Direct-to-Consumer Personal Genome Testing and Cancer Risk Prediction

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Abstract: The last several years has witnessed an explosion in genomics, with the advent of genome-wide association studies revealing hundreds of DNA variants significantly associated with most common diseases, including cancer. On the heels of these scientific advances came the direct-to-consumer (DTC) genetic testing industry. Genome-wide scans for disease have been marketed and sold directly to the public, without the involvement of a health care provider. Unlike genetic testing for mutations in known hereditary cancer susceptibility genes such as *BRCA1/2*, these genomic profiles examine DNA variants, which typically have a minimal risk impact, and account for only a fraction of the heritable component of cancer. Furthermore, risk information provided to consumers does not account for family history or other known risk factors. The clinical validity and utility of personal genome scans for disease risk prediction remain for the most part unestablished, although some argue lack of evidence of harm and the possibility that positive impacts on health behaviors or genetic awareness may result from consumer use. The DTC genetic testing industry has sparked significant controversy not only among the scientific community, but also among professional societies and government agencies.

In this review, we present some of the history and methodological considerations of DTC genomic profiling, with a focus on cancer risk prediction. The literature regarding consumer awareness and utilization is explored, including understanding, expectations, and behavioral and psychological responses to DTC genomic risk prediction. Primary care provider and genetic professional knowledge and perceptions of DTC genomic profiling are also addressed. Ethical and scientific controversy surrounding the DTC genetic testing industry is presented, along with policy recommendations, regulatory actions, and the changing landscape of the DTC genetic testing market in response. Although our understanding of the human genome holds much promise in the realm of cancer prevention and treatment, DTC genomic profiling for cancer risk prediction is unlikely in its current form to have any significant impact on the health of the public. Time will tell if the next venture in genomic medicine, whole genome sequencing, will be accompanied by the translational research and emphasis on public/provider education required to ensure its successful application toward reducing the burden of cancer at a population level.

Key Words: Genomic profiling, direct-to-consumer, cancer, GWAS

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A 32-year-old woman presents for her annual physical examination. The patient indicates her sister was diagnosed with breast cancer at age 39 years. The clinician refers the patient for genetic counseling and schedules her for a baseline mammogram. The patient goes online and discovers she can learn her "genetic risk" for breast cancer for a few hundred dollars. She is very reassured when her results come back indicating she has a "7.2% lifetime risk of developing breast cancer, which is 40% less than for females of European ancestry." Based on these results, she cancels her mammogram. At her next annual visit, her breast examination reveals a concerning lump in her left breast. The patient is ultimately diagnosed with a stage IIB triple negative invasive ductal carcinoma. The delayed cancer genetics evaluation reveals a strong paternal family history of breast and ovarian cancer, and she is found to carry a *BRCA1* mutation.

A 35-year-old man sees an ad for a $99 special on personal genome testing and sends in his sample. The report he receives back indicates he is at increased risk for prostate cancer. He talks with his parents to ask about prostate cancer in the family and learns instead that several individuals in his mother's family had early colon cancer. Intrigued by this, he asks his doctor about a connection between colon and prostate cancer, and the doctor refers him to a cancer genetic specialist who works with the family and ultimately determines they carry a Lynch syndrome gene mutation.

A 25-year-old with a low risk of breast cancer—based on family history and other traditional risk factors—is given the "one size fits all perfect gift" of a personal genome scan that will tell her about her genetic risk for more than "200 diseases and conditions." When she learns her breast cancer risk is "50% greater than the average women" and is in the "red zone," she schedules a consultation with a breast surgeon and requests a mammogram. She is recommended to have a repeat mammogram in 6 months to follow microcalcifications. However, because of her anxiety, a biopsy is performed, and result of which is negative. While waiting for her biopsy results, she tells her sister that she had a positive genetic test for breast cancer, whose physician then orders *BRCA1/2* testing.

Although the above scenarios are hypothetical, they are quite plausible and are used to illustrate some of the concerns—and possible benefits—associated with direct-to-consumer (DTC) availability of genomic-based tests, which provide risk information for health conditions such as cancer.

In this article, we describe the history and methodological considerations behind DTC genomic profiling, using examples that focus on cancer risk prediction. We explore the literature regarding consumer and provider knowledge and utilization of DTC genetic testing and the controversy that has surrounded this industry. In addition, we address policy recommendations and regulatory actions and the changing landscape of the DTC genetic testing market in response. Finally, we take a brief look at public health implications of DTC genetic testing and the future of genomic-based medicine.

DEFINITION, HISTORY, AND METHODOLOGICAL CONSIDERATIONS

What Is DTC Genetic Testing?

Direct-to-consumer genetic testing refers to genetic tests that are marketed to the public, where the consumer is able to

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order the test online or by phone, usually without the assistance of a health care provider. Although the term DTC genetic testing has been used in many contexts, our focus will be tests that scan for multiple common DNA variants associated with disease, as opposed to tests for rare single-gene conditions or DTC marketing.

According to the Genetics and Public Policy Center, as of August 2011 there were 27 companies offering DTC genetic testing for more than 250 health conditions and traits.[1] Along with information about ear wax type, dancing ability, or risk-taking tendencies, one can learn about genetic risks for multiple common and serious health conditions such as Alzheimer disease, diabetes, heart disease, and cancer. These companies vary in the types of tests they offer, and how their risks are calculated, but share the commonality that although the tests are performed in a Clinical Laboratory Improvement Amendment–certified laboratory, those involving genomic risk profiling have not undergone research-based evaluation of clinical validity or utility and are not Food and Drug Administration regulated.

The data from the Genetics and Public Policy Center included information on 11 companies offering DTC genetic testing for a total of 44 different types of cancer.[1] Nine of these companies did not require involvement of a health care provider to order testing. Table 1 provides information on the 5 companies that still offer testing in this manner, along with information on the types of cancers included and approximate cost.

The Development of the DTC Genetic Testing Industry

Direct-to-consumer genetic testing was a natural entrepreneurial offshoot of the Human Genome Project. In particular, the advent of genome-wide association studies (GWASs)—which first appeared in the literature in 2005 and have risen almost exponentially since—sought to find genetic markers associated with common diseases, in part to fulfill the promise of the Human Genome Project to provide personalized genomic medicine.[7] These studies use millions of "single-nucleotide polymorphisms" or SNPs that have been found throughout the human genome. Essentially, a case-control approach is used, where the genomes of 100s to 1000s of individuals with a particular condition (eg, breast cancer) and a population of controls without the condition are scanned for SNPs that show differential distribution between the 2 groups, resulting in odds ratios for the associated genotypes.

Early GWASs were plagued by multiple erroneous assumptions that discredited most of the initial results. However, over time, more rigorous methodology, involving much larger sample sizes, higher levels of statistical significance, replication, and control for population stratification, was used. These studies have resulted in identification of more than 1400 SNPs with "true" associations for more than 237 human traits and diseases, including breast, prostate, colon, lung, thyroid, and many other cancers.[8]

The rise of DTC genetic testing very closely followed the early influx of GWAS publications, with many companies entering the market in 2008.[9] These companies not only capitalized on this research, but also recognized the limited access to genetic testing in the existing health care infrastructure and the desire of consumers for convenience, privacy, and the right to own their own genetic information.[9]

Although the success of GWASs in identifying SNP-based disease associations cannot be argued, the initial promise of this approach in allowing for "personalized genomic medicine" has yet to be realized, despite the claims of the DTC testing companies. This is in part because the vast majority of SNPs are associated with very low odds ratios for common diseases—typically in the range of 1.1 to 1.4—and thus have minimal impact on absolute risk.[10–13] Furthermore, identified SNPs account for only a small proportion (5%–10%) of the known heritability of most common diseases.[13–15] Finally, much remains unknown regarding the impact of both gene-gene interactions and gene-environment interactions on an individual's predisposition to disease.[16]

DTC Genomic Profiling for Cancer Risk

Most cancer genetic testing available DTC is performed using genomic profiles, which involve testing for multiple SNPs that have been associated with a specific cancer. The most common method used to calculate the person's disease risk involves conversion of the odds ratios of the genotype at each SNP to relative risks, then combining them in a simple multiplicative model. This overall relative risk is then compared with the general population risk for this cancer, to provide a percent increase and/or a revised absolute risk (Fig. 1). This method is highly dependent on the background population risks used, and assumes all SNP effects are independent.

Although most of the companies use well-validated SNPs, they do not all use the same ones in the same way. This means that the disease risk estimates provided may differ from company

TABLE 1. Cancer Risk Prediction Tests Offered by DTC Genetic Testing Companies Without Involvement of a Health Care Provider (as of April 15, 2012)

Company Name	Cancers Screened by Genomic Risk Profiling	Cost
23andMe[2]	Basal cell, bladder, breast, breast cancer modifiers, breast/ovarian, colorectal, chronic lymphocytic leukemia, esophageal, esophageal squamous cell, esophageal linked with alcohol and smoking, follicular lymphoma, Hodgkin lymphoma, kidney, larynx, lung, melanoma, meningioma, myeloproliferative neoplasms, nasopharyngeal, neuroblastoma, oral and throat, ovarian, pancreatic, prostate, sarcoma, squamous cell stomach, testicular, thyroid	$207
deCODE[3]	Basal cell, bladder, brain-glioma, breast, chronic lymphocytic leukemia, colorectal, lung, ovarian, pancreatic, prostate, testicular, thyroid	$500
GenePlanet[4]	Breast, endometrial, gastric, lung, prostate	~$525
Accu-Metrics[5]	Basal cell, bladder, breast, colorectal, lung, prostate, thyroid	$989
Map My Gene[6]	Acute lymphoblastic leukemia, acute myelogenous leukemia, adenocarcinoma, bladder, breast, cervical, cholangiocarcinoma, chronic lymphocytic leukemia, chronic myelogenous leukemia, colon, endometrial, gall bladder, gastric, laryngeal, bronchial, liver, melanoma, myeloma, nasopharyngeal, oral, osteosarcoma, ovarian, prostate, retinoblastoma, renal, rectal, small cell lung, thyroid, tongue, urothelial	~$2200 (100 diseases)

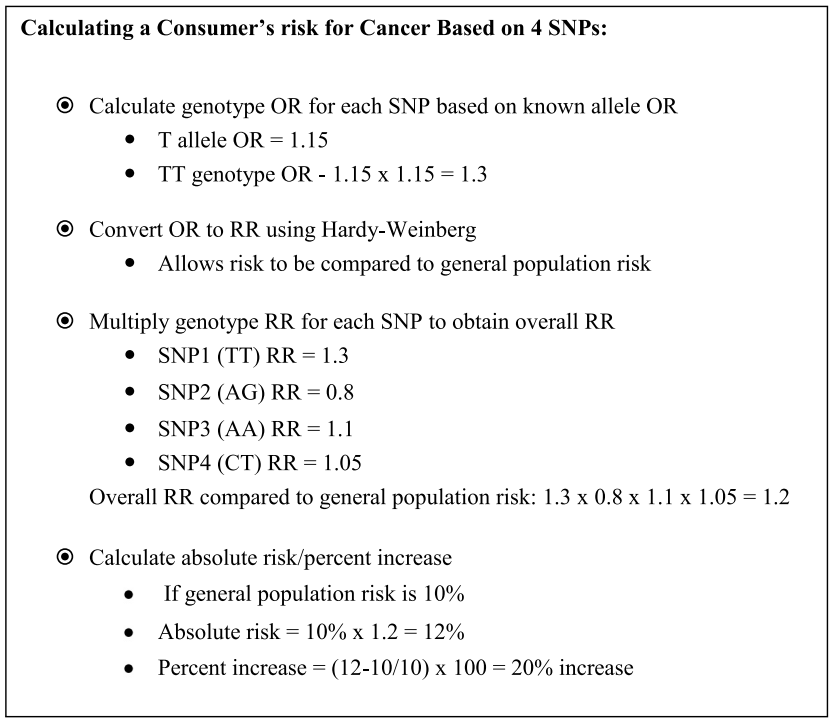

FIGURE 1. Calculating a Consumer's risk for Cancer Based on 4 SNPs.

to company, with one predicting an increased and the other an average or decreased risk. Evidence of this phenomenon has been reported in several publications and attributed to differences in the number/type of SNPs, variation in risk modeling approaches, and average general population risks used.[17–19] Table 2 illustrates the differences in the number of SNPs used and their reported effects for the 2 largest DTC genomic profiling companies (23andMe[2] and deCODE[3]) for some common cancers.

Perhaps even more concerning are data that suggest that as new disease-associated SNPs are added to a specific disease profile, a person's risk may be reclassified.[16,20] Both 23andMe and deCODE provide consumers with ongoing updates, such that a person who originally received a "lower than average" result for a specific cancer may find themselves at "average" or "above average" risk in the future. Although the possibility of risk reclassification is disconcerting, so too is the finding by Singleton et al[21] that only half of the Web sites of companies offering genomic risk profiling discussed how consumers would receive updated risk information, or even that their risks *could* change.

It is also important to clarify that the cancer risk estimates provided do not adjust for family history of the cancer or take into account other known risk factors. For example, a man who is morbidly obese, smokes 2 packs of cigarettes a day, and has a father with colon cancer at age 50 years will be given the same predicted risk for colon cancer as a man without these risk factors who has the same SNP profile.

Value of Genomic Risk Profiling for Cancer

All of the above issues underline the importance of considering both clinical validity and utility when interpreting the results of SNP-based genomic profiles as a measure of disease risk. Specifically, how accurate is the risk prediction provided by the SNP profile, and will this information result in changes in medical management or health behaviors that improve outcome? The accuracy of the risk prediction can be measured by the area under the receiver operating characteristic curve, or AUC, which plots sensitivity against the false-positive rate. A test that predicts no better than chance will have an AUC of 0.5—essentially a flip of the coin—whereas a test with an AUC of 1.0 can perfectly predict who will and will not develop the disease. Unfortunately, few studies have been conducted that provide the data needed to assess the clinical validity of most cancer risk prediction tests based on genomic profiling. Those that have been published, however, suggest these profiles have limited predictive ability.

For example, Wacholder et al[22] reported an AUC of only 0.597 for a breast cancer profile involving10 SNPs. Even adding these 10 SNPs to the Gail risk model for breast cancer only slightly improved its predictive ability from an AUC of 0.58 to 0.62.[22,23] Similarly, in the case of prostate cancer, Zheng et al[24] reported an AUC of 0.61 using age, geographic region, and family history, which rose only to 0.63 when the 5 strongest SNPs were added to the model. Although AUC data are not available for many of the cancers listed in Table 1, the use of a small number of SNPs with odds ratios typically less than 1.4 would suggest similarly poor predictive accuracy. Furthermore, the question of whether the use of genomic profiling leads to appropriate alterations in medical management or behavior that actually results in improved health outcomes (ie, clinical utility) remains, at this point, essentially unanswered.[25]

It should be noted that although the majority of testing performed by DTC genetic testing companies focuses on these SNPs with low cancer-associated odds ratios, there are exceptions.

TABLE 2. Comparison of 2 Companies' SNP profiles for Breast, Colon, Ovarian, and Prostate Cancer

Cancer	Company	No. SNPs Used	Sample Report SNP Effects
Breast cancer	23andMe	7	"Established report" with SNP genotype ORs ranging from 0.82–1.04
	deCODE	Up to 17* (Note: includes SNP for CHEK2 1100delC mutation associated with 2-fold RR)	SNP genotype RRs ranging from 0.83–1.42
Breast and ovarian cancer (*BRCA1/2* Ashkenazi Jewish mutations)	23andMe	3	Lifetime risks associated with *BRCA1/2* mutations are discussed
Ovarian cancer	23andMe	2	"Preliminary report" with both SNP genotype ORs of 1.2
	deCODE	1	SNP genotype RR of 1.13
Colorectal cancer	23andMe	4	"Established report" with SNP genotype ORs ranging from 0.8–1.19
	deCODE	Up to 8*	SNP genotype RRs ranging from 0.91–1.16
Prostate cancer	23andMe	12	"Established report" with SNP genotype ORs ranging from 0.64–1.3
	deCODE	Up to 29*	SNP genotype RRs ranging from 0.81–1.17

*Depending on ancestry.

OR indicates odds ratio; RR, relative risk.

For example, 23andMe evaluates 3 SNPs that are essentially markers for the 3 *BRCA1/2* Ashkenazi Jewish founder mutations. In sharp contrast to the other breast cancer risk SNPs, identification of one of these *BRCA1/2*-related mutations is highly predictive of disease, with odds ratios for breast and ovarian cancer of 10- to 20-fold and mean lifetime risks of 65% and 40%, respectively.[26] The significance of being negative for the 3 *BRCA1/2*-associated SNPs is primarily relevant for individuals of Jewish ancestry. Those of other ethnic groups would require full sequence analysis of these genes, which is not available DTC. Thus, DTC genomic profiling for cancer risk may result in the unexpected revelation of a significant hereditary cancer risk or false reassurance that such a risk has been ruled out. Some companies also test for SNPs in genes that have been suggested as modifiers of *BRCA1/2* penetrance, which could be misinterpreted as actual BRCA mutations.

CONSUMER ISSUES ASSOCIATED WITH DTC GENETIC TESTING

Awareness, Attitudes, and Utilization

Despite the widespread availability of DTC genetic testing for the past several years, it is unclear the extent to which consumers are either aware of or accessing DTC genetic testing for health reasons. In a 2008 cross-sectional survey of US consumers, whereas 22% of individuals were aware of DTC genetic testing for health risks, only 0.3% had actually accessed such tests.[27] A 2008 study in the United Kingdom found only 13% were aware of Internet-based personal genome testing.[28] Data obtained from the 2009 Behavior Risk Factor Surveillance System of 4 cooperating states (combined n = 16,439) demonstrated awareness of DTC genomic profiling for health risks ranged from 15.8% to 29.1%, although fewer than 1% of participants in each state reported having used testing.[29] Even in 1 study of social networkers, almost half of the participants (47%) were aware of DTC genetic testing, yet only 6% had ever undergone testing[30,31] Although 23andMe reports that more than 100,000 individuals have accessed their test,[32] a 2010 publication, which used the Web site traffic of 3 largest companies as a proxy for test uptake, concluded that the demand for genomic profiling was relatively low.[33]

Data from the Multiplex Initiative[34] provide an important look at issues of utilization within the context of a research setting. This project was designed to mirror the approach used by commercial DTC genetic testing companies, but uses Web content that focuses on health literacy and risk communication.[35,36] Testing was provided at no cost, and those who chose to pursue received education from a research coordinator regarding the risks and benefits of testing. Among 1959 people who were eligible and completed the baseline survey, 612 (31%) visited the Web site to consider testing. Of those who registered a decision (n = 528), almost half decided against undergoing testing.

Much of the existing literature regarding consumer attitudes and utilization of DTC genetic testing is based on data obtained on so-called early adopters, who generally have confidence in their ability to understand genetics and navigate the Internet and health care system and perceive that results will influence their health behaviors.[36,37] Another group that appears particularly interested in DTC genetic testing is of those who are simply interested in "setting the trend," many of whom proudly blog about their results.[38] While relaying optimism about the promises of genomic research, they may express skepticism about the current technology. Yet other early adopters express belief in the importance of the information to their health, as well as curiosity and fascination with the science.[39] Some would-be consumers are more cynical and report that DTC companies are "just trying to sell something" and that this approach is merely a "marketing ploy," intended to generate revenue for the company without a direct benefit to the consumer.[40]

Several studies have examined characteristics associated with awareness of and/or interest in online personalized genomic risk assessment. As expected, Internet-savvy individuals are more likely to be aware of testing.[36,41] Other predictors of consumer awareness of DTC genetic testing include white race, higher levels of education, greater income, older age, female sex, and numeracy variables.[27,42] In a UK study of the public, only 5% indicated a hypothetical interest in testing that costs £259, but 50% expressed interest in a free test.[28] Individuals with higher levels of

education and those of white race have also been shown to be more willing to pursue testing, with effects influenced by socioeconomic status, affiliation with a health care system, and cost.[36,43,44] In the Multiplex Initiative, further predictors of test utilization included motivation to change health behaviors, confidence in genetics knowledge, and perceived severity of the health conditions involved.[31,36]

Understanding, Perceptions, and Expectations

Previous studies have shown that general genetic concepts are often misunderstood by the general public, and DTC genomic profiling with its use of multiple low-risk variants adds an additional layer of complexity.[45] Genetic literacy—the ability to understand or interpret genetic and genomic information—varies greatly in the population and presents a challenge to the "one size fits all" approach of DTC genetic testing companies.

A recent study involving the Coriell Personalized Medicine Collaborative—a project that provides SNP-based disease risk information at no cost to early adopters with high literacy levels—demonstrated a reasonable understanding of genomic risk information.[46] However, DTC genetic testing is marketed to the general population, who likely has lower levels of health literacy, not to mention genetic literacy. In their study of social networkers, McGuire et al[30] reported that less than half were confident in their ability to comprehend their results or the risks/benefits of DTC genetic testing.

In another study, more than 30% of participants reported at least 1 misconception about DTC genetic testing.[47] Of particular concern is that some individuals may believe the DTC test results are definitive and ignore the information provided by their family history.[37] Even if individuals do not fully trust the DTC results, when a discrepancy exists between the results of the DTC genetic testing and the interpretation of familial risk, it can create significant confusion. As illustrated in a recent case report, extensive education and counseling may be required to assist patients in these circumstances, and it remains uncertain to what extent a true understanding of the meaning of their results can be achieved.[37]

In addition, consumers appear to have somewhat unrealistic expectations of DTC genetic testing, presuming that on presentation of their results to their clinicians an evidence-based individualized health plan can be devised. In 1 study, more than 90% of DTC testers were planning to share their results with their physicians, and 67% expected clinical recommendations to follow.[47] McGuire et al[30] found that 78% of consumers planned to share their results with their medical providers, with 34% believing the results represented a medical diagnosis. In a qualitative study from the Coriell Personalized Medicine Collaborative, 25 of 60 participants reported sharing their DTC results with their health care providers, and of these, 15 expected their physicians to change their health care plan or advise them of mechanisms to reduce their risk.[46] Recently, Leighton et al[48] conducted a study of the general public's response to DTC tests and found that 86.9% of respondents would seek information about their tests from their personal physicians, believing that future medical management would be affected by these tests.

Behavioral Change

If DTC genetic testing is to demonstrate clinical value, it must motivate individuals to change their behavior. Although this remains in debate, most studies published to date suggest DTC genetic testing as ineffective in promoting significant behavioral or lifestyle changes.[49–51] In a meta-analysis of 5 studies conducted by the Cochrane Collaboration, communicating DNA-based risk of disease was not found to affect smoking rates.[51] The Cochrane review also reported that 2 studies assessing physical activity and 1 study assessing medication or vitamin use found no impact of reporting genomic-based disease risks. In contrast, 2 studies examining dietary intake did find genomic test results to influence behavior. Among participants in the qualitative Coriell study, only 1 of 3 of DTC test recipients reported making a lifestyle change, although an additional third indicated they planned to do so.[46] In a recent survey of 1048 DTC customers, 16% had changed their use of a medication or supplement, one-third said they were being more careful about their diet, and 14% said they were exercising more.[50] However, these behaviors appeared to be strongly influenced by the participant's subjective interpretation of risk, as well as their family history and self-perceived health status.

There is some evidence that consumer access to DTC genomic profiling leads to increased screening or laboratory tests, which may or may not be medically appropriate.[37,50] The likelihood of consumers obtaining additional medical interventions appears to be strongly influenced by whether they share their results with their health care provider.[50] Among 1048 consumers of DTC genomic profiling tests, 28% reported sharing the results with their health care provider. Of these, 26% indicated they had received additional laboratory tests, as opposed to 2% of the consumers who had not shared their results.[50] Although on the surface this appears a beneficial outcome of DTC genetic testing, if the only indication for additional medical evaluation is the genomic profiling result, the cost of additional clinician visits and resulting medical interventions may far outweigh any positive impacts on the individual's health. Support for this concern is suggested by Giovanni et al,[52] who estimated that the potential downstream costs of referrals and additional testing following DTC results ranged from as low as $40 to as high as $26,000.

Psychological Consequences

The psychological consequences of DTC genetic testing have just begun to be explored. Some authors cite heightened and undue anxiety as a potential negative consequence of DTC genetic testing.[53] Based on experience from a recent clinical scenario involving a DTC test, the author concluded that DTC genetic testing may be detrimental to mental health in the absence of genetic counseling, causing anxiety, confusion, and misinformation.[54] In addition, Gollust et al[47] found that 30% of study subjects were concerned about the "worry" that resulted from the DTC genetic testing information, particularly learning about a disease for which they did not want to know their risk. In 2010, Bloss et al[43] reported that 47% of the DTC participants expressed psychological concerns about testing, with greater concern among young participants, women, those employed by a health care organization, and those with higher baseline anxiety. However, in a later study by the same author, there was no significant difference in pretest and posttest anxiety, suggesting that any psychological changes may be short term.[49] Furthermore, in the qualitative study of participants from the Coriell Personalized Medicine Collaborative, the most common emotional responses to testing results were actually reassurance and acceptance.[46] Further research is needed to determine the extent to which these findings are applicable to the average consumer of DTC genetic testing services.

PROVIDER KNOWLEDGE AND ATTITUDES ABOUT DTC GENETIC TESTING

Primary Care

Although many DTC genetic testing participants expect their providers to be fully versed in genetics and genomics,

staying abreast of this rapidly changing field presents a challenge for the average health care provider. Studies from both Canada and the United States have documented the inability of primary care physicians to interpret genetic results and their lack of confidence in this regard.[55–57] A systematic review by Scheuner et al[58] in 2008 concluded that primary care providers, despite some genetics training, are ill prepared to discuss genetic/genomic results and are unable to translate advances in genomics into clinically relevant practice. Direct-to-consumer genomic profiling, which provides risk information potentially more complicated to interpret than single-gene tests for hereditary disease susceptibility, may find physicians ill prepared to counsel their patients about the results. In a survey of North Carolina primary care physicians, only 39% were even aware of DTC genetic testing, and 85% felt unprepared to answer patient questions with regard to these tests.[59] Although 43% of respondents believed that DTC genetic testing had some clinical utility, more than 75% recognized a need for additional expertise in test interpretation.[59] Even among physicians who belong to a group that routinely offers genomic risk profiling as part of their practice, of 154 providers who had ordered genomic risk profiling for either themselves or a patient, 60% expressed concerns about the clinical utility of testing.[44]

The above data are particularly relevant in light of a 2008 survey of 1880 US health care providers, only 42% of whom reported being aware of DTC genomic testing for health risks. Of this group, 42% reported having had a patient inquire about DTC genomic testing, whereas 15% reported they had a patient present with the test results for discussion the past year.[27] Among the providers aware of DTC genomic testing, 52% indicated that personal genome results were somewhat or very likely to influence their care of patients. Among those whose patients had provided DTC genetic test results, 75% reported having used this information to alter their patient's medical management.[27] It is unclear if these changes in care are due to a belief of the provider in achieving a clinical benefit or the result of patient pressure to increase surveillance.

Genetics Professionals

A few studies have examined the knowledge and attitudes of genetic professionals toward DTC genetic testing, or how often they are involved with patients who have accessed such testing. In 2010, Giovanni et al[52] surveyed 3 genetic professional organizations in the United States, asking about consultations that related to DTC genetic test results. Although the response rate was low, participants reported having seen patients both who were self-referred and who were referred by another clinician. Although 52.3% of these genetics professionals found the information gained from the DTC results "clinically useful," this appeared primarily related to *BRCA1/2* results—which are in general no longer available DTC. In contrast, a small study of genetic professionals who themselves underwent genomic profiling found their perception of the current or future importance of such results to medical practice decreased after testing.[60] A larger study by Hock et al[61] involving 312 members of the National Society of Genetic Counselors found 83% had received 2 or fewer inquiries regarding DTC genetic testing, whereas only 14% had received requests for discussion or interpretation of test results. Recently, Brett et al[62] published a similar study of members of the Human Genetics Society of Australasia, in which 11% reported seeing at least 1 patient subsequent to his/her receipt of DTC genetic testing results. Surprisingly, only 7% of respondents to this survey reported that they felt confident about interpreting and explaining the results. In a study that contrasted the public's perception of a DTC genomic risk profile for colon cancer with that of genetic counselors, the latter were significantly less likely to believe the results would be medically helpful.[48] Although more data are needed, these combined results suggest that few consumers of DTC genetic testing are seeking the input of genetic providers, who, although not confident about their ability to interpret results, may perceive them as less than clinically useful.

CONTROVERSY, POLICY AND REGULATION, MARKET CHANGES, AND PUBLIC HEALTH ISSUES

Controversy

Many publications have addressed the pros and cons as well as ethical issues associated with DTC genetic testing.[12,63–73] Although a thorough review of the multiple arguments for and against DTC genetic testing is beyond the scope of this article, the key issues are outlined in Table 3. It should be noted that several of these arguments, both pro and con, are currently theoretical in nature, and more research is required to validate the claims on both sides of the aisle.

Perhaps one of the most significant criticisms of the DTC genetic testing companies revolves around their marketing practices. The Web sites of many DTC companies include seemingly contradictory statements about the intended purposes and value of their tests. A company may claim that the tests are for educational or entertainment purposes, while overtly stating that the information can be used to improve your health. These Web sites also emphasize the value of risk assessment for an individual's physician in determining what preventive actions should be taken to protect his/her health[21,55–57,59] and inconsistently acknowledge the importance of family history in assessing cancer risk.

Although many of the company Web sites have done an exceptional job with presentation, including the use of colorful diagrams to illustrate risk comparisons and easily navigated Web pages, these sites are tailored to those with a high educational level and are thus likely to confuse consumers with lower health literacy.[74] Of great concern, both 23andMe and deCODE's Web sites use the relative rarity of single-gene cancer susceptibility syndromes as a marketing ploy, which is easily misinterpreted. The following 2 quotes from deCODE's Web site education on ovarian cancer exemplify this point: "Scientists already know that variants in the *BRCA1* and *BRCA2* genes significantly increase a woman's chances of developing ovarian cancer. However, these variants are rare and account for less than 5% of all ovarian cancers" and "The deCODEme Complete Scan identifies validated ovarian risk variants of the more common type and uses them to provide a personalized interpretation of the associated genetic risk for the disease."[3] The clear implication is that the deCODEme test will be more useful to the majority of people, a claim without established clinical validity.

A further illustration of the potentially misleading information provided on DTC genetic testing Web sites is provided in an analysis by Singleton et al.[21] They reviewed Web sites of 23 companies offering health-related DTC genetic testing and found that statements of testing benefits outweighed those addressing risks and limitations by a ratio of 6:1. Although 96% of the Web sites emphasized the potential for the genetic test to prevent disease or reduce morbidity/mortality, only 30% indicated there are current limitations to the predictive ability of the tests, and 65% did not mention any risks associated with genetic testing.[21]

Policy Recommendations and Regulations Regarding DTC Genetic Testing

In recognition of the issues noted above, several professional societies as well as advisory bodies have issued recommendations

TABLE 3. Pros and Cons of DTC Genetic Testing[12,30,64,66–73]

Pros	Cons
Increase in consumer awareness and knowledge of genetics	Limited evidence of clinical validity/unknown clinical utility
Increased access to genetic testing/information	False or misleading claims that may lead to anxiety or false reassurance
Greater patient autonomy	Inadequate counseling/consent
Enhanced patient privacy	Misinterpretation of test results (by providers as well as consumers)
Opportunity for participation in genetic research	Consumer pursuit of unnecessary or inappropriate medical care or purchase of expensive health products
DTC availability and associated convenience may increase clinical uptake of genetic testing	Increased health care costs associated with unnecessary provider visits or medical tests/procedures
Potential for motivating healthy behaviors	Failure to seek appropriate preventive care if falsely reassured
Diminishes issues of genetic exceptionalism	Lack of adequate government oversight/regulation
Encourages genetic innovation and entrepreneurialism	Bypasses ethical and privacy protections inherent within the health care system (eg, genetic testing of minors for adult onset conditions)

and opinion statements regarding DTC genetic testing over the last several years.[75] A consistent message of these documents is concern for misinterpretation of genetic test results, the lack of involvement of an appropriately trained professional, and the need for federal regulation to protect consumers.[70,76–81] In part, the issues raised by these groups led to a 1-year investigation of DTC genetic testing by the US General Accounting Office. The investigation revealed evidence of deceptive marketing practices, consumer privacy concerns, and inaccurate or misleading medical advice from company consultants.[82] In July 2010, testimony at the General Accounting Office hearing led to a report that concluded that tests provided by the DTC genetic testing companies were "misleading and of little or no practical use."[83] Last year, the American Medical Association issued a letter to the FDA urging it to recommend genetic testing be conducted only under the supervision of a qualified genetics provider.[84] Although the FDA has indicated it will be tightening regulations on the industry, and warning letters have been issued to several DTC companies, there has yet to be any substantial regulatory changes enacted.[73,85,86] However, some states do have legal requirements mandating physician involvement in the ordering of genetic tests,[9] and many European countries have specific DTC genetic testing legislation, whereas others have banned the practice outright.[73,87]

One step toward greater transparency regarding genetic tests being offered to the public is the Genetic Test Registry, a project initiated in 2010 by the National Center for Biotechnology Information.[88] The Genetic Test Registry is intended to be a central place for clinicians and the public to access detailed information on genetic tests, including methodology, purpose, validity, price, and ordering information. Although the concept is promising, as the project has unfolded several challenges to its successful implementation have been identified.[89,90] Currently, the information is voluntarily added by test providers, and unfortunately, at the time of writing, none of the DTC companies listed in Table 1 have chosen to participate. It remains unclear whether regulatory agencies, such as the FDA, will require participation in the future or instill other mechanisms of oversight.

Changes in the DTC Genetic Testing Market

Likely in response to these recommendations and calls for greater regulation, there has been a recent trend by some DTC genetic testing companies to change their service models. Although some companies appear to have stopped offering health-related testing altogether, others that formerly did not require clinician involvement to order testing or receive results of genomic risk profiling tests are now doing so.[9,91] There is, however, a great deal of variation in this process, with some only requiring physician involvement in the ordering—with convenient referral to a physician already participating in their program—whereas others release results only to the consumer's provider.[91] Some companies are also working to promote their services within corporate wellness programs and partnering with the limited number of Genomic Medicine Institutes in the country to serve as resources for consumers and providers.[91]

Although requiring involvement of a health care provider may decrease the number of inappropriate tests performed and ideally allow for more integration of family history, it does not adequately address the issue of the clinician's ability to accurately interpret and act on test results, or improve the clinical validity of the testing. Nor does it address the possibility that physicians are merely ordering the tests at the request of their patients, without adequately researching the implications. Thus, although a positive step, these changes may ultimately prove to be an inadequate attempt to respond to previous criticism by the FDA and the medical community.

Whether to placate critics or provide for greater legitimacy in the eyes of the consumer, several DTC genetic testing companies are now emphasizing the role of genetic counseling in the testing process. In some cases, they have hired genetic counselors directly, making them available to answer questions or concerns expressed by clients using a customer service model. Having a genetic counselor available to answer questions, although likely helpful to clients in some circumstances, is not the equivalent of a comprehensive pretest genetic counseling session, which involves an exploration of family history and a detailed explanation of the risks, benefits, and implications of testing, as well as possible psychological and emotional ramifications. Furthermore, whether the services are being offered by qualified individuals is uncertain as illustrated by a company whose "official" genetic counselor is a nutritionist.[92] Even when legitimate board-certified genetic counselors are involved, if they are an employee of the company, one may question their ability to provide an unbiased opinion as to the risks, benefits, and limitations of a given test. Furthermore, although companies may be providing or contracting genetic counseling services, these services often come at a price, and consumer uptake has been reported to be low.[49] All of the above notwithstanding, a company that actively employs genetic counselors has been

successful in their efforts to increase consumer utilization of their genetic counseling service after return of DTC genomic profiling results.[85]

Potential Public Health Implications of DTC Genetic Testing

Given the relatively low awareness and uptake of DTC genetic testing, the public health implications of DTC genetic testing are largely theoretical at this time, although significant concerns have been raised.[64,93] Key concerns focus on disparities related to access and ability to understand or benefit from the results. In addition, if consumers begin widely using DTC genetic testing, this could lead to a diversion of health care and research dollars toward follow-up and evaluation of DTC genetic tests and away from potentially more productive cancer prevention efforts.[94] Alternatively, if genomic risk profiling is ultimately shown to improve health, either through inducing positive lifestyle changes or increasing patient compliance with recommended screening or prevention strategies, a positive public health impact might be realized. Even should this come to pass, however, disadvantaged populations, who have historically been low users of genetic testing in general[95] and who appear less aware of DTC genetic tests,[29,42] would be less likely to reap the benefits.

CONCLUSIONS

Whether DTC genetic testing that involves SNP-based genomic profiling will ever become the answer to personalized medicine for the masses is at this point very uncertain. It seems thus far that, despite the controversy, its impact has been relatively limited. Both increased regulation and scientific scrutiny of the clinical validity and utility of such tests appear likely to limit widespread use in the future—at least for access without involvement of a health care provider. At this point in time, DTC genomic profiling for cancer risk prediction is clearly of limited use with respect to guiding medical management recommendations, particularly as family history and other established risk factors are not assessed. And while being able to provide tailored cancer screening and prevention strategies for everyone based on their genetic makeup is an attractive approach, personal genomic profiling is unlikely to prove beneficial in this regard even if additional SNPs are identified.[16]

More likely the future of predictive genetic testing for cancer and other diseases, both common and rare, will focus on whole genome sequencing. According to the National Human Genome Research Institute, the cost to sequence a human-size genome in 2001 was $100,000,000.[96] In January 2012, Life Technologies announced that they were able to sequence an entire human genome for $1000 in only 2 hours.[97] Although such technology allows for identification of rare variants, copy number, and structural variations with potentially large effects on disease risks, it is also accompanied by the finding of multiple genetic variants of unknown clinical significance.

Although this is an important step toward integration of genomics into health care and holds much promise, the sheer volume of information obtained per genome and the complexities of interpretation imply challenges to the researcher, health care provider, and patient that go far beyond those associated with DTC genomic risk profiling.[98] It can only be hoped that the lessons learned over the past decade will provide the necessary awareness to ensure that whole genome sequencing does not become available to online consumers without either the scientific foundation to demonstrate its utility or the involvement of a knowledgeable health care provider. Inarguably, meeting the educational needs of clinicians, health care systems, and the public will be essential if genomic medicine is to fulfill its promise of improving the health of the population. It remains unclear, however, whether there are the capacity, infrastructure, and will to ensure such educational efforts are successfully accomplished.

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