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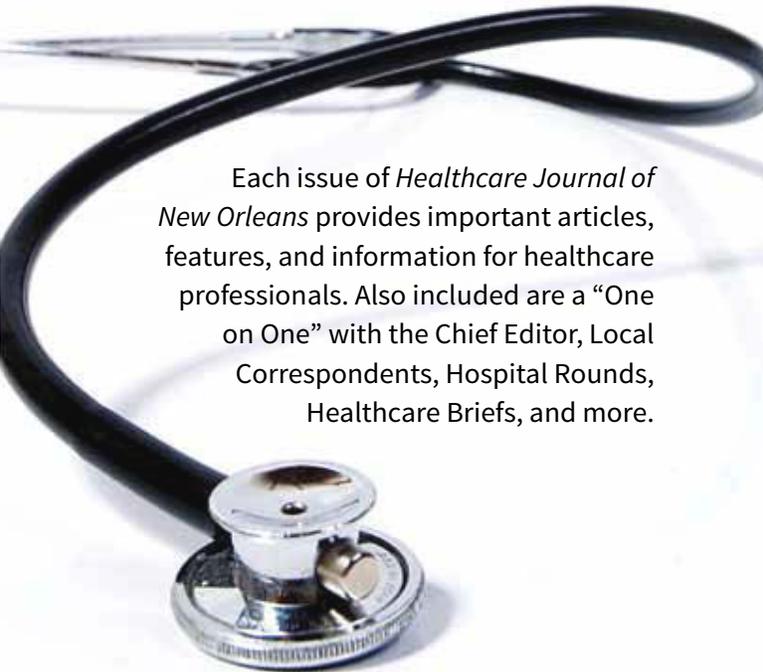
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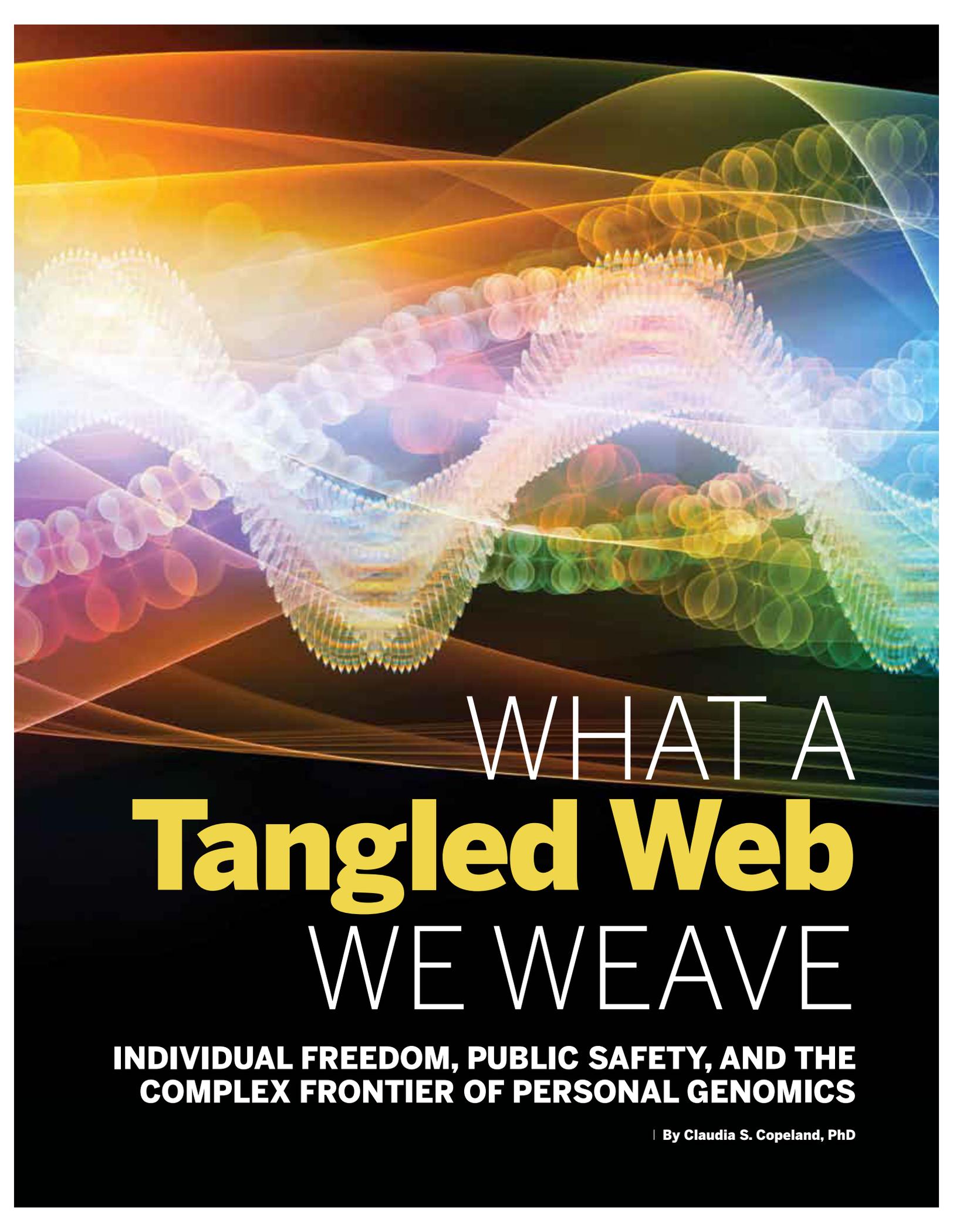
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WHAT A
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**INDIVIDUAL FREEDOM, PUBLIC SAFETY, AND THE
COMPLEX FRONTIER OF PERSONAL GENOMICS**

| By Claudia S. Copeland, PhD

IT'S CHEAP, IT'S EASY—\$99 and a simple swab to generate a DNA sample, and in a few weeks you possess DNA sequence data and analysis for your own genome. Along with ancestry information, personal genomics services like 23andMe used to provide information on personal risk for health conditions based on genetic factors. The service was popular; customers found it to be helpful and fascinating, so when the FDA decided to shut down 23andMe's genome-based health analysis services in early December 2013, many Americans reacted with anger and indignation. What right did the FDA have to prevent them from accessing knowledge about their own genomes?

The FDA, though, has a responsibility to prevent “quackery” by requiring that drug and medical device manufacturers prove that their products are safe and effective. Doing this is expensive; that is why pharmaceutical companies maintain exclusive rights to manufacture their products for several years before “generics” can be legally made. Clinical research into safety and effectiveness is considered part of the process of making a drug or medical device. No such research, however, has been carried out by 23andMe or any of the other personal genome analysis companies. According to

the FDA, they were marketing their product as a medical device without any proof of safety or efficacy. Genotyping analysis can certainly be considered safe in terms of physical harm from the procedure, but is there any solid evidence that it is effective? And what about psychological harm from being diagnosed with disease risk without the benefit of a health professional to put things in perspective and provide counseling?

Personal genotyping involves analysis of select regions of the DNA making up an individual's genome. DNA is made up of four types of nucleotides, or DNA bases:



adenine (A), thymine (T), cytosine (C), and guanine (G). These bases are arranged end-to-end to form long strings of distinct sequences. (They are often referred to as base pairs, since, in the living body, each base is bonded to a complementary base, with each C bonded to a G and each A bonded to a T, to form two complementary strands connected together in a highly stable, twisted-ladder structure.) In the same way that 26 letters can encode thousands of English words, sequences of these four DNA bases encode thousands of genes. The genes then direct the building of proteins and functional RNA, the two molecules



that, along with minerals such as calcium, zinc, and iron, form the structures and tools that make up our bodies. By looking at an individual's DNA sequence, much can be learned about that person's health

risks—for example, once a woman knows the sequence of her tumor suppressor genes BRCA1 and BRCA2, she will know if she has a harmful BRCA mutation, associated with increased risk of breast and ovarian cancer.

Since whole-genome sequencing is prohibitively expensive for most individuals, personal genome analysis services focus on a subset of variable regions of the genome, which may be correlated with different diseases, traits, and responses to medications. For example, variants might be correlated with the risk of Alzheimer's disease, non-disease traits like eye color, or response to the anti-coagulant Warfarin. These regions, known as markers because they "mark" a spot that varies between different individuals, are immobilized on chips to make tools called whole-genome genotyping arrays. These arrays allow a sample of DNA to be compared with thousands of reference markers. (The chip used by 23andMe includes over 700,000 markers identified by the International HapMap Project, a collaboration between researchers from around the world to develop a "map" of common patterns of human DNA sequence variation.)

Among the most useful types of genetic variation are single nucleotide polymorphisms, and these are the types of markers used by 23andMe. SNPs are variations involving just one DNA nucleotide. For example, if some members of the population have the sequence CCTGA at a certain genome location, and the others have the sequence CCCGA at the same location, this is a T/C polymorphism at that location. SNPs can be neutral, representing variations such as eye color or blood type that have little if any effect on health, or they can be harmful mutations seen in a small

percentage of the population, such as the carcinogenic BRCA mutations.

The former can be of interest for people who would like to learn more about their ancestry. In Louisiana, where even multi-generational “natives” have immigrant roots from all over the world, gaining this knowledge can be particularly fascinating and enlightening. One “Creole” musician with multi-generational roots in Southern Louisiana spoke of his results: as expected, he had African genes, but he found it gratifying to learn which specific part of Africa his ancestors were from. In addition, he was intrigued to find a substantial percentage of Iberian ancestry, with almost none of the

French ancestry that would be expected in most New Orleans Creoles. This dovetailed with what had always felt like an “instinctual” connection to Portuguese-diaspora music, and set him on a fascinating path to discovering more about the culture of his ancestors and their diaspora.

This type of analysis is undisputed as a legitimate service by personal genome companies; if a customer misinterprets part of the analysis, he will not end up hurt as a result. The FDA gets concerned, though, when polymorphisms are reported that are correlated with an increased risk for disease conditions, because these correlations have never been tested for diagnostic efficacy; that is, they have been characterized for the purpose of biology, not medicine.

This is not to say that they have nothing to do with health; on the contrary, epidemiology is a common focus of genomic biology, and whole-genome genotyping arrays have been extremely useful in studying variation in traits relevant to disease. Genome-wide association studies (GWASs) look at a population of individuals with certain disease traits, and seek to find genome variants that are associated with the condition. For

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example, Tulane epidemiologist Hao Mei and his colleagues found several genes associated with blood pressure response to salt. They did this by giving 1,906 people a low-salt diet for a week, followed by a high-salt diet over the following week. Looking at blood pressure, they separated the subjects into those who were salt-sensitive (whose blood pressure changed in response to the salt) and those who were not, and ran whole-genome analyses on the subjects. Comparing the two groups, they were able to find two SNPs that were correlated with salt sensitivity. One was significantly correlated, the other only borderline, but when they were considered together, they were considered together, they affected blood pressure in an additive way. This information clearly advances our understanding of genetics and blood pressure, and might even be helpful to clinicians dealing with patients with high blood pressure, but would certainly not be valid as the basis for any sort of diagnosis.

Personal genome analysis of health-related traits is based on research like this; research that, as opposed to clinical trials, is

intended to increase our understanding of disease characteristics, but is not designed to develop or test a particular diagnostic strategy per se. It's a fine distinction, but an important

one, especially since even diseases with strong genetic bases generally have complex causes that include much more than just the genetic variation. For example, according to the National Cancer Institute, about 12 percent of women in the general population will develop breast cancer at some point during their lives. By contrast, according to the most recent estimates, 55 to 65 percent of women who inherit a harmful BRCA1 mutation and around 45 percent of women who inherit a harmful BRCA2 mutation will develop breast cancer. Having either of these mutations, then, indicates a greatly increased risk of breast cancer. Nevertheless, 35-55% of women with a harmful BRCA mutation will NOT get breast cancer, so even for this gene (among the clearest-cut cases of gene-disease correlation), the genetic correlation is only one part of a complex set of causes of the disease.





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Three researchers from the European Society of Human Genetics, Patch et al., deride the tests as “genetic horoscopes.” They cite analyses suggesting that “this genetic astrology could be regarded as producing no more than entertaining horoscopes; there is, however, a potential for harm and the need to consider mechanisms to ensure that these tests are evaluated and used appropriately.”

Untrained customers getting personal genome information may be unprepared to understand this complexity. Considering the salt-sensitivity results of Dr. Mei, knowing whether a patient with high blood pressure has this variation might be helpful to a physician. However, what if an individual using a personal genome service finds one of these mutations? No personal counseling is included in the service; only an online readout of results. Might such a person be compelled to lower their salt intake, perhaps leading to eating fewer vegetables if they find them bland without salt, when an examination at the doctor’s office would have found no blood pressure problems and no need to worry about sodium intake? What about someone who found they did not have the gene, and concluded that lowering their dietary salt would not help their blood pressure anyway, so why bother?

Criticism of personal genome analysis

has been ongoing. Aside from errors—even though the error rate in 23andMe’s system is less than .01%, across the whole genome there will be errors—there is the general issue of whether the healthcare conclusions from the data really provide meaningful information to the customer. Based on review and meta-analyses, Dutch researchers Janssens et al. concluded that “there is insufficient evidence to conclude that genomic profiling is useful in measuring individual genetic risks for common diseases, or in developing personalized diet and lifestyle recommendations for disease prevention.” A 2006 study by the U.S. Government Accountability Office conducted an investigation in which a number of randomly selected companies were provided with samples for testing, and found that



the information reported after analysis was medically unproven and ambiguous. Three researchers from the European Society of Human Genetics, Patch et al., deride the tests as “genetic horoscopes.” They cite analyses suggesting that “this genetic astrology could be regarded as producing no more than entertaining horoscopes; there is, however, a potential for harm and the need to consider mechanisms to ensure that these tests are evaluated and used appropriately.”

Some of this might be dismissed as hyperbole, but it is not unreasonable to anticipate some very real problems stemming from mail-order genetic testing. David Dobbs, in a piece in *The New Yorker*, describes the scenario of receiving unwanted test results: “Kenneth Britten, a neurobiologist and a customer, learned he has one copy of the gene that increases Alzheimer’s risk, which raises his nominal risk to about one in seven. But he then did enough reading to learn that because neither of his parents developed Alzheimer’s, he could essentially erase this extra nominal risk if he started exercising regularly before he developed symptoms...but he’s a neurobiologist in his prime. A fifty-five-year-old who is confused and depressed and learns that he carries two copies of the risk gene and stands an eighty-percent chance of getting Alzheimer’s might reach for a gun, which is the kind of scenario that some genetic counselors worry about.” Add to this the inevitability of errors, and it becomes clear that there is a potential for harm in delivering pseudo-medical information without the involvement of a healthcare professional. While people should be able to access information about their own genomes, in no other medical setting would information this momentous be given out without personal, face-to-face counseling about implications and next steps.

One company, Gentle, has taken steps

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to address both the problem of counseling and efficacy. They offer full sequencing rather than genotyping, which is a more comprehensive approach (though it is full sequencing of the exome only—the exons, or protein-coding regions—rather than the whole genome). Importantly, they also offer counseling—in fact, their doctor, designated the “Royal Doctor,” or the customer’s own personal physician, is given the results of the analysis first; the customer does not receive the results until after the counseling session. According to the company’s website: “The Royal Doctor will hold a thorough teleconference consultation about your

genetic results. He will explain the impact of your test results for your health and that of your (future) children. In addition, he will give useful advice on preventive measures you can take in order to stay healthy. After this consultation, the doctor will release your results so you can explore them yourself through the iPad and web apps.” This platinum service, however, comes at a price: whereas 23andMe charges \$99 for whole-genome genotyping, Gentle’s whole exome sequencing service rings in at \$1,990.

At over 20 times the cost of 23andMe’s services, the pricetag of the more sophisticated Gentle analysis might be prohibitive for many customers.

In addition, Gentle has the disadvantage of ONLY looking at exons; this is problematic because most individual variation is found outside protein-coding regions.

So, what’s a poor, libertarian-minded genomics customer to do? If she wants health-related annotation of her raw personal genomics data, she could do her own bioinformatics searches if she has the skills and time to do so. But there is at least one other option: SNPedia.

While companies like 23andMe are

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now barred from providing diagnostic or health-related information, they do provide raw SNP data as well as ancestry analysis. SNPedia, a wiki that collects and shares health-related information about DNA variations, offers free access to its information, and cheap access to Promethease, a program that annotates raw data from personal genotyping services. For \$5, customers who have obtained personal genomic data about themselves, from any company, can input that data into Promethease and obtain a report of risk assessments and other health-related information from SNPedia. The site is

so geared towards 23andMe input that they have a video tutorial that shows exactly how to upload personal data from 23andMe into Promethease (<http://www.youtube.com/watch?v=mbbRhGJhsg8>). Narrated by co-owner Mike Cariaso, the video also goes over how to navigate the Promethease report, in great detail. The personal report allows searching based on disease, frequency, or other keywords, and shows a wealth of community-collected information on each SNP, including summaries of functional information about

the SNP, “good” or “bad” classification of the trait, and frequencies in different ethnic populations. Different parts of the report can be accessed for specific concerns, such as SNPs related to drug reactions.

(A user can pull up a list of medicines, and click on a given drug to see what SNPs he has and what research has said about these SNPs. For example, he may have an SNP associated with particularly rapid metabolism of a given drug.) The entry for each SNP includes links to research papers in PubMed so that the customer can read the original research and evaluate it for themselves.

The allure of such a treasure trove of individualized information is seductive, for people both with and without suspicions about their genetic health risks. While the FDA is tasked with protecting the public from ineffective or unsafe medical devices, the desire of individuals to learn more about themselves is strong, and they will find ways around FDA regulations in order to do so. Clearly, whether you believe personal genomics is possibly dangerous, “genetic astrology,” or a valid, useful service, it appears that this horse is out of the barn, running fast, and unstoppable. ■

