

Letting the Genome Out of the Bottle

TO THE EDITOR: The Perspective article by Hunter et al. (Jan. 10 issue)¹ concludes that commercialization of personal genomics is premature in light of the lack of data to support the analytic and clinical validity and clinical utility of these tests. Although the authors' description of the current state of the art is accurate, they and others² minimize the important point that clinical practice has already been influenced by the possibility of personal genomics, and it is consumers' attitudes — not outcomes data — that are the critical drivers of such changes.

Despite what most geneticists and physicians would view as a lack of actionable results from personal whole-genome scans, consumers appear to be embracing this opportunity to uncover the secrets of their genomes. It seems highly likely and logical that patients would turn to their physicians for interpretation of such data, since they will not be able to rely on online commercial testing services for guidance. Rather than dismiss the accuracy and usefulness of these tests for predicting and reducing the risk of disease, physicians should view test results as an opportunity for a “teachable moment,” in which they can help patients understand the current limitations of genomic information and explain the preventive steps that can be taken to reduce the risk of disease, regardless of one's genome. Patients should understand that the absence of a genome-based predisposition to a disease does not necessarily alleviate one's overall risk of contracting that disease.

For physicians to help patients make sense of genomic information, the way physicians view the field of genetics must change. Physicians are overwhelmed with information and are rightfully reluctant to expend the time and effort necessary to learn about new applications that are considered unlikely to change their daily practice. Although this might have been a valid argument with regard to medical genetics, which is largely the study of relatively uncommon disorders, it no longer holds true for today's genomic medicine. Everyone has a genome. And increasing numbers of consumers will find it attractive to take control of their own genomes — whether it is advisable to do so or not. Among patients who find the

allure of the sirens of the genome too tempting to resist, advice to the contrary and interpretation of results as meaningless will fall on deaf ears.

If physicians are not able to provide information on genomics, patients will simply turn elsewhere. Not only is there an evidence gap regarding the validity and clinical utility of personal genomics, there is also an information gap. Enhancing physicians' knowledge of genomic and personalized medicine, regardless of its incomplete status, will help narrow that gap and provide patients with the navigational information they need in an era of medicine in which they are not passive but active participants.

Susanne B. Haga, Ph.D.

Huntington F. Willard, Ph.D.

Duke Institute for Genome Sciences and Policy
Durham, NC 27708

1. Hunter DJ, Khoury MJ, Drazen JM. Letting the genome out of the bottle — will we get our wish? *N Engl J Med* 2008;358:105-7.
2. Drazen JM, Phimister EG. Publishing genomewide association studies. *N Engl J Med* 2007;357:496.

TO THE EDITOR: In their Perspective article, Hunter et al. express caution and skepticism regarding the first wave of commercially available genomic tests, successfully conveying the warning of caveat emptor, but the article is shortsighted and ultimately counterproductive with regard to the achievement of progress in health care that we so desperately need in this country. Seeking genomic profiling to determine one's risk of disease implies a desire to undertake prevention, and prevention of preventable diseases is ultimately the only solution to our health care crisis. The notion of preventive health intervention has taken decades to become established in the medical community and is now accepted by the public. Only in the realm of cardiovascular disease has preventive therapy developed to the level of the standard of care, and this development was accomplished through appropriate stratification of risk, according to physiological and biochemical and now genetic indicators of risk. The field of cancer is not far behind and requires similar tools for risk assessment, which will come only from genomic analysis. Genomic tests are far from perfect, but they are a start, and they signal

a change in the public's thinking about health that should be encouraged, not dismissed.

M. William Audeh, M.D.

Cedars-Sinai Medical Center
Los Angeles, CA 90048
william.audeh@cshs.org

THE AUTHORS REPLY: We agree with Haga and Willard that physicians will be key interpreters of individual genetic information and that enhancing physicians' knowledge in this field is necessary to ensure accurate interpretation. It is for this reason that we call for urgent attention to the translational studies needed to assess both the clinical implications of common genetic variants and their added value in communicating risk information that is useful for disease prevention and health promotion. Although consumers may become the drivers of demand for genomewide testing, we hope that their experiences will be captured in comprehensive research studies that will inform subsequent evidence-based practice, rather than be lost in a series of improvised physician-patient encounters. Certainly, teachable moments that are based on validated information are plentiful in medical practice. We also

hope that the early-adopting consumers who find "the allure of the sirens of the genome too tempting to resist" do not find themselves caught between the Scylla of genetic determinism and the Charybdis of uncertain data.

We agree with Audeh that a greater appreciation of disease prevention in both the medical and lay communities is a key to progress. However, we urge that tools for risk stratification be firmly evidence-based, as they are for cardiovascular disease, and that they use the totality of validated risk-factor information, including family history. Premature adoption of poorly understood genome profiles may harm the public perception of the utility of risk assessment based on common genetic variants and could ultimately lead to reluctance to undertake testing, once we have the requisite information about its clinical validity and utility.

David J. Hunter, M.B., B.S., Sc.D.

Harvard School of Public Health
Boston, MA 02115

Muin J. Khoury, M.D., Ph.D.

Centers for Disease Control and Prevention
Atlanta, GA 30341

Jeffrey M. Drazen, M.D.

Serotonin Syndrome Associated with Triptan Monotherapy

TO THE EDITOR: Triptans are serotonin-receptor agonists used in the treatment of migraine headaches. When administered in combination with certain drugs, such as selective serotonin-reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), triptans may precipitate the serotonin syndrome, a potentially life-threatening condition characterized by a triad of clinical manifestations — changes in mental status, autonomic hyperactivity, and neuromuscular abnormalities.^{1,2} The cause of the serotonin syndrome is related to altered serotonin synthesis, release, reuptake, metabolism, or receptor agonism.³ We investigated whether triptan monotherapy is associated with the serotonin syndrome by searching for such cases in the Food and Drug Administration's Adverse Event Reporting System (AERS).

We reviewed triptan adverse-event reports cod-

ed with the term "serotonin syndrome," as well as reports containing terms other than "serotonin syndrome" that were nonetheless indicative of this syndrome (e.g., agitation, tachycardia, and tremor). Cases searched in AERS included reports for triptans marketed in the United States: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. We excluded cases of potentially confounding medical conditions (e.g., hyperthyroidism) and cases documenting concomitant therapy with drugs known to be associated with the serotonin syndrome (e.g., SSRIs). Twenty-seven AERS cases of the serotonin syndrome related to drug-drug interaction were associated with co-prescription of various combinations of triptans and SSRIs. Our review elicited 11 cases (mean age of the patients, 39.9 years): 3 specifically coded as serotonin syndrome and 8 coded with additional terms