UCLA, president-elect of the society.

"Inaccurate results may be confusing and life-changing; therefore, greater efforts are needed to make the limitations of ancestry testing more explicit."

The ASHG unveiled the guidelines for genetic ancestry testing at its annual meeting here, warning that the tests could spawn profound social and medical consequences.

The ASHG said the guidelines were needed to focus on ancestry genetics testing because an increasing number of companies are offering both ancestry and health-related tests.

Physicians and consumers need to be aware that the accuracy of ancestry test results, and their applicability to any medical decision-making, is limited by the statistical methods used, according to the ASHG statement.

The new statement includes five recommendations:

- Greater efforts are needed to make the limitations of ancestry testing known to consumers and scientists, and, likewise, the public is responsible for a better understanding of the implications of the tests.
- Additional research is needed to understand the extent to which accuracy is influenced by the populations sampled in existing databases, by geographical patterns of human diversity, and by marker selection and statistical methods.
- The consequences of ancestry testing need to be assessed, and guidelines should be developed regarding ancestry estimation in consumer, research, and healthcare settings.
- Scientists should consult with scholars on the historical, sociopolitical, and cultural context to inform their research and commercial efforts.
- Mechanisms for greater accountability of the direct-to-consumer ancestry testing industry should be explored.

The ASHG expects about a half-million people to purchase genetic ancestry tests this year, choosing among tests from about 30 companies.

For those consumers, said Charmaine Royal, Ph.D., co-chair of the ASHG Ancestry Testing Task Force Committee, "the desire to learn about ancestry should be coupled with a drive to understand the subtleties of the problem."

For example, some follow ancestral lines of one parent, while others use more genome-wide markers.

Mitochondrial DNA tests trace the mother's lineage and Y-chromosome tests track paternal ancestry, while ancestry informative marker (AIM) or single nucleotide polymorphism (SNP) tests examine non-sex chromosomes inherited from both parents.

The problem with these tests is that they both exclude a significant part of a person's genetic heritage, researchers have said. Maternal and paternal tests only trace one bloodline, leaving out many ancestors.

For instance, a mitochondrial DNA test tells something about the mother's mother's mother's lineage, said Deborah Bolnick, Ph.D., of the University of Texas in Austin, a co-author of an article in an October 2007 issue of *Science* that called on societies to develop policy statements on the limitations and potential dangers of genetic ancestry testing.

"If you go back 10 generations, each test will tell you about only one of 1,024 ancestors," Dr. Bolnick said. "Such limited information will not allow a physician to accurately assess disease risk, which depends on your broader ancestry and many other factors."

SNP testing could be problematic because gene variants influenced by natural selection may be found among several populations around the world, and thus produce false leads.

For example, if an SNP is associated with malarial resistance, it may be common in populations exposed to malaria even if they do not share recent ancestry, Dr. Bolnick said.

"There is uncertainty surrounding ancestry estimates based on SNP testing, and physicians may not want to base their assessment of disease risk on unreliable or inaccurate information," she said.

In the case of a Florida accountant linked to Genghis Khan, for example, a genetic testing company found a set of genetic markers common in people from Eurasia, particularly in the areas the Mongol hordes conquered.

But since the body of Genghis Khan has never been found, there was no exact genetic reference, so the direct link was mere inference.

Another problem is that the tests assess ancestry by comparing consumer DNA to a worldwide database of DNA samples. If a test-taker's DNA is similar to a database sample from a particular population, it suggests that the test-taker has relatives in that population.

But Dr. Bolnick said the databases are incomplete, meaning the tests may miss some of the locations where a test-taker has relatives. And they contain samples from living individuals, not those alive when the test-taker's ancestors lived.

"Because people move and social identities change over time, these tests cannot be positive that a test-taker's ancestors lived in a particular region or held a specific ethnic identity," Dr. Bolnick said.

Even if ethnicity is determined via an ancestral genetics test, there's still a snag. While race and ethnicity are used to determine disease risk, no one's sure if race is associated with disease susceptibility because of biological or genetic factors, or whether these associations exist as a result of environmental factors.

Most researchers believe it's a combination of both.

Social quandaries that could arise because of ancestral genetic testing range from questionable claims of membership to ethnic groups, such as Native Americans, in order to obtain benefits, and skewed census data as a result of people changing their ethnicity on government forms, according to the ASHG.

Ancestry testing is just one aspect of the services most direct-to-consumer genetics testing companies offer. Most primarily market themselves as a tool for optimizing health.

Redwood Shores, California-based Navigenics, the Icelandic DeCodeMe highlight assessing genetic risk for disease on their homepage.

So does Mountain View, Calif.-based 23andMe, which recently dropped its price of genetic testing to \$399 -- not much more than the cost of an iPhone.

The companies say genetic testing for disease risk factors improves healthcare, and the idea is for patients to work with their doctors for best results.

In an open letter to the medical community, for example, 23andMe said its goal is to "help our customers understand their own genetic information and how the current biomedical literature pertains to it."

But Joanna Mountain, Ph.D., senior director of research for 23andMe, said ancestry genetics testing won't cause a major "change in the way patients talk with their doctors."

She said 23andMe's health-and-traits genetics testing is completely separate from the ancestry testing it offers.

She added that the ASHG guidelines were "preliminary" in that they hadn't "surveyed what commercial companies are doing," and that studies need to be done on what issues may actually arise from consumer ancestry genetics testing.

Dr. Mountain said her company -- along with the rest of the genetic testing industry -- is not currently regulated.

According to the Federal Trade Commission, the FDA and CDC regulate the manufacturers of genetic testing, but only to the extent of mandating that the tests must be performed "in a specialized laboratory and the results should be interpreted by a doctor or trained counselor who understands the value of genetic testing for a particular situation."

Several statements and recommendations on direct-to-consumer genetic testing have been published in recent years following an industry explosion.

Last April, the American College of Medical Genetics issued guidelines for all direct-to-consumer gene testing, after the ASHG issued their own guidelines, published in *Obstetrics & Gynecology*, in December 2007.

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