Evaluating the utility of personal genomic information

Morris W. Foster, PhD[1,2], John J. Mulvihill, MD[2], and Richard R. Sharp, PhD[3]

Abstract: In evaluating the utility of human genome-wide assays, the answer will differ depending on why the question is asked. For purposes of regulating medical tests, a restrictive sense of clinical utility is used, although it may be possible to have clinical utility without changing patient's outcomes and clinical utility may vary between patients. For purposes of using limited third party or public health resources, cost effectiveness should be evaluated in a societal rather than individual context. However, for other health uses of genomic information a broader sense of overall utility should be used. Behavioral changes and increased individual awareness of health-related choices are relevant metrics for evaluating the personal utility of genomic information, even when traditional clinical benefits are not manifested. In taking account of personal utility, cost effectiveness may be calculated on an individual and societal basis. Overall measures of utility (including both restrictive clinical measures and measures of personal utility) may vary significantly between individuals depending on potential changes in lifestyle, health awareness and behaviors, family dynamics, and personal choice and interest as well as the psychological effects of disease risk perception. That interindividual variation suggests that a more expansive overall measure of utility could be used to identify individuals who are more likely to benefit from personal genomic information as well as those for whom the risks of personal information may be greater than any benefits. ***Genet Med* 2009:11(8):570–574.**

Key Words: *genetic testing, personalized medicine, utility, health awareness, ethics*

A core criterion of most evaluations of clinical utility for genetic tests is the potential for the results to influence patient's management. If patient's care is not affected, genetic tests usually have not been considered to have clinical utility.[1,2] Next generation sequencing and genotyping technologies, however, increasingly will make ever-larger amounts of personal genetic information readily available at ever-diminishing costs.[3] Although some of that information will be about known variants and could influence patient's management, most will be of no direct medical value. Nonetheless, both physician-ordered and direct-to-consumer service arrangements are being developed in an evolving regulatory environment to make personal genome data available to individuals.[4]

From the [1]Department of Anthropology, University of Oklahoma, Norman, Oklahoma; [2]Department of Pediatrics, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; and [3]Department of Bioethics, Cleveland Clinic, Cleveland, Ohio.

Morris W. Foster, PhD, Department of Anthropology, 455 W. Lindsey, Rm. 505C, University of Oklahoma, Norman, OK 73019. E-mail: morris.w.foster-1@ou.edu.

Disclosure: Dr. Foster serves as chair of Illumina's Ethics Advisory Board. He owns no Illumina stock, but is paid as a consultant to give advice about ethical issues involving genotyping and sequencing. The other authors declare no conflict of interest.

Submitted for publication October 22, 2008.

Accepted for publication February 24, 2009.

Published online ahead of print May 27, 2009.

DOI: 10.1097/GIM.0b013e3181a2743e

These changes in technology and access suggest a re-examination of how the utility of personal genetic information is measured. As the information about one's genome becomes more generally available (whether from one's physician or an online service), the evaluation of utility shifts from examining the value of asking a specific question about a particular gene for which variants are known to examining the value of a vast amount of information that includes multiple known variants and variants that are unknown, ambiguous, or have no significance. Measuring the utility of that greater range of information entails considering a broader spectrum of potential informational impacts, including those that primarily affect the patient rather than the patient's medical care, which may lead us to expand how we define the overall utility of personal genomic information.

In this commentary, we use existing composite measures of clinical utility of genetic tests to argue for the inclusion of additional measures of personal utility in a more expansive composite measure of overall utility. We detail the different components of clinical and personal utility, how each might be measured, and the challenges of combining those in a validated measure of overall utility that could be used to guide individualized patient and physician's decision making about personal genetic testing.

UTILITY AS A COMPOSITE MEASURE

Even in the case of single-gene tests, multiple factors are involved in assessing a test's clinical utility. Although there are several tests for which there is broad professional consensus about indications for genetic testing, there is a range of reasonable opinions regarding clinical utility for most genetic tests. Often, divergent opinions on a test's clinical utility reflect a lack of population-based evidence of clinical benefit.[5] Other times, differences of opinion reflect questions about the reliability of a test or its analytic validity.[6] Still other times, it may be unclear how patient's management should be changed as a result of identifying a genetic marker of disease predisposition or diagnosis.[7] In these and other situations where the clinical implications of a genetic test are ambiguous, the preferences of individual patients often shape a physician's perceptions of a test's utility and guide decisions to pursue clinical genetic testing.

These considerations highlight how the concept of clinical utility is a composite category that incorporates multiple factors affecting decisions to recommend genetic testing. As with most medical judgments, determinations of clinical utility are open to interpretation and can be contested. Specific disputes about clinical utility may occur among individual physicians who disagree about the usefulness of a diagnostic test for a particular patient or between medical experts who review evidence in support of practice guidelines. Standards of clinical utility evolve over time and with increasing knowledge. Finally, the concept of clinical utility admits of degrees. A genetic test may have more or less utility for patient's management, depending on the context in which the test is used.

These additional perspectives highlight a second important feature of clinical utility; namely, that even when there is broad

professional consensus about the standards of evidence that must be met to establish clinical utility, there may be disputes about the extent to which clinical utility is achieved in a particular testing context. For example, a test that identifies a genetic predisposition to breast and ovarian cancer may be useful in determining the need for prophylactic surgery for at-risk women but may have limited utility for counseling patients about reproductive options. No genetic test has unqualified clinical utility. Genetic tests have utility for specific purposes, in particular clinical settings, for appropriate patient populations.

The multiple components used to assess clinical utility for single-gene tests suggest the possibility of developing an expanded suite of measures to evaluate the utility of multigene personal genomic information, both to empower individuals in making decisions about having personal testing and to assist medical professionals in using personal genomic information in a manner that could benefit their patients. An expansive measure of clinical utility also could inform the open question of whether personal genomic services should be regulated. Although personal genomic information clearly lacks clinical utility based on the criterion of medical action,[8] it may offer other benefits that can be measured and that could make indirect contributions to patient's well-being. Those indirect benefits may be shown to have sufficient, measureable utility in the cases of some patients such that personal genome testing can be integrated with clinical practice rather than being excluded as lacking strict medical value.

EXPANDING UTILITY

Indeed, by reframing the question from that of the utility of genetic testing based on direct medical action to one that includes indirect health-related and other nonmedical benefits of personal genomic information, there are multiple ways in which utility may be measured in addition to, as well as apart from, evidence of benefits that directly inform medical decisions. That expanded sense of utility also allows for the possibility that utility may be measured differently from one individual to another, which presents an additional problem for evaluating access to genome-wide technologies.

Patient's outcomes

A long-standing goal of genomic research has been to develop diagnostics for earlier identification of genetically based conditions to reduce mortality and morbidity and improve quality of life. The most successful example is neonatal genetic screening, which has demonstrable utility with respect to patient's outcomes. For conditions that can be diagnosed genetically but for which no therapeutic options currently exist, such as Huntington disease, the utility of clinical testing depends much more on measures such as the psychological impact of risk perception and has proven to vary between individuals.[9] For conditions that have both genetic and environmental contributors, such as most cancers, clinical utility depends crucially on the accuracy of risk prediction or estimation, which is inherently imprecise.[10] The focus of the discussion about clinical utility of genetic predisposition testing for complex diseases like cancer weighs the degree of imprecision of risk estimation against the implications of test results on therapeutic or reproductive choices and psychological quality of life.

Personal genome information presents the additional complication of returning very large amounts of data about variants that will range in precision from complete penetrance to completely unknown significance, making the usual criterion of "clinical validity" less straightforward as a measure of utility. Some variants found in an individual's genome will have clinical validity whereas most will not. Alternatively, the accuracy and transparency of the interpretations made of the potential significance of the full range of an individual's personal genomic information may become a key criterion for evaluating its utility for anticipating health risks, whether done by a software program or by a physician.[11] The quality of such interpretations will depend on how current knowledge (which will change over time) is systematically used to neither understate nor overstate the constellation of risks that are encoded in individual genomes and to educate health consumers both about the potential and the limits of genetic contributions to well-being.

Clinician's informational impacts

Genetic testing can affect how clinicians both think about diagnoses and make treatment choices, either of which may or may not change patient's outcomes.[12] Diagnostic thinking can be measured by the percentage of times that clinicians change their subjective evaluation of diagnostic possibilities after a test.[13] Therapeutic choice can be measured by the percentage of times clinicians alter therapeutic plans after a test.[13]

Patient's informational impacts

Genetic information also can affect how patients think and act. Of immediate clinical relevance, knowing the genetic basis for a condition can reinforce patients' adherence to clinical advice to the extent that understanding etiology improves compliance for disease prevention or treatment.[12] In addition, having access to their own personal genomic information can enhance individuals' sense of choice and control, leading them to take greater ownership in learning and acting on the health implications of those data and in protecting the privacy of their genetic results.[14] One manifestation of patient's autonomy is the ability to use personal genetic information to make reproductive decisions. Another manifestation is personal accountability for health-related choices, which is not premised on taking any specific action but instead informs a more general sense of self-identity. Having greater knowledge or control over one's sense of identity, though, has been shown to enhance health-seeking behaviors.[15,16] Of course, one's personal genetic information also has potential consequences for biological family members, and so can affect familial relationships. Validated instruments for measuring patient's adherence, perceived individual's choice, and familial dynamics exist and can be adapted to measure the utility of access to personal genomic information.[17–19]

Cost effectiveness

The economic effectiveness of genetic testing can be evaluated, using measures such as cost of genetic screening versus cost of subsequent treatment without screening or using a measure of quality-adjusted life years that result from genetic screening and treatment. Societal investments in newborn screening for inborn errors of metabolism and hearing loss that can be treated in infancy, for example, are justified using such measures.[20] Similarly, targeted genetic tests that have been clinically validated and are ordered based on specific indications for disease risk or drug response also can be cost effective in the context of limited public health or third-party payer resources.[21] From a societal perspective, though, large-scale genetic sequencing or genotyping is not a cost-effective tool today because those analyses are still relatively expensive and produce data of unknown or uncertain significance. From a personal perspective, however, individual's investment in ob-

taining one's genomic information may be cost effective depending on level of discretionary household's income and the overall utility the results hold for the person tested. This calculation includes both medically relevant dimensions familiar to a more restricted definition of clinical utility and more expansive dimensions of personal utility that may hold individual's benefit (or risk) but are not medically actionable and could be based entirely on the latter.

Awareness of health risks

Presumably, an individual who is interested in obtaining information about their personal genome likely also is motivated to increase his or her awareness of disease risks. The increased utility of that awareness can be measured by instruments that survey health beliefs, knowledge, and attitudes as well as by evidence of participation in various kinds of health screenings conducted in clinical settings (such as cholesterol tests or colonoscopies) and frequency of self-surveillance activities (such as at health fairs or self-screening for testicular cancer or monitoring of blood pressure).[22] Heightened screening and surveillance can contribute to earlier disease detection and better patient's outcomes. The utility of heightened awareness of health risks also can be measured by health-promoting changes in lifestyle behaviors, such as cessation of tobacco use, increased exercise, or a healthier diet.[23] Because many chronic diseases share most of the same risk factors (such as obesity, poor diet, smoking, and excessive alcohol use), genomic estimations of heightened risks for specific diseases can result in changes in health awareness and behaviors that are of general utility.

At the same time, though, increased concerns about personal health can have psychological impacts, which can be measured using quality-of-life instruments.[24] For some individuals, those psychological costs can be so great as to outweigh any benefit of health awareness. Conversely, individuals who have no genetic indications for specific disease risks mistakenly may take that genetic finding to mean they are not at risk for chronic diseases that can arise from environmental and behavioral causes,[25] a potential result that can be measured using the methods described earlier for health awareness.

CALCULATING UTILITY

This inventory of dimensions suggests various formulae for calculating a narrowly defined clinical utility of personal genome-wide information.

Clinical utility (restrictive) = patient's outcomes + clinician's information impact + patient's information impact (adherence only)

If clinical utility also includes cost effectiveness, as in societal evaluations for public health and managed care purposes or individual's choices in spending discretionary household income, the formula would be as follows.

Clinical utility (restrictive) = patient's outcomes + clinician's information impact + patient's information impact (adherence only)/cost (societal or individual or both)

Several conclusions are possible based on these more restrictive (and traditional) calculations of clinical utility. It is possible for personal genomic information to have no utility for patient's outcomes, but nonetheless to have clinical utility due to informational impacts on clinicians and patients that change the former's decision making or improve the latter's adherence to clinical advice.[12] Indeed, even if the only change is an improvement in patient's adherence, clinical utility can be marginally improved. The question then becomes whether the information is to be funded collectively (societal) or individually. An incremental increase in patient's adherence, for example, may not be cost effective from a societal perspective, whereas significant changes in patient's outcomes or in clinician diagnostic thinking or therapeutic choice (or some combination of those) may justify the expenditure of limited societal resources.

It is also possible for measures of clinical utility to be negative, as in the case of genetic tests that report false positives and/or mutations of unknown significance, and expend societal and individual resources without any patient's benefit while potentially increasing a patient's and family's psychological stress, or tests that report false negatives or have limited sensitivity and fail to trigger appropriate medical action and perhaps give patients and/or clinicians a false sense of certainty about the absence of a genetic predisposition.

The inventory also suggests a formula for calculating the personal utility of genomic information, in which "personal" is defined as those benefits or harms that are manifested primarily outside medical contexts (although these may indirectly affect medical outcomes):

Personal utility = patient's information impacts (− adherence) + awareness of health risks/cost (societal or individual or both)

The potential for improving health through individual initiative outside medical settings has long been a primary goal of public health efforts. Although genomic information may not make that large a direct contribution to preclinical disease prevention and surveillance, nonetheless, it is possible that it can have a significant indirect contribution through empowering individual health awareness and positive health behaviors. At the same time, though, it is also possible to have negative measures of changes in familial dynamics and screening and lifestyle behaviors as well psychological impacts of disease risk perception. Those negative measures of personal utility could, as part of an expanded measure of overall utility, suggest that personal genomic information actually can harm individual's well-being on a case-by-case basis. Whether the measures are positive or negative will depend to a considerable extent both on the ways in which the information is presented to and interpreted for lay clients by physicians or providers of direct-to-consumer (DTC) genomics services as well as the degree to which individuals themselves take ownership of understanding and protecting their personal genomic information.[26]

Measures of restricted clinical utility and personal utility can be combined into a summary measure of overall utility, with the understandings that others may propose additional measures for inclusion in an overall composite and that situational factors unique to some individuals also may be relevant for inclusion in their personal calculations of overall utility:

Overall utility = clinical utility (restrictive) + personal utility

Overall utility can be positive even in the absence of the more traditional medical benefits of a restrictive definition of clinical utility, particularly if cost effectiveness is based on individual resources rather than societal resources. The primary contributors to such a conclusion would be the benefits of enhanced patient's autonomy (including personal choice and interest), increased health surveillance and screening behaviors, and changes to healthier lifestyle behaviors. Factors contributing to an absence of overall utility would include a lack of either societal or individual cost effectiveness, a lack of positive changes in healthy behaviors (due either to no effects or a negative effect resulting from a false sense of genetic protection from disease susceptibility), negative psychological affects due

to genetic indications of heightened risk for disease, or consistent false positive findings that require expensive clinical follow-ups and also contribute to negative psychological affects.

As with a more detailed, composite sense of clinical utility, both personal and overall utility may vary between some individuals. For example, some family dynamics may be disrupted by the implications of information about inherited disease risk or biological relatedness whereas others actually may be enhanced by such information. Individuals who mistakenly believe themselves to be immune to chronic disease based on genomic estimations of risk will differ from individuals who shift to healthier behaviors. Perhaps of greatest concern are those who are psychologically harmed by learning their personal genomic information in comparison with those who derive some psychological benefit from being able to anticipate future health risks.

Rather than average of these differing responses across some sample population – which would be the procedure for societal decision making about clinical utility – an alternative procedure would develop a prescreen to identify individuals who are likely to have negative measures of an overall measure of utility that includes the personal components detailed earlier. Those individuals would be advised against having personal genome-wide genotyping or sequencing outside of medical contexts. This overall measure also could indicate whether medical benefits from personal genomic information obtained by physicians could outweigh an expanded inventory of harms (mainly psychological but also familial) to which those individuals might be vulnerable, a calculation that is currently not made systematically in counseling individuals about genetic testing.

The difficulty with any overall metric that incorporates multiple dimensions each of which is measured with a different instrument lies in calibrating those varying scores. To some extent, this can be simplified by the distinction between restrictive clinical utility and additional measures of personal utility. If a restrictive sense of clinical utility is demonstrably present, the question in evaluating overall utility is whether an expanded dimension (such as psychological perception of disease risk) can be so devastating as to outweigh direct medical benefit. Such an evaluation, however, will only be possible on an individual, case-by-case basis. If direct medical benefits are absent, then it is a question of whether beneficial personal utility is present and can be shown to be socially or individually cost effective.

Calibrating measures of personal utility, though, may be more problematic. What degree of negative psychological affect from risk estimation, for example, outweighs positive changes in screening or lifestyle behaviors? How should changes in self-surveillance be weighted in comparison with changes in family dynamics? Would changes to individual behavior be necessary to demonstrate a health promotion benefit to personal genome testing or would alterations in beliefs and attitudes be sufficient? Are psychological considerations such as lowered stress or increased satisfaction with health-related lifestyle choices the primary metrics to use in evaluating beneficial change? What would be the basis for using these particular measures of health-related utility over some others, such as perceived need to consult with a physician about future disease risks and preventive actions that might be taken now to reduce those risks? These and other comparisons of different aspects of a broadly defined personal utility of genomic information must be investigated empirically before a standard metric for overall utility can be put into practice, perhaps coordinated with ongoing efforts to develop evidence-based standards for introducing genomic applications into clinical practice.[27]

Indeed, a considerable amount of empirical social research will be necessary before an overall metric can be validated for use either by individuals trying to decide whether personal genomic information would be of benefit to them or by regulators or professional organizations trying to establish guidelines for recommending use of personal genome testing in medical settings. Once validated, though, an overall metric could be obtained as part of either genetic counseling intake or online DTC applications using a survey instrument that evaluates all contributors to utility detailed earlier (and perhaps others) for each individual. That evaluation then would become the basis for guiding both patients and providers in deciding if and how personal genomic analysis could best be carried out. Although such a metric no doubt would be controversial, its application on a case-by-case basis (rather than as a uniform rule) would provide the opportunity for individualized decisions about obtaining personal genomic information. At that point, the distinction between "clinical" and "personal" utilities would largely be an academic one, as both the practitioner and the patient would be focused on weighing the multiple components of an overall measure of utility rather than determining which are "clinical" and which are "personal."

WHICH UTILITY?

Although the rapid rise and media prominence of DTC genomic services have resulted in a preoccupation with regulation amid concerns that the companies marketing those services are overselling their potential benefits,[28,29] the more fundamental question is about the utility of genome-wide information that includes findings of multiple known variants and many more variants of unknown significance. Although a more restrictive definition of clinical utility is an important metric for evaluating targeted genetic diagnostics proposed for specific medical uses, it is a misleading metric with respect to the many other ways in which individuals may be affected by information about their personal genomic information.[30] More restrictive calculations of clinical utility fail to take note of benefits that some individuals may experience from enhanced autonomy, greater health awareness, and changes in screening and lifestyle behaviors, nor do they take into account the psychological harms or disruptions to familial dynamics that some individuals may experience from both heightened and lowered disease risk estimations.

Such individual differences in the benefits of genomic information argue for greater access to personal genomic data for those for whom there is positive overall utility. Individual differences in overall utility also argue for a greater investment in developing framing strategies for interpreting personal genomic information to reduce or reverse the negative utility that some may experience (which may be overstated in the literature) as well as to optimize potential benefits with respect to behavioral and lifestyle changes (which appear to be underrealized in current practice).[31] The accuracy and transparency with which personal genome information is interpreted in the context of current knowledge also may replace a criterion of clinical validity that is appropriate for traditional single gene forms of genetic testing but is too narrow to evaluate the utility of genome-wide data.

To be truly "personal," personalized genomic medicine has to integrate measures of individual concepts of what information is most relevant to well-being along with measures of the medical value of that information. This may be an underappreciated interpretation of "personal" genomics. In this sense, personalized medicine transforms patients into copractitioners in their own overall health promotion and care. The challenge

we should take from that is to find ways to better integrate patients as comanagers of their health rather than to develop new regulations to limit patients' access to their own health information in an era of increasing patient's empowerment and health consumerism.

ACKNOWLEDGMENTS

This work was supported by NIH grants CA114626 (to M.W.F.), RR017703 (to M.W.F.), HG004500 (to R.R.S.), and HG003390 (to R.R.S.).

REFERENCES

1. Khoury MJ, Yang QH, Gwinn M, et al. An epidemiologic assessment of genomic profiling for measuring susceptibility to common diseases and targeting interventions. *Genet Med* 2004;6:38–47.
2. Sanderson S, Zimmern R, Kroese M, et al. How can the evaluation of genetic tests be enhanced? Lessons learned from the ACCE framework and evaluating genetic tests in the United Kingdom. *Genet Med* 2005;7:495–500.
3. Mardis ER. The impact of next-generation sequencing technology on genetics. *Trends Genet* 2008;24:133–141.
4. Gniady JA. Regulating direct-to-consumer genetic testing: protecting the consumer without quashing a medical revolution. *Fordham Law Rev* 2008; 76:2429–2475.
5. McCullen MA, Crawford DHG, Hickman PE. Screening for hemochromatosis. *Clin Chim Acta* 2002;315:169–186.
6. Loughrey MR, Waring PM, Tan A, et al. Incorporation of somatic BRAF mutation testing into an algorithm for the investigation of hereditary nonpolyposis colorectal cancer. *Fam Cancer* 2007;6:301–310.
7. Berg AO, Piper M, Armstrong K, et al. Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. *Genet Med* 2007;9:819–825.
8. Hunter DJ, Khoury MJ, Drazen JM. Letting the genome out of the bottle: will we get our wish? *N Engl J Med* 2008;358:105–107.
9. Broadstock M, Michie S, Marteau T. Psychological consequences of predictive genetic testing: a systematic review. *Eur J Genet* 2000;8:731–738.
10. Offit K, Biesecker BB, Burt RW, et al. Statement of the American Society of Clinical Oncology: genetic testing for cancer susceptibility. *J Clin Oncol* 1996;14:1730–1736.
11. Shirts BH, Parker LS. Changing interpretations, stable genes: responsibilities of patients, professionals, and policy makers in the clinical interpretation of complex genetic information. *Genet Med* 2008;10:278–283.
12. Grosse SD, Khoury MJ. What is the clinical utility of genetic testing? *Genet Med* 2006;8:448–450.
13. Tatsioni D, Zarin DA, Aronson N, et al. Challenges in systematic reviews of diagnostic technologies. *Ann Intern Med* 2005;142:1048–1055.
14. Foster MW, Sharp RR. The contractual genome: how direct-to-consumer genomic services may help patients take ownership of their DNA. *Person Med* 2008;5:399–404.
15. McCullough LB, Wilson NL, Teasdale TA, et al. Mapping personal, familial, and professional values in long-term-care decisions. *Gerontologist* 1993; 33:324–332.
16. Denscombe M. Uncertain identities and health-risking behaviour: the case of young people and smoking in late modernity. *Br J Sociol* 2001;52:157–177.
17. Hays RD, Kravitz RL, Mazel RM, et al. The impact of patient adherence on health outcomes for patients with chronic disease in the medical outcomes study. *J Behav Med* 1994;17:347–360.
18. Ende J, Kazis L, Ash A, Moskowitz MA. Ware patient satisfaction questionnaire—short version. *J Gen Int Med* 1989;4:23–30.
19. Stein REK, Riessman CK. The development of an impact-on-family sale—preliminary findings. *Med Care* 1980;18:465–472.
20. Arn PH. Newborn screening: current status. *Health Aff* 2007;26:559–566.
21. Griffith GL, Edwards RT, Gray J. Cancer genetics services: a systematic review of the economic evidence and issues. *Br J Cancer* 2004;90:1697–1703.
22. Halbert CH, Lynch H, Lynch J, et al. Colon cancer screening practices following genetic testing for hereditary nonpolyposis colon cancer (HNPCC) mutations. *Arch Intern Med* 2004;164:1881–1887.
23. Sanderson SC, Wardle J. Will genetic testing for complex diseases increase motivation to quit smoking? Anticipated reactions in a survey of smokers. *Health Educ Behav* 2005;32:640–653.
24. Walter FM, Emery J, Braithwaite D, Marteau TM. Lay understanding of familial risk of common chronic diseases: a systematic review and synthesis of qualitative research. *Ann Fam Med* 2004;2:583–594.
25. Lerman C, Marshall J, Audrain J, et al. Genetic testing for colon cancer susceptibility: anticipated reactions of patients and challenges to providers. *Int J Cancer* 1996;69:58–61.
26. Foster MW, Sharp RR. Out of sequence: how consumer genomics could displace clinical genetics. *Nat Rev Genet* 2008;9:419.
27. Khoury MJ, Berg AO, Coates R, Evans J, Teutsch SM, Bradley LA. The evidence dilemma in genomic medicine: we need a roadmap for the appropriate integration of genomic discoveries into clinical practice. *Health Aff* 2008;27:1600–1611.
28. Howard HC, Borry P. Direct-to-consumer genetic testing: more questions than benefits? *Person Med* 2008;5:317–320.
29. Katsanis SH, Javitt G, Hudson K. A case study of personalized medicine. *Science* 2008;320:53–54.
30. Grosse SD, Wordsworth S, Payne K. Economic methods for valuing the outcomes of genetic testing: beyond cost-effectiveness analysis. *Genet Med* 2008;10:648–654.
31. Heshka JT, Palleschi C, Howley H, Wilson B, Wells PS. A systematic review of perceived risks, psychological and behavioral impacts of genetic testing. *Genet Med* 2008;10:19–32.

